Documents for the Record – 3/21/2024

Majority:

- March 15, 2024 - Statement submitted by the Association for the Advancement of Blood & Biotherapies
- March 19, 2024 - Statement from ARUP Laboratories
- March 19, 2024 - Statement from Mayo Clinic
- March 19, 2024 - Statement from the Association for Diagnostics & Laboratory Medicine
- March 20, 2024 - Stakeholder coalition letter on CLIA modernization
- March 20, 2024 - Statement submitted by Sanford Health
- March 20, 2024 - Statement submitted by the American Registry of Radiologic Technologists
- March 20, 2024 - Statement submitted by the American Society for Microbiology
- March 20, 2024 - Statement submitted by the American Society of Radiologic Technologists
- March 20, 2024 - Statement submitted by the Association of American Medical Colleges
- March 20, 2024 - Statement submitted by the Children's Hospital Association
- March 20, 2024 - Statement submitted by the Medical Group Management Association
- March 20, 2024 - Statement submitted by the National Organization for Rare Disorders
- March 20, 2024 - Statement submitted by the Nationwide Children's Hospital
- March 20, 2024 - Statement submitted by University of Colorado Anschutz Medical Campus Chancellor and School of Medicine Dean
- March 20, 2024 - Statement submitted the American Association of Bioanalysts and the National Independent Laboratory Association
- March 21, 2024 - Article submitted by Rep. Burgess
- March 21, 2024 - Document submitted by Rep. Burgess
- March 21, 2024 - Statement from the LUNGevity Foundation
- March 21, 2024 - Statement submitted by Dr. Oral Alpan
- March 21, 2024 - Statement submitted by the American Academy of Dermatology
- March 21, 2024 - Statement submitted by the American Cancer Society Cancer Action Network
- March 21, 2024 - Statement submitted by the American Hospital Association
- March 21, 2024 - Statement Submitted by the American Society for Clinical Pathology

Minority:

- March 21, 2024 - Article from the Center for Science in the Public Interest, "House panel to discuss FDA proposal to regulate lab-developed tests"
- March 21, 2024 - Statement submitted by the American Medical Association
- March 18, 2024 - Letter submitted by Dr. Daniel Hayes, Michigan Medicine
- February 8, 2024 - Article in Expert Review of Molecular Diagnostics, "The impact of companion diagnostic testing on medical decision making and IVD regulations"
- January 18, 2024 - Article, "FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made"
- September 22, 2023 - Memo from Brittany Schuck, FDA, "Examples of IVDs Offered as LDTs that Raise Public Health Concerns"
- September 22, 2023 - Memo from Elizabeth Hillebrenner, FDA, "Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2"
- July 3, 2023 - Article, "To Protect Patients And Spark Innovation, Codify The FDA's Oversight Of Laboratory-Developed Tests"
- November 30, 2022 - STAT article, "Better lab test standards can ensure precision medicine is truly precise"
- June 27, 2022 - Article in the Journal of Clinical Oncology, "Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities"
- October 22, 2021 - Report, "The Role of Lab-Developed Tests in the In Vitro Diagnostics Market"
- November 16, 2015 - Report from FDA, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies"

4550 Montgomery Avenue | Suite 700, North Tower | Bethesda, MD 20814 | 301.907.6977 | aabb.org

Association for the Advancement of Blood & Biotherapies

December 1, 2023

Robert M. Califf
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Proposed Rule: Medical Devices; Laboratory Developed Tests (Docket No. FDA-2023-N-2177)

Dear Commissioner Califf,

The Association for the Advancement of Blood & Biotherapies (AABB) appreciates the opportunity to provide comments in response to the Food and Drug Administration's proposed rule entitled "Medical Devices; Laboratory Developed Tests" (Docket No. FDA-2023-N-2177).

AABB is an international, not-for-profit association representing institutions and individuals involved in transfusion medicine and biotherapies. The association is committed to "improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide." AABB works toward this vision by developing and delivering standards, accreditation, and educational programs that optimize patient and donor care and safety. AABB individual membership includes physicians, nurses, scientists, researchers, administrators, medical laboratory scientists and technologists, and other health care providers.

Executive Summary

AABB appreciates FDA's commitment to protecting public health and concern regarding certain laboratory developed tests (LDTs). We commend FDA for acknowledging the lifesaving, unique nature of tests required to ensure safe, compatible blood transfusions as well as tests that ensure the safety of biotherapies, such as human cells, tissues, and cellular and tissue-based products (HCT/Ps). AABB appreciates that FDA proposes to exclude or exempt from enforcement discretion certain tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories. However, we are concerned that FDA's proposed policy falls short of protecting patients' access to the range of tests required to ensure safe blood transfusions and biotherapies, which could negatively impact patient care.

FDA's proposed regulation is quite vague and does not provide the regulated community with sufficient information to evaluate the potential impact of the proposed rule. Due to the number of unanswered questions throughout the preamble and FDA's recognition that it will need to publish several guidances to clarify its enforcement approach, it is impossible for laboratories to fully assess whether the regulations will apply to their tests, and if they do, how they will apply.

Based on the information currently available and the limited timeframe for reviewing the proposed rule, AABB believes that the proposed rule would create unnecessary regulatory burdens for some of the urgent, lifesaving LDTs performed by blood establishments, transfusion services, and accredited cell and gene therapy laboratories. AABB requests that FDA specifically exclude from its proposed regulation of LDTs or extend enforcement discretion to all tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories for the following reasons:

- Existing regulatory and accreditation requirements protect the quality and safety of tests performed by these facilities.
- The lifesaving tests performed in these laboratories have not contributed to the safety concerns that led to the proposed rule, often rely on established testing procedures, and reflect medical practices that are critical to patient care.
- The proposed rule threatens patients' access to critical, lifesaving medical services and has the potential to result in negative health outcomes.
- The burdens and costs associated with the proposed rule will discourage laboratories from developing and performing tests, which will negatively impact patients.

Prior to moving forward with the rulemaking process, AABB encourages the Center for Devices and Radiologic Health (CDRH) to work with the Center for Biologics Evaluation and Research (CBER), federal advisory committees, provider groups, accreditation organizations, and other public and private stakeholders to ensure that its approach is evidence-based, risk-based, and does not inadvertently interfere with patients' access to the full course of lifesaving treatments.

1. **FDA should exclude or continue enforcement discretion for all LDTs conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories because the existing regulatory and accreditation requirements protect the quality and safety of tests provided by these facilities.**

Blood establishments, transfusion services, and accredited cell and gene therapy laboratories may conduct LDTs in laboratories including blood banks and transfusion services, immunohematology reference laboratories (IRLs), molecular testing laboratories, human leukocyte antigen (HLA) laboratories, flow cytometry laboratories, donor testing laboratories, perioperative services, and cellular therapy laboratories. AABB urges FDA to recognize that the existing regulatory framework ensures that blood establishments, transfusion services, and accredited cell and gene therapy laboratories provide high quality, safe, effective care.

- These laboratories are all part of federal, state, or locally licensed facilities and satisfy relevant licensure requirements.

- These laboratories are certified under the Clinical Laboratory Improvement Amendments (CLIA) program, which "regulates labs testing human specimens and ensure that they provide accurate, reliable, and timely patient test results."[1]
- Extensive FDA regulatory requirements apply to these laboratories, such as registration requirements; licensure requirements for donor screening and infectious disease tests as well as blood grouping and phenotyping reagents; premarket approvals and 510(k) clearance for certain products; new drug application (NDA) products; and reporting requirements related to adverse reactions (HCT/P establishments) and fatalities (blood establishments and HCT/P establishments).
- Some of the laboratories are subject to heightened regulations under State regulatory frameworks, such as the New York State Department of Health Clinical Laboratory Evaluation.

In addition, the quality and safety of care provided by blood establishments, transfusion services, and accredited cell and gene therapy laboratories is supported and continuously validated by accreditation programs. For example, AABB-accredited laboratories adhere to longstanding and internationally recognized standards that evaluate the facility's quality management system and provide tools to monitor performance, capture deviations, and analyze suboptimal outcomes. The standards relate to organizational requirements; resources; equipment; supplier and customer issues; agreements; process control; documents and records; deviations, nonconformances, and adverse events; internal and external assessments; process improvement; and safety and facilities.[2]

AABB appreciates that FDA recognizes the rigorous regulatory requirements that govern donor screening tests required for infectious disease testing, the detection of blood group and Rh factor, and Human Leukocyte Antigen (HLA) tests used for blood transfusions. However, as highlighted in the case studies included in sections 2 and 3 below, we do not believe that the proposed rule excludes or extends enforcement discretion to all urgent, lifesaving tests provided for these purposes. Rather, some tests would be exempt from the new regulatory paradigm, other tests would remain subject to enforcement discretion, and other tests would be regulated as LDTs.

We recommend that FDA recognize that the existing regulatory and accreditation requirements are sufficient safeguards for protecting the quality and safety of tests performed by blood establishments, transfusion services, and accredited cell and gene therapy laboratories, and exclude or extend enforcement discretion to all tests performed by these facilities. If FDA continues to believe that other quality assurances are needed for LDTs conducted by these

---

[1] Centers for Medicare & Medicaid Services, MLN Fact Sheet, CLIA Program & Medicare Lab Services (May 2023), available at https://www.cms.gov/outreach-and-education/medicare-learning-network-mln/mlnproducts/downloads/cliabrochure.pdf.

[2] *See* AABB Standards, Blood Banks and Transfusion Services, 33rd Edition; AABB Standards, Cellular Therapy Services, 11th Edition; AABB Standards, Immunohematology Reference Laboratories, 12th Edition; AABB Standards, Molecular Testing for Red Cell, Platelet, and Neutrophil Antigens, 6th Edition; AABB Standards for Perioperative Autologous Blood Collection and Administration, 10th Edition; AABB Standards for Out-of-Hospital Administration Services, 1st Edition; AABB Standards for a Patient Blood Management Program, 4th Edition, *available at* https://www.aabb.org/standards-accreditation/standards.

laboratories, AABB encourages FDA to accept evidence of accreditation, including AABB accreditation, as a sufficient safety measure. If FDA determines that additional oversight is necessary, AABB recommends that CDRH work with accreditation organizations and CBER to minimize burdens and leverage existing requirements and inspections to the maximum extent possible.

2. **FDA should exclude or extend enforcement discretion to the lifesaving tests performed by blood establishments, transfusion services, and accredited cell and gene therapy laboratories since they have not contributed to the safety concerns that led to the proposed rule, often use established testing procedures, and engage in medical practices that are critical to patient care.**

The tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories have not contributed to the safety concerns that led to the proposed rule. These laboratories perform urgent, lifesaving laboratory procedures and tests for patients being treated in healthcare settings. The tests are not marketed or sold to consumers. Additionally, the testing procedures are often established, may be reflected in FDA guidances, and are an integral part of medical practice.

Many LDTs performed by blood establishments, transfusion services, and cell and gene therapy laboratories involve testing procedures that have been rigorously validated and performed for years. They may provide patients with access to accurate and high-quality laboratory tests for conditions for which no commercial test exists or where an existing test does not meet clinical needs. A laboratory may customize a test to meet the individual needs of a patient or may use reagents that are not licensed, approved, or cleared by FDA. Additionally, the tests may be manual, automated, or hybrid (i.e., semi-automated), so they may not be considered "1976-Type LDTs."

Some established laboratory practices and procedures that could inadvertently be captured by the proposed rule are reflected in authoritative resources used by laboratory professionals, such as the *AABB Technical Manual*. Examples include, but are not limited to:

- Method 3-18 Treating Red Cells Using DTT or AET
- Method 3-19 Neutralizing Anti-Sd[a] with Urine
- Method 3-20 Adsorption procedure
- Method 4-2 Glycine-HCI/EDTA Elution Procedure
- Method 4-9 Adsorbing Warm-Reactive Autoantibodies Using Allogeneic Red Cells
- Method 4-11 Performing the Donath-Landsteiner Test
- Method 4-12 Detecting Drug Antibodies by Testing Drug-Treated cells
- Method 5-2 Testing for Fetomaternal Hemorrhage – Modified Kleihauer-Betke test[3]

[3] *See e.g.*, Cohn, C., Delaney, M., Johnson, S. et. al. *AABB Technical Manual*, 21st Edition: Methods and Appendices. (2023), *available at* https://www.aabb.org/aabb-store/resources/technical-manual-methods.

Other tests that could be captured by the proposed rule are recognized in FDA Guidance. FDA recognizes in its *Labeling of Red Blood Cell Units with Historical Antigen Typing Results, Guidance for Industry* that blood establishments use unlicensed reagents or unapproved molecular tests when providing care, and provides instructions for their use.[4] Since the language in the preamble to the proposed rule suggests that tests encompassed by the proposed exclusion for tests that prevent incompatible blood transfusions must be licensed, approved, or cleared by FDA, the tests covered in the FDA guidance may not be captured. These tests may be manual, automated, or hybrid, so they may not be considered "1976-Type LDTs."

Tests performed by blood establishments, transfusion services, and cell and gene laboratories reflect medical practices and inform time-sensitive medical care. Pathologists, other physician subspecialties, such as blood banking/transfusion medicine physicians, and physician extenders provide care through laboratory medicine.[5] For example, pathologists "practice medicine by establishing diagnoses, monitoring disease progression and treatment, determining disease risk and cause of death, and overseeing blood and cellular transfusions. This may include directing laboratories or developing new testing methods using patient tissues, blood cells and body fluid specimens."[6] For instance, physicians and laboratory professionals:

- Use their medical judgement to make timely decisions about blood compatibility for patients with rare blood types, such as patients with sickle cell disease or thalassemia. They practice medicine by directing or performing laboratory tests that identify antigen-matched blood and reduce a patient's risk of experiencing adverse events, such as hemolytic transfusion reactions, life-threatening anemia, pain crisis, acute chest syndrome, and/or acute renal failure. The tests are often individualized within each medical facility and are not approved, licensed, or cleared by FDA since they use reagents derived from donors and patients with rare blood types.
- Regularly use LDTs when furnishing care to pediatric patients since routine tests are often not approved for the pediatric patient population or need to be modified to be used for children.
- May conduct metagenomic next-generation sequencing for the broad-based detection of rare or unexpected pathogens and may use the results from the tests to inform patient care.[7]

Additionally, laboratory medicine is at the forefront of advancing personalized medicine and driving medical innovation. LDTs are critical for personalized medicine because they leverage an individual's genetic information to guide decisions regarding preventing, diagnosing, and

---

[4] Center for Biologics Evaluation and Research. Labeling of Red Blood Cell Units with Historical Antigen Typing Results: Guidance for Industry. December 2018.
[5] *See* ACGME Program Requirements, FAQs, and Applications for Pathology Specialties, *available at* https://www.acgme.org/specialties/pathology/program-requirements-and-faqs-and-applications/.
[6] *I.e.* ACGME Program Requirements for Graduate Medical Education in Anatomic Pathology and Clinical Pathology, *available at* https://www.acgme.org/globalassets/pfassets/programrequirements/300_pathology_2023.pdf (effective July 1, 2022, update effective July 1, 2023);
[7] Gould CV, Free RJ, Bhatnagar J. et. al., Transmission of yellow fever vaccine virus through blood transfusion and organ transplantation in the USA in 2021: report of an investigation. *The Lancet Microbe*, Vol. 4, No. 9, e711-721 (Aug. 3, 2023).

treating disease. Furthermore, researchers invest significant effort in developing new biotherapies and several LDTs are used to evaluate novel products.

Please see section 3 below for other examples of LDTs provided by blood establishments, transfusion services, and accredited cell and gene therapy laboratories that are safe, integral parts of lifesaving care provided to patients.

AABB urges FDA to avoid finalizing a proposed rule that conflicts with authoritative resources and existing FDA guidance, and that interferes with patients' access to established medical practices and services that inform the practice of medicine. Rather, we encourage FDA to exclude or continue enforcement discretion for all tests conducted by blood establishments, transfusion services, and accredited cell and gene therapy laboratories.

3. The proposed rule threatens patients' access to safe blood transfusions and biotherapies and has the potential to result in negative health outcomes.

The proposed rule has the potential to negatively impact health equity and reduce patients' access to the full course of lifesaving treatments for patients with conditions such as sickle cell disease, cancer, and rare diseases. Below, we have provided a few examples of case studies to demonstrate how pathologists and other medical professionals use LDTs when treating different patient populations that require blood transfusions and biotherapies. The case studies illustrate the types of lifesaving LDTs provided by blood establishments, transfusion services, and accredited cell and gene therapy laboratories, but are not intended to be a comprehensive representation of the types of LDTs performed by these facilities or the patient populations that rely on these tests.

AABB is concerned that laboratories may no longer offer these tests and others if they are subject to new burdens and costs associated with being regulated as devices. Additionally, the proposed rule could impact laboratories' willingness to share new methods and rare reagents with each other, which would negatively impact patient care. Many patients requiring blood transfusions or biotherapies have challenges accessing subspecialized care, and the Biden Administration and the Department of Health and Human Services have prioritized addressing barriers through commendable efforts such as the Cancer Moonshot Initiative and the HHS Equity Action Plan. We believe that the proposed rule has the potential to adversely impact these efforts by creating obstacles to accessing safe, compatible blood transfusions and timely biotherapies.

Case Study 1: Course of treatment for a child receiving a stem cell transplant for sickle cell disease.

A 7-year-old male patient is admitted to a hospital to receive an allogeneic stem cell transplant to treat sickle cell disease. The patient will be treated by a variety of providers, including but not limited to those who specialize in hematology, immunology, bone marrow transplantation, and pathology.

While FDA proposed to continue applying the general enforcement discretion approach to HLA tests required in advance of transplants, including HLA allele typing, for HLA antibody

screening and monitoring, or for conducting real and "virtual" HLA crossmatch tests, additional LDTs are necessary throughout the patient's course of treatment, including post-transplant. Examples of LDTs used throughout the patient's course of care may include:

- Genotyping LDTs to confirm the patient's type of sickle cell disease.
- Flow cytometry panels to characterize the patient's blood after transplant and to enumerate the stem cell graft provided by the healthy donor.
- Colony forming units (CFU) assays, which evaluate the qualitative and quantitative features of stem cell grafts.
- Post-transplant patient and donor chimerism [i.e., short tandem repeat (STR) assays] to assess engraftment and evaluate the potential for relapse.
- Testing biomarkers critical to the transplant process.

Case Study 2: Course of treatment for an oncology patient receiving CAR T-cell therapy to treat his multiple myeloma.

A 57-year-old male patient received a commercial CAR T-cell therapy to treat his multiple myeloma. Following administration of the therapy, the patient will need to be monitored by his clinical care team for signs of toxicity or therapy failure. Examples of LDTs that may be used to support the patient's care include:

- Flow cytometry panels to count the number of cells that have been engineered into CAR T-cells.
- Immunoassay LDTs to rapidly determine the presence and severity of cytokine release syndrome, an acute inflammatory syndrome associated with CAR T-cell therapy that can lead to organ failure and death, as well as to distinguish it from other clinical responses with similar symptoms.

Case Study 3: Course of treatment for a patient with leukemia receiving a stem cell transplant.

A 41-year-old female patient is admitted to a hospital to receive a bone marrow transplant to treat her leukemia. The bone marrow donor is a family member, however due to geographic and socioeconomic restrictions, the family member must donate their bone marrow at an institution separate from where the patient is being treated. Because of this the donated bone marrow must be cryopreserved prior to shipment to the patient. In this scenario, the patient will rely on a variety of LDTs to ensure optimal care, such as:

- Flow cytometry panels, which are used to diagnose leukemia and to enumerate the bone marrow donation at the collection site and again at the facility treating the patient.
- Flow cytometry panels to measure the effectiveness of pre-transplant conditioning regimens provided to the patient.
- Colony forming units (CFU) assays, which evaluate the qualitative and quantitative features of bone marrow after thawing and preparation for transplant.

- Post-transplant patient and donor chimerism to assess engraftment and evaluate the potential for relapse.
- Flow cytometry panels for evaluating the presence of any minimal residual disease following transplant.

Case Study 4: Course of treatment for a patient with sickle cell disease requiring multiple blood transfusions.

A 20-year-old female patient with sickle cell disease has received several red blood cell transfusions throughout her life and requires another blood transfusion. She has rare antigen phenotypes and due to being a recipient of chronic transfusions, she has multiple red blood cell alloantibodies. Thus, the patient is at increased risk of experiencing adverse reactions to blood transfusions, which can be life-threatening. Examples of LDTs that are instrumental to her care include:

- Molecular genotyping tests, which will be conducted on the patient and the donor to identify closely matched blood, which is important for optimal patient outcomes.
- Blood compatibility tests, including adsorptions and elutions, incorporate laboratory prepared reagents and well-characterized anti-sera derived from rare donors and patients. Laboratories use established quality control to verify reactivity of the non-licensed reagent or anti-sera.
- Expired reagent red blood cells may be used to confirm or rule-out a suspected antibody. Laboratories use quality to verify the reactivity of the expired reagent red cells.

We encourage FDA to avoid finalizing a proposed rule that has the potential to threaten patients' access to lifesaving laboratory procedures that support safe, compatible blood transfusions as well as safe cell and gene therapies.

4. **The burdens and costs associated with the proposed rule will discourage laboratories from developing and performing tests, which will negatively impact patients.**

The proposed rule does not adequately capture the human resources required and anticipated costs that will be incurred by blood establishments, transfusion services, and accredited cell and gene laboratories and services if they need to comply with the medical device regulatory requirements.

Due to the existing laboratory workforce shortage, blood establishments, transfusion services, and accredited cell and gene therapy laboratories cannot absorb the significant, new regulatory requirements laid out in the proposed rule. The American Society for Clinical Pathology recently published an article that highlights pervasive vacancies in medical laboratories in the United States. In addition to current workforce shortages, the pipeline of individuals entering the field will not meet the needs of the future. For example, blood banks have the highest staff vacancy

rate – 18.9% - as well as an 18.1% rate of employees expected to retire within the next five years.[8]

We anticipate that it would be difficult for blood establishments, transfusion services, and cell and gene therapy laboratories to identify new, qualified individuals who understand the complex, specialized work conducted by these laboratories and can support compliance with the FDA's medical device regulatory requirements. Further, costs related to hiring and training new staff are not accounted for in the proposed rule. The workforce shortage will impact limit laboratories' abilities to catalogue their LDTs, complete novel submissions for FDA, and learn and comply with medical device regulatory requirements.

In addition to human resources and the costs associated with completing and submitting required applications and information to FDA, blood establishments, transfusion services, and accredited cell and gene therapy laboratories would be subject to user fees for tests regulated as LDTs. User fees would be new expenses for these laboratories, which operate under extremely tight budgets.

If blood establishments, transfusion services, or accredited cell and gene therapy laboratories need to redirect existing resources or incur increased costs to address unnecessary regulatory burdens, it is possible that the increased costs would be passed on to the healthcare system and patients. The laboratories would likely need to reduce the number of tests they offer and may not be able to provide test results in a timely manner. This would result in patients not having access to medically necessary tests that prevent adverse events and inform lifesaving healthcare.

Conclusion

AABB appreciates FDA's dedication to protecting public health. We are committed to working with the Agency to ensure that policies promote quality and safety, while also protecting patients' access to lifesaving laboratory procedures that are critical for blood transfusions and biotherapies. If you have any questions or need additional information, please contact me at [redacted] or [redacted].

Sincerely,

[*Signature on file*]

Leah Mendelsohn Stone, JD
Vice President, Public Policy and Advocacy
Association for the Advancement of Blood & Biotherapies

[8] Edna Garcia, Iman Kundu, Melissa Kelly, Ryan Soles, The American Society for Clinical Pathology 2022 Vacancy Survey of medical laboratories in the United States, *American Journal of Clinical Pathology*, 2023; aqad149, https://doi.org/10.1093/ajcp/aqad149.

ARUP LABORATORIES

A nonprofit enterprise of the University of Utah and its Department of Pathology

500 Chipeta Way
Salt Lake City, UT 84108
800-522-2787
aruplab.com

March 19, 2024

The Honorable Brett Guthrie
Chairman
Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
2322A Rayburn House Office Building
Washington, DC 20515

RE: Health Subcommittee Hearing on Regulation of Diagnostic Tests [March 21, 2024], Written Comment on Behalf of ARUP Laboratories from Jonathan Genzen, MD, PhD

Chairman Guthrie and Ranking Member Eshoo,

My name is Jonathan Genzen, and I am a clinical pathologist, a physician whose board-certified medical specialty involves the oversight and provision of clinical laboratory diagnostics for patient care. I serve as chief medical officer and senior director of government affairs at ARUP Laboratories, a nonprofit enterprise of the University of Utah's Department of Pathology, where I also hold an academic position as a clinical professor. I previously served as ARUP's chief operations officer during the COVID-19 pandemic. In these roles and in my other activities as a laboratory medical director and physician/scientist, I have developed a direct and systematic understanding of how clinical laboratory diagnostics impact public health. It is from this perspective that I would like to express my grave concerns regarding the negative impacts on public health and patient care of the FDA's proposed rule on laboratory-developed tests (LDTs).[1]

Clinical pathology is also commonly known as laboratory medicine, and indeed, medicine is practiced inside of clinical laboratories and in many facets of activities. As a CLIA director and a physician, I am legally and medically responsible for the development and operation of all clinical laboratory testing performed under my certificate. I hold this responsibility with profound respect and dedication to ensuring that our laboratory continuously provides outstanding clinical laboratory diagnostic services to our health system, our customer laboratories, and most importantly, to the patients who rely on us for safe and accurate testing.

ARUP Laboratories and LDTs

ARUP is the nation's largest nonprofit clinical reference laboratory, with customers representing more than 2,000 hospitals and medical centers across all 50 states. We perform laboratory diagnostic testing that impacts millions of people each year, and we provide clinical laboratory services for our academic medical center – University of Utah Health. With more than

[1] FDA Proposes Rule Aimed at Helping to Ensure Safety and Effectiveness of Laboratory Developed Tests. September 29, 2023. https://www.fda.gov/news-events/press-announcements/fda-proposes-rule-aimed-helping-ensure-safety-and-effectiveness-laboratory-developed-tests.

100 board-certified MD and PhD physicians and scientists who oversee clinical testing, ARUP provides laboratory services across all medical disciplines. Our ARUP Institute for Clinical and Experimental Pathology® has more than 60 research and development (R&D) scientists focused on test development, assay maintenance and enhancement, and research activities. Consistent with our academic mission and commitment to sharing knowledge with the clinical community, ARUP's medical directors and R&D scientists publish more than 130 peer-reviewed studies each year involving clinical laboratory diagnostics.

There are more than 3,000 different assays on ARUP's test menu. Of these, more than 1,000 are LDTs. As such, our ability to support clinical laboratory testing for patient care would be directly impacted by the FDA's proposed rule on LDTs. Our concerns with the proposed rule are outlined in detail in our November 28, 2023, public comment letter to the FDA.[2] I will summarize some of our concerns in the present written comments for this subcommittee hearing.

LDTs and the Benefits to Patient Care

As a physician, I am very concerned that the FDA, in its proposed rule and public statements, is promoting a decreased confidence in the quality of clinical laboratory services to the American public in order to enact LDT regulatory oversight. That portrayal is completely discordant with my own experiences in clinical laboratories and from interactions with truly incredible colleagues across the country. The community of more than 100,000 clinical laboratory professionals prides itself in a culture dedicated to patient care and continuous quality improvement, yet the FDA continues to convey a narrative to the public that many LDTs are unsafe, often using rarer, esoteric, multivariate genetic testing as anecdotal evidence of its concerns.

A study of all clinical laboratory orders within our academic health system over an entire year, however, demonstrates a very different view on the common utilization of LDTs by clinical providers.[3] For example, 93.9% of all test orders by clinicians during 2021 were for FDA-cleared/approved assays, while only 3.9% of orders were for LDTs. FDA statements regarding the proposed rule "leveling the playing field" do not accurately portray the current clinical laboratory testing market, which is dominated by FDA-cleared and approved assays when quantified by the relevant metric, which is clinical order frequency.[4]

Furthermore, the most frequently ordered LDTs are typically single analyte assays used for essential clinical care when no FDA-cleared/approved alternatives exist.[5] These are often low-volume tests (in terms of total order numbers) but spread out across many different types of LDT assays. It is the nature of this issue – low volume / high differentiation – that creates

[2] https://www.regulations.gov/comment/FDA-2023-N-2177-5561
[3] Rychert J, Schmidt RL, Genzen JR. Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System. *Am J Clin Pathol*. 2023 Sep 1;160(3):297-302.
[4] FDA proposes long-awaited LDT enforcement rule. September 29, 2023. *Regulatory Focus*. https://www.raps.org/news-and-articles/news-articles/2023/9/fda-proposes-long-awaited-ldt-enforcement-rule
[5] Rychert J, Schmidt RL, Genzen JR. Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System. *Am J Clin Pathol*. 2023 Sep 1;160(3):297-302.

unfavorable current market conditions for LDTs, and this is the true barrier to entry for in vitro diagnostic (IVD) manufacturers who cannot justify resources for test development and regulatory submissions if there is negligible financial return. Rather than solve this conundrum in support of patient care and diagnostic innovation, the proposed rule exacerbates the problem by dramatically increasing compliance costs for clinical laboratories and making many LDTs cost prohibitive for everyone. As noted in our recent clinical laboratory survey, only 3% of survey respondents reported having sufficient financial resources to support newly imposed FDA user fees.[6] If laboratories cannot support user fees, they cannot continue offering essential diagnostic services. In this context, I am particularly concerned about the negative impact of the proposed rule for diagnostic testing in cancer, pediatrics, and rare disorders.

Costs to Society and Patients

In its justification of the proposed rule last fall, the FDA also released a regulatory impact analysis.[7] As outlined extensively in our public comment letter, I believe that the FDA dramatically overestimated risks of LDTs, it ignored the clinical benefits of LDTs, and it did not evaluate the negative impact from loss of essential testing that the proposed rule would cause to public health. Furthermore, we have shown that the FDA made numerous significant material errors in dramatically overestimating the financial "benefits" of the proposed rule to society – a staggering 250-fold error – and it underestimated and overlooked many components of the true costs to patients and health systems. Additionally, the regulatory impact analysis did not evaluate how many laboratories would have to discontinue essential testing services due to increased compliance costs and user fees, which will likely be several million dollars each for many LDTs. The FDA also did not evaluate how many tests would be eliminated from the market and the associated negative impact to patients that would follow, nor the financial impact associated with corresponding increases in pricing due to consolidation and decreased market competition. I believe these errors and omissions are inconsistent with the intent of the Administrative Procedure Act, and that the FDA should not advance the final rule before working to better understand the true impact of the proposed rule on the American public.

Ultimately, it is our profound concern that the costs of the FDA proposed rule to most clinical laboratories would be prohibitive. Our recent survey of clinical laboratorians from across the country reinforces these concerns – 83.9% of clinical laboratorian respondents whose labs perform LDTs believe that their lab would be negatively impacted by the proposed rule, and a majority expect to remove tests from their menus if the proposed rule is finalized.[8] This would have a clear and lasting negative impact on clinical laboratories, hospitals, health systems, and patients.

---

[6] Smith L, Carricaburu LA, Genzen, JR. The FDA's Proposed Rule on Laboratory-Developed Tests: Impacts on Clinical Laboratory Testing and Patient Care. https://www.medrxiv.org/content/10.1101/2024.02.28.24303459v2.

[7] Laboratory Developed Tests Regulatory Impact Analysis (Proposed Rule). https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/laboratory-developed-tests-regulatory-impact-analysis-proposed-rule.

[8] Smith L, Carricaburu LA, Genzen, JR. The FDA's Proposed Rule on Laboratory-Developed Tests: Impacts on Clinical Laboratory Testing and Patient Care. https://www.medrxiv.org/content/10.1101/2024.02.28.24303459v2.

LDTs and Responding to Public Health Threats

I am also extremely concerned about the negative consequences of the proposed rule on the ability of clinical laboratories to respond to future pandemics and public health threats. A consequence of the proposed rule is that it would prohibit LDT offerings for emerging threats prior to either FDA-clearance/approval through traditional slow pathways, or a formal declaration of a public health emergency and activation of the Food, Drug, and Cosmetic Act Section 564 emergency use authorization (EUA) provisions. This would delay national responses to emerging infectious diseases, as well as chemical and radiologic threats. Any LDT regulatory oversight proposals should encourage the use of clinical laboratory diagnostics to facilitate a rapid and effective national response, rather than hinder it.

LDTs and the Important Role of CLIA

Despite the January 18, 2024, joint letter from the FDA and CMS regarding LDTs,[9] as a physician, I strongly believe that CMS has an essential role to play in current and future LDT oversight, particularly in the context of test modifications, low and moderate-risk LDTs in CLIA high-complexity laboratories, facilitating LDT transparency, and collaboration with CLIA-deemed accreditation organizations. The Clinical Laboratory Improvement Advisory Committee (CLIAC) should be empowered to discuss LDT oversight in all its ongoing and future CLIA modernization efforts, as I believe that this is in the best interest of promoting public health. As examples, several external CLIA accreditation organizations already require evidence of clinical validity for LDTs, even though this requirement is not specifically outlined in CLIA performance standards. Another justification used for FDA oversight of LDTs has been the lack of sufficient information about the extent and numbers of LDTs currently in use. CMS could easily compile this information from CLIA applications and CLIA accreditation organizations, and this would provide greater visibility of existing LDTs for future oversight proposals and for the public.

Grandfathering Provisions

The FDA's proposed rule also does not contain any grandfathering provisions, which would enable existing LDTs to remain on the market despite a new regulatory structure. We support grandfathering provisions in any LDT oversight proposal, as they would help to ensure patient access to essential testing services. Grandfathering provisions, however, would only delay the negative impacts of the current proposed rule, but they would not eliminate the negative impacts long term. Clinical laboratories need ongoing flexibility to maintain and update LDTs under existing CLIA performance standard requirements without risking loss of grandfathered status. For example, equipment replacement, supply chain disruption, and automation requirements to meet changing test volume demands can impact existing LDTs. If laboratories cannot adapt to these disruptions, laboratory services will be delayed, and patients may be further harmed by the proposed rule.

[9] FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made. January 18, 2024. https://www.fda.gov/medical-devices/medical-devices-news-and-events/fda-and-cms-americans-deserve-accurate-and-reliable-diagnostic-tests-wherever-they-are-made/.

Test Modifications

I would also like to emphasize the importance of keeping test modifications in high-complexity clinical laboratory settings under existing CLIA oversight and performance standards.[10] Test modifications are a relatively common (and beneficial) practice under CLIA to validate alternative specimen types received from clinicians, alternative specimen containers, specimen stability parameters, automation of manual processes, and to address to critical supply chain needs. Laboratories can currently perform these activities under CLIA validation requirements. The proposed rule, however, would introduce conflicting requirements, and laboratories could no longer adapt to health system needs without introducing significant additional compliance costs and delays in patient care. Again, under the proposed rule, most laboratories would be faced with discontinuing essential services in the context of test modifications that would become cost-prohibitive and/or delayed by new review requirements.

Practice of Medicine

I am also concerned that the FDA's proposed rule impinges upon the practice of medicine. The Medical Device Amendments does not authorize the FDA to regulate laboratory medicine activities. The proposed rule, however, would restrict the ability of physician laboratory directors to use their medical judgment, by locking down test interpretive comments in "labeling" requirements, for example, and by prohibiting test modification activities by physician laboratory directors outside of FDA review. Furthermore, the proposed rule conflicts with several state medical practice acts that include broad definitions of the practice of medicine and the act of diagnosis that are consistent with routine activities performed within the clinical laboratory by board-certified pathologists.[11] The FDA's proposed rule also raises significant First Amendment concerns regarding restrictions on what physicians could say regarding test interpretations or share in the form of scientific findings outside of FDA review. There are medical activities within the laboratory, and the proposed rule impinges upon these activities by licensed physicians.

Lack of Statutory Authority

It should be emphasized that we do not believe that the FDA has the statutory authority to regulate LDTs as medical devices. I have extensively researched the regulatory history of LDTs and have published numerous peer-reviewed articles in this topic.[12,13,14,15] LDTs are services, not products or physical devices. LDTs are not mentioned in the Medical Device Amendments of

---

[10] 42 CFR 493.1253 - Standard: Establishment and verification of performance specifications.

[11] Utah Medical Practice Act. https://le.utah.gov/xcode/Title58/Chapter67/C58-67_1800010118000101.pdf.

[12] Genzen JR, Mohlman JS, Lynch JL, Squires MW, Weiss RL. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017 Oct;63(10):1575-1584. https://pubmed.ncbi.nlm.nih.gov/28687634/.

[13] Genzen JR. Regulation of Laboratory-Developed Tests. *Am J Clin Pathol*. 2019 Jul 5;152(2):122-131. https://pubmed.ncbi.nlm.nih.gov/31242284/.

[14] Mohlman JS, Genzen JR, Weiss RL, Schmidt RL. Reliability and Validity of Proposed Risk Stratification Methods for Laboratory Developed Tests. *Lab Med*. 2019 Apr 8;50(2):194-201. https://pubmed.ncbi.nlm.nih.gov/30169875/.

[15] Rychert J, Delgado JC, Genzen JR. Modification of In Vitro Diagnostic Devices: Leveling the Playing Field. *Clin Chem*. 2020 Jun 1;66(6):760-762. https://pubmed.ncbi.nlm.nih.gov/32278318/.

1976 (MDA), nor were they discussed in Congressional hearings prior to its passage.[16] In fact, it wasn't until16 years after the enactment of the MDA that the FDA first acknowledged an awareness of the existence of LDTs.[17] LDTs are not commercially distributed through interstate commerce, and, concordantly, clinical laboratories have been specifically exempted from FDA registration for decades.[18] Prior analysis from HHS itself also asserts that the FDA's authority over IVDs does not likely extend to states and state-owned entities (e.g., state-owned university laboratories and public health laboratories as two prominent categories).[19] Finalization of the proposed rule is therefore in conflict with existing statutory authority.

Conclusion

In summary, my primary concern regarding the FDA's proposed rule on LDTs is that – in its effort to minimize the purported risk of "unsafe" LDTs – the proposed rule would eliminate access to many more existing safe and effective LDTs that are critical to ongoing patient care, but that are not financially sustainable under FDA user fees and compliance costs in hospital laboratory settings. What is equally troubling is that the FDA did not evaluate the negative public health impacts of the proposed rule. I am also concerned that increased costs caused by the proposed rule would contribute to further healthcare inequities between those able to afford and access such services and those who cannot.

As a board-certified pathologist, I strongly believe that the adverse public health consequences of discontinuing safe LDTs will vastly outweigh the purported benefits of the proposed rule, both in terms of patient safety and economic impact. For this reason, I ask that the FDA and HHS halt the advancement of the rule and work more closely with clinical laboratory stakeholders and CMS to devise a balanced regulatory framework that will not negatively impact public health or create further undue burden on the clinical laboratory community, hospitals, healthcare systems, and patients.

Sincerely,

Jonathan Genzen, MD, PhD
Chief Medical Officer and Senior Director of Government Affairs
ARUP Laboratories

---

[16] Genzen JR, Mohlman JS, Lynch JL, Squires MW, Weiss RL. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017 Oct;63(10):1575-1584. https://pubmed.ncbi.nlm.nih.gov/28687634/.

[17] Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation (Draft Compliance Policy Guide). Food and Drug Administration. Center for Devices and Radiological Health. Rockville, MD. August 3, 1992.

[18] 21 CFR 807.65, subpart i.

[19] Federal Authority to Regulate Laboratory Developed Tests. June 22, 2020. Robert Charrow, General Counsel. To Stephen Hahn, M.D., Commissioner of Foods and Drugs.

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
mayoclinic.org

Mayo Clinic Statement for the Record

U.S. House of Representatives Committee of Energy and Commerce

Subcommittee on Health Hearing

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

March 21, 2024

Chairs McMorris Rodgers and Guthrie and Ranking Members Pallone and Eshoo:

On behalf of Mayo Clinic, we thank you for holding this important and timely hearing on the FDA's proposed rule for regulating laboratory-developed tests (LDTs). For over 150 years, Mayo Clinic has been committed to inspiring hope and promoting health through integrated clinical practice, education, and research, putting the needs of the patient first. We are proud to be top-ranked for quality more often than any other healthcare organization and have more top-ranked specialties than any other hospital in the country. The clinical laboratories in the Department of Laboratory Medicine and Pathology at Mayo Clinic are CLIA-certified, College of American Pathologists (CAP)-accredited, and New York State-permitted, with a test menu of more than 1,800 LDTs.

We have serious concerns that the proposed rule will cause significant disruption to the diagnostic testing industry, and more broadly, healthcare in the United States. Those risks are much greater than the risks posed by the examples of poor-quality LDTs that FDA describes in the proposed rule. If finalized as written, the proposed rule will be detrimental to innovation, patient care, and patient access to crucial diagnostic services. Mayo Clinic strongly opposes using medical device regulations for LDTs and urges the Committee to adopt a legislative approach for enhancing LDT regulation, taking into consideration the unique nature of clinical diagnostics.

LDTs are Critical for High-Quality Patient Care

Diagnostic testing is critically important to healthcare; as FDA states in the proposed rule, 70% of medical decision-making is based on laboratory test results. FDA further acknowledges the proposed rule will cause some tests to come off the market because "the laboratory chooses not to invest resources to meet" new requirements, but views this as an acceptable outcome. Mayo Clinic disagrees with this conclusion. We are concerned that the proposed rule will likely require laboratories with limited resources to either cease developing and offering LDTs altogether or dramatically limit the number of LDTs they offer. Given the expense and resource demands required by the rule, Mayo Clinic may have to remove tests from our menu. Our primary concern is that many high-quality, accurate LDTs will no longer be available in an effort to remove a comparably small number of poor-quality LDTs. The detrimental impact on patient care, particularly related to rare disease testing, cannot be overstated.

FDA is Not Prepared to Regulate LDTs

According to an analysis by Pew Charitable Trust, there are approximately 12,000 diagnostic laboratories that develop LDTs in the United States. While the lack of a central database makes it difficult to determine the exact number, we feel a conservative estimate would place the number of LDTs nationally at over 100,000. For context, FDA approved 3,229 510(k), 23 De Novo, and 22 PMA submissions in 2022. The FDA received several thousand EUA requests for COVID-related medical

devices and LDTs and was not able to keep up with this level of submission demand; the proposed rule would generate at least an order of magnitude greater submissions. Therefore, we are very concerned that it could take decades for the FDA to review all existing LDTs on the market today. The proposed rule is far too broad and not a feasible solution.

Many High-Quality LDTs That Patients Rely on Will Leave the Market

As a practical matter, diagnostic laboratories can only absorb a finite amount of incremental cost before difficult decisions must be made with regard to investing resources to maintain existing tests or removing them from the laboratory's test menu. The 2024 user fee for a 510(k) submission is $21,760. If Mayo Clinic were required to submit a 510(k) on 1,800 tests, that would equal an incremental $39 million for just the user fees. However, using FDA's definition of low, moderate, and high-risk medical devices, it is likely that many of our tests would require a De Novo submission ($145,068 user fee) or PMA ($483,560 user fee). After conducting a cursory review of our test menu, we approximate the number of Class III devices at 330 and Class II devices at 800. According to our estimates, the cost of maintaining our existing tests would approach $280 million in user fees. This figure does not include the incremental costs needed for supporting this effort, updating test documentation to include requirements that were not in place when the test was first validated (for example, design controls), managing the submission process, and facilitating interactions with FDA; an estimate of these total costs for Mayo Clinic is $450 million.

Due to the direct and indirect costs incurred for complying with FDA medical device requirements, it is highly likely that many laboratories will either exit the LDT market altogether or dramatically curtail their LDT test menu and development pipeline. This would have a significant detrimental impact on diagnostic innovation and limit patient access to needed diagnostics. Again, this result would not further FDA's stated mission.

LDT Regulation Needs Updating, But Medical Device Regulations are Excessive and Damaging

CLIA is over 35 years old and needs updating. However, CMS and FDA have publicly stated that CLIA revisions are not sufficient to address the concerns FDA has expressed regarding LDTs. Mayo Clinic acknowledges that some FDA involvement in LDT regulation may be appropriate, but applying medical device regulations is a disproportionate and inappropriate response. The diagnostic services provided through LDTs are performed by highly trained medical professionals in highly regulated clinical laboratories, have a different risk profile than physical devices such as a pacemaker or artificial hip that are implanted into a patient. Medical device regulations would impose onerous requirements on LDTs, requiring additional studies, data, and/or documentation that may not meaningfully improve test performance or offer additional benefit, but only serve to increase the cost and time required to achieve FDA approval (see, for example, FDA Trial Regulation of Laboratory Developed Tests (LDTs): An Academic Medical Center's Experience with Mpox In-house Testing). Many of these additional costs will be passed on to patients and payors for those LDTs that remain on the market, contributing to the escalation of healthcare costs with minimal objective, proven benefits to patient safety.

Regulations Must Balance Oversight With Innovation

LDT regulation should include the following concepts, all of which appear in the VALID Act:

- **Grandfather existing LDTs** – While it is unknown how many LDTs are currently on the market, there are easily tens of thousands of them. These are tests that have been safely used for many years, tests that patients rely upon. Submitting documentation to the FDA for all of these LDTs would be a tremendous burden on both clinical laboratories and the FDA, and the disruption would be disastrous to quality patient care.

- **A three-tier risk classification system** – LDTs should be classified as low, moderate, or high risk, with increasing regulatory burden for higher risk tests. Risk should be determined by factors such as whether the test uses a novel technology, if the test results are used alone or in conjunction with other results, and the patient impact should an inaccurate test result occur.
- **Reasonable standards of analytical (AV) and clinical validity (CV)** – Clinical laboratories should expect clear, objective requirements for AV/CV that align with best practices, such as those outlined in guidance documents from the Clinical Laboratory Standards Institute. For CV, laboratories should have the option to leverage a variety of resources such as literature references, consensus standards, data registries, real-world data, etc., as it is not feasible in many cases for clinical laboratories to conduct prospective clinical trials.
- **Exempting tests for rare diseases** – LDTs are often the only tests available for rare diseases due to the limited commercial viability of such low-volume tests. Tests for diseases that affect fewer than 10,000 patients per year should be exempt from submission requirements.
- **Reasonable allowances for modifications** – Clinical laboratories update their LDTs to make them more efficient, more sensitive, less expensive, etc. All of these modifications are validated prior to use. Unless such modifications have a meaningful impact on analytical and/or clinical validity, a submission should not be required. In addition, modifications performed following a preapproved change control plan should also not require a submission.
- **Minimizing overlap with CLIA** – Clinical laboratories are already highly regulated through CLIA, state regulations, and accrediting organizations. While some overlap with these requirements is probably unavoidable, every effort must be made to minimize duplicative or, worse, conflicting regulatory requirements.
- **LDT-specific user fees** – The medical device user fee negotiations have historically explicitly excluded LDTs, and medical device user fees are not appropriate for LDTs. Given the number of LDTs (>100,000) compared to the number of medical devices, using the same fee structure would disproportionately impact LDT developers, which are often not commercial entities. A custom user fee system should be used to support LDT regulations, in addition to robust appropriations.

Conclusion

Thank you for your consideration of Mayo Clinic's comments regarding FDA regulation of LDTs. We look forward to continuing our collaborative engagement with the Committee, FDA, and other stakeholders. Please do not hesitate to contact Shannon Bennett, Director of Regulatory Affairs, at [redacted] if you or your staff would like to discuss these issues in greater detail.

STATEMENT
of the
Association for Diagnostics & Laboratory Medicine
to the
U.S. House of Representatives
Committee on Energy and Commerce Health Subcommittee

Re: Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule

Presented by Octavia M. Peck Palmer, PhD, FADLM
President, ADLM

March 21, 2024

The Association for Diagnostics & Laboratory Medicine (ADLM) welcomes the opportunity to provide testimony to the House Energy and Commerce Subcommittee on Health regarding the regulation of diagnostic testing and the impact of the Food and Drug Administration's (FDA's) October 3, 2023 proposed rule on the ability of healthcare providers to offer timely, quality patient care. We have serious concerns about the FDA's proposal. If finalized, this rule will create a costly, dual regulatory structure that will limit patient access to many life-saving tests.

- **ADLM believes the FDA should withdraw their proposed rule and work with the laboratory community, patients, and Congress to update the Clinical Laboratory Improvement Amendments (CLIA) standards, the current mechanism for regulating laboratory developed tests (LDTs)**.

Overview

ADLM agrees that increases in the number and complexity of LDTs may necessitate a review of the regulations governing these critically important clinical testing services. In 1988, Congress passed the Clinical Laboratory Improvement Amendments (CLIA), which established a uniform framework for overseeing laboratory testing. These standards, administered by CMS, establish rigorous personnel, quality control and proficiency testing requirements, regular inspections and required corrective actions, if necessary, for all laboratory tests, including LDTs.

In addition, many of the testing facilities that perform LDTs actively participate in the New York State, Joint Commission, College of American Pathologists (CAP) or other oversight programs, where they must meet requirements even more stringent than CLIA. ADLM is concerned that extending FDA oversight to LDTs will duplicate the existing regulatory structure, diverting limited laboratory resources from the provision of care to new, unnecessary administrative

requirements. The additional costs associated with agency oversight may also force many laboratories providing LDTs to discontinue this vital patient service.

It is important to note that the FDA regulatory structure is designed for medical device manufacturers, not clinical laboratories. Manufacturers develop IVD instruments and test kits to assist laboratories; laboratories create LDTs to help physicians when no comprehensive IVD product is available for a particular condition or purpose. The number of labs permitted to perform LDTs is limited to a relatively small number of highly equipped laboratories with well-trained personnel. The FDA estimates that roughly 11,000 to 12,000 (or approximately four percent) of laboratories are eligible to perform LDTs.

ADLM supports modernizing both the IVD and LDT regulatory processes, but through distinct, separate approaches that optimize the regulation of each and assure quality patient care.

Legal Authority to Regulate LDTs

The FDA claims to have the legal authority to regulate LDTs. There are legitimate questions surrounding this assertion. In 2015, distinguished jurists Paul D. Clement and Lawrence H. Tribe published a white paper disputing the FDA claim, stating that the FDA was seeking to "*saddle a dynamic and innovative industry with sweeping new regulatory burdens without statutory basis*."[1]

Clement and Tribe further stated:

- *"Clinical laboratories have been regulated by the federal government in various ways, going back to at least 1967, and yet at no time was there any suggestion of the FDA's ability to regulate laboratory-developed testing services."*[2]

- *"The very enactment of the CLIA amendments in 1988 would be well-nigh inexplicable if Congress had intended in the 1976 MDA [Medical Device Amendments], as FDA asserts, to subject laboratory-developed testing services to the FDCA's [Federal Food Drug and Cosmetic Act] device regulations."*[3]

- *"Indeed, neither CLIA's statutory text nor legislative history in 1988 makes any reference to preexisting FDA authority to regulate laboratory-developed testing services, let alone the sweeping authority to regulate such services as "medical devices."*[4]

Similarly, the Department of Health and Human Services (HHS) General Counsel echoed these concerns in its 2020 analysis of the FDA's legal authority to regulate LDTs. The counsel stated:

---

[1] Paul D. Clement and Lawrence H. Tribe, *Laboratory Testing Services, As the Practice of Medicine, Cannot Be Regulated As Medical Devices,* January 2015.
[2] Ibid, page 15.
[3] Ibid, page 15.
[4] Ibid, page 15.

- *"the Agency's jurisdiction to regulate these devices is not uniform and not as plenary as it is for a traditional device."*[5]

- *"it appears likely that LDTs, even if they satisfy the constitutional and statutory "interstate commerce" requirements of the FDCA, would likely not satisfy the separate "commerce distribution" requirements of the premarket review provisions at sections 510(k) and 515."*[6]

- *"many first-line sophisticated laboratories are operated by state public health departments or academic medical centers at large state universities. These laboratories, by definition, are not "persons," within the meaning of the Act, and not subject to many of the Act's requirements…"*[7]

ADLM believes the question as to whether the FDA has the legal authority to regulate LDTs should be determined before this rule is finalized. Furthermore, the agency must have similar questions since it actively sought congressional passage of the Verifying Accurate Leading-edge IVCT Development (VALID) Act in 2022, which would have explicitly granted it oversight over these tests.

Legislative History

The FDA claims that Congress gave the agency authority to regulate medical devices dating back "to at least 1938"[8] and that test systems developed and sold by medical device manufacturers are the same as testing services provided by clinical laboratories; therefore, hospitals and commercial laboratories conducting such testing are manufacturers as well. While Congress has passed legislation giving the FDA authority over the development and sale of test kits, the authority to regulate testing services has been with CMS and its predecessors.

- In 1965, Congress passed the Social Security Amendments Act, which created the Medicare and Medicaid programs. In 1966, the Social Security Administration (SSA) issued testing standards for clinical laboratories participating in the programs. These standards were enforced by the SSA and later the Health Care Financing Administration (HCFA)—the precursor to CMS.

- In 1967, Congress passed the Clinical Laboratories Improvement Act, which established separate standards for testing facilities engaging in interstate commerce. These rules were administered by the Centers for Disease Control (and Prevention) (CDC).

- In 1974, the Medicare/Medicaid and CLIA'67 programs adopted each other's standards, with the two programs later merging under HCFA (now CMS) oversight.

---

[5] Department of Health and Human Services Memo to FDA on the agency's legal authority to regulate LDTs, June 2022, page 2.
[6] Ibid, page 2.
[7] Ibid, page 2.
[8] FDA Medical Devices; Laboratory Developed Tests proposed rule, October 3, 2023 *Federal Register*, page 68019.

- In 1988, Congress passed CLIA'88, which unified and expanded the federal laboratory programs. HHS designated HCFA as the lead federal agency, which it has remained for the past 30 years.

FDA involvement in regulating testing performed in clinical laboratories has been at the periphery, at best. The legislative and regulatory history of laboratory testing supports CMS as the primary overseer of testing, not the FDA.

Cost-Benefit Analysis

The FDA's cost-benefit analysis of the proposed rule illustrates the need for gathering and evaluating additional data before any rule is advanced or action taken. As the FDA acknowledges, there are significant limitations in the data it used to conduct its regulatory analysis. Much of the information referenced by the agency is anecdotal or based on articles published in the popular press, not scientifically based evidence-driven studies. The result is a cost-benefit analysis that is so wide-ranging that it provides little meaningful insight into the impact of the proposed regulatory change.

According to the FDA, the annualized economic benefits from the proposal range from $2.67 billion to $86.01 billion over 20 years at a seven percent discount rate, whereas the annualized costs range from $2.52 billion to $19.45 billion over a similar period. The costs to the agency range from $265 million to $1.06 billion with a portion of this offset by user fees. These broad estimates reflect the agency's lack of information.

We are concerned that the agency is vastly overstating the benefits of greater oversight, while understating the direct and indirect costs to healthcare providers and patients, including the expenses associated with patients failing to have access to timely lifesaving diagnostic tests. One industry analyst suggests the proposed rule will result in "a staggering $50 billion"[9] in costs to the laboratory industry over the first five years, while the suggested benefits are based on "highly speculative conjectures"[10] over 20 years.

ADLM believes that any analysis of LDTs must clearly delineate how many clinical laboratories will be affected and the number of LDTs that will be subjected to additional oversight. Further, the report must, at a minimum, address:

- the impact on the communities serviced by those clinical laboratories, with a special focus on the medically underserved individuals and vulnerable populations (e.g., children);
- the financial and resource costs of adopting the regulatory changes (e.g., hiring staff, generating required evidence, developing submissions, etc.); and
- the healthcare impact (e.g., decline in innovation, decrease in competition, patients unable to access tests, bad patient outcomes [increased disease-associated morbidity and mortality rates]).

[9] Bruce Quinn, "*FDA Regulation of LDT's: The Hidden Facts You Need to Know*," October 10, 2023, page 3.
[10] Ibid, page 16.

These issues are not adequately addressed in the FDA economic analysis associated with the proposed rule. We recommend that an independent entity, such as the General Accountability Office, conduct such an analysis. Such a report should be provided to Congress for review and consideration prior to this proposal being finalized.

The Central Importance of LDTs to Patient Care

LDTs of the 21st century play a critical role in providing quality patient care in the United States. These in-house developed tests are vital to screening and treating newborns for a myriad of genetic diseases, diagnosing, and ensuring appropriate care for substance abuse victims, and minimizing organ rejection rate for transplant recipients. LDTs are also central to:

- detecting bacterial speciation for determining the appropriate antimicrobial drug therapy and eliminating the practice of administering broad-spectrum antibiotics, which is critical to reducing antibiotic resistance in the country;
- providing cellular and genetic cancer information that allows physicians to develop personalized treatment for patients; and
- determining if children have been exposed to lead, which can cause developmental delay (long-lasting cognitive impairment) if not treated earlier.

This last example is a particularly good illustration of the vital rule LDTs play in providing the delivery of quality care. Lead exposure remains a significant public health crisis in the United States. The FDA has issued recalls for "LeadCare," blood lead test kits used at the point-of-care to rapidly assess blood lead concentrations. These recalls have affected hundreds of thousands of test results, primarily involving young children and women. It was only by sending the specimens to clinical laboratories that utilized definitive, LDT-based lead measurement that those affected were accurately diagnosed and treated.

FDA Proposed Regulatory Framework

The FDA states that laboratories that develop LDTs are medical device manufacturers and must be subject to the same requirements. The agency assumes that hospitals, small community testing facilities, and other providers can afford the technical and administrative staff necessary to perform the studies, file the submissions, provide supplemental information, and continue an ongoing dialogue with the FDA to gain agency clearance or approval of an LDT. We are concerned that the costs associated with this duplicative regulatory structure will be significant for many healthcare facilities, forcing them to discontinue or scale back these services. Rather than improving innovation and health equity, as the agency suggests, this proposal will do the opposite by limiting patient access to these vital tests.

Unintended Consequences of the FDA Proposed Rule

ADLM is concerned that the proposed rule will adversely affect the care provided to a wide spectrum of patient groups, particularly those in medically underserved populations, who will have less access, or delayed access, to these vital tests. LDTs are developed to fill a void—either a test kit is not available, the test kit on the market does not provide the information needed by the clinician, or the FDA-approved or cleared test is of limited diagnostic value. Listed below are just a few patient care areas that will be harmed by the FDA initiative:

Drug Testing

Substance abuse is a significant issue in the United States, contributing to numerous health problems, including liver disease, mental health disorders, and the spread of infectious diseases like HIV/AIDS and Hepatitis C through needle-sharing among intravenous drug users. In 2021, there were nearly 71,000 drug overdose deaths in the U.S. involving synthetic opioids, with a 22% increase from the previous year (2020) and synthetic opioids accounted for nearly 90% of opioid-involved deaths in 2021.[11]

Commercial diagnostic assays are typically based on workplace drug testing requirements and are not suitable for patient care because they report the classes of drugs present, not the specific drug taken. Medical laboratory professionals develop LDTs to identify the differing types of drugs (at low concentrations) so the physician can appropriately diagnose and treat the patient. Beyond the opioid epidemic, there is growing concern about the development and availability of new psychoactive substances (NPS). These substances, often referred to as "designer drugs" or "legal highs," have the same effect as illicit drugs while circumventing existing drug regulations.

It is important for clinical laboratories to have the needed flexibility to rapidly develop methods that detect these NPS. It is not clinically appropriate to wait for the development of commercially diagnostic assays, since these tests are often outdated by the time they are released. During that review phase, illicit drug manufacturers have already produced modified drugs to evade detection. LDTs are critical to diagnosing and treating these individuals.

A good example of this problem is the FDA-approved immunoassay drug screens for fentanyl. Most main chemistry analyzers using these assays are unable to detect fentanyl or any of its modified forms. LDTs are crucial to diagnosing and treating a person who has used this drug. If these LDTs are delayed by the regulatory pathways, when they are finally authorized or approved, they will already be obsolete because the relevant substances will have changed.

Pediatric Testing

Our pediatric population is one of our most vulnerable populations as they cannot advocate for themselves and often cannot communicate their clinical symptoms. Additionally, children are reliant on parents/guardians to coordinate their care, which is often complicated by work schedules, finances, and transportation challenges. Specialty care for children is also primarily available in large metropolitan areas, increasing the need to travel long distances for parents/guardians who care for children with complex health needs. An important example of this is NBS testing and follow-up.

NBS tests for inborn errors of metabolism (IEM) provide vital information for diagnosing and treating children with rare, often life-threatening, medical conditions. Although each individual disorder is rare, collectively it is estimated that one in roughly 2,000 newborns will have some sort of IEM. Phenylketonuria (PKU) is an example of a common inborn error of metabolism in

---

[11] Centers for Disease Control and Prevention
https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm.

which Children are unable to convert the amino acid phenylalanine to tyrosine due to a defective enzyme (phenylalanine hydroxylase).

If left untreated, the dangerous buildup of phenylalanine in the baby will result in devastating neurological symptoms, brain damage, and possibly death. However, children can lead normal, healthy lives by simply dietary modifications. Unfortunately, there are no FDA-approved tests to screen for or diagnose children with PKU or most other IEM. Screening tests like NBS are made very sensitive so no infant with the disorder will be missed. That sensitivity, however, results in a relatively high false positive rate. Thus, a positive NBS test must be confirmed by a second definitive test for the condition. These confirmatory tests are all LDTs.

Although the initial sample for NBS is collected while mother and baby are still in the hospital, confirmatory and follow-up testing are done as outpatients unless the infant is critically ill. Children's hospitals often have NBS follow-up testing in-house, allowing them to coordinate patient management in real-time with physicians and families who have traveled hours to have this testing performed. Any problems with specimen collection, results, and interpretations can be clarified and resolved on-site, preventing delay in treatment and diagnosis, numerous multi-hour trips or overnight stays which are a significant hardship to our patients, particularly those who live in rural settings and lack resources for travel and alternative local accommodations.

If these low-volume LDTs, which are well established and save many lives annually, were to require FDA submission – few hospitals would be able to continue to perform these tests. This would necessitate these in-house tests being sent to one or two central testing centers, requiring multiple days between specimen collection, and obtaining the results. The proposed rule, if adopted, may severely limit access to these life-saving tests for these children.

Molecular oncology

Another key area that could be adversely affected by the FDA proposed rule is the treatment of patients that have cancer. Broad molecular profiling of patient tumors by next-generation sequencing tests is standard of care in the diagnosis, prognosis, and therapy selection for patients that have cancer. Molecular testing in the realm of oncology encapsulates several methods that are commonly used to help pathologists reach a diagnosis, assist care teams to anticipate disease progression, and allow the physician and patient to select the therapeutic plan that minimizes toxicity. Few of these methods are in a pre-packaged, FDA-approved "kit" format, thus forcing clinical laboratories to develop these diagnostic tools locally. Furthermore, several drugs approved by the FDA over the last decade have no biomarkers of efficacy available beyond LDTs, including immune checkpoint inhibitor therapies such as pembrolizumab.

A key benefit of molecular profiling is the ability to simultaneously analyze hundreds of genes, decreasing the cost of testing and increasing patient safety because less tissue from invasive biopsies is required for NGS testing. Accelerating the pace of discovery in cancer research has been a national objective for decades, including the "Cancer Moonshot" initiative that emphasizes the need for advances in technology innovation, scientific discoveries, and therapeutic options. ADLM is concerned the duplicative FDA oversight of these tests will further limit the ability of healthcare providers to offer these tests. We are not averse to exploring

additional ways to improve oversight of LDTs. However, any changes should take place through the congressionally mandated CLIA standards, of which the FDA is a partner with CMS and CDC.

The Need to Address Modified Tests

One frequently asked question is "what is an LDT?" While there is agreement that a test that is developed from scratch when no other test is available is an LDT, there are many tests that are designated as LDTs simply because the laboratory has made a slight modification to an FDA-approved test. Generally, this change is made (e.g., such as using a differing type of sample or modifying the stated stability of the sample) so that the lab can provide better service to their patients and obtain more specific and accurate information for the ordering provider.

For example, an FDA-approved test may call for a serum sample that is stable for one hour at room temperature. The lab's patient population may be over an hour away, so the lab performs a validation study that utilizes a dried blood spot sample, which is stable for 24 hours at room temperature, and gives the same result as the serum required by the test. ADLM believes that these types of test modifications that do not alter the clinical or analytical validity of the FDA-approved test should not be considered LDTs and or subject to additional regulation.

This point is especially important in the pediatric realm, where FDA-approved tests often are not validated using samples from pediatric patients. Further, it is important that all these tests not become LDTs simply because pediatric reference intervals are not in the Instructions For Use associated with the test system. Pediatric hospital labs will not be able to operate at all under these conditions, limiting patient access to testing and disrupting the delivery of healthcare. ADLM suggests that future discussions pertaining to LDTs address these tests.

Need to Define the LDT Problem

One of the reasons for the greater LDT oversight, according to the FDA, is the quality of the testing. The agency makes this global statement without providing sufficient evidence to support its claim. The FDA frequently references anecdotal stories, news articles, FDA experience, and industry publications in support of its point. What is often lacking is sufficient evidence-based studies that support its position. In the past, when Congress asked the agency to provide supporting data it took two years to find twenty examples of tests that might be problematic—many of these claims were later disproven.[12]

One of the few studies the FDA references in the proposed rule was a 2022 paper -- *Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics* -- published in the *American Journal of Clinical Pathology*, which claimed the LDTs reviewed were inaccurate.[13] Yet, a more comprehensive study, *SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate*

---

[12] Association for Molecular Pathology, December 13, 2015,
Facts FDA Ignored: An analysis of the FDA report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies" https://www.amp.org/AMP/assets/File/position-statements/2015/AMPResponseFDACaseReportFinal.pdf?pass=64.

[13] Pfeifer, J.D., R. Loberg, C. Lofton-Day, et al., "*Reference Samples To Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics*," *American Journal of Clinical Pathology,* 157(4):628–638, 2022.

Excellent Laboratory Performance, published in *Archives of Pathology & Laboratory Medicine* reviewed the earlier analysis and, using the same samples, demonstrated that the LDTs in the study were in fact highly accurate.[14]

The FDA repeatedly references a January 1, 2022, New York Times article, *"When They Warn of Rare Disorders, These Prenatal Tests Are Usually Wrong" in* support of expanded regulation of LDTs. Unfortunately, the agency fails to address the inaccuracies in the story, which mistakenly conflates screening and diagnostic tests as the same. The key takeaways from that story should be about the marketing techniques of some labs, and the need for physician education—issues the ADLM would agree need to be addressed--not the accuracy of LDTs.

ADLM is concerned that the agency is seeking to discredit a well-established form of testing, which is highly regulated, and provides accurate, vital information needed to diagnose, treat, and monitor many diseases. If the agency believes such testing is imperiling patient health, we urge the FDA to recommend that CLIAC place this on their agenda for immediate discussion, and they recommend that Congress hold hearings to explore the public health concerns and value of these tests.

The agency should not be seeking to take on the regulation of LDTs, where there is limited evidence of an existing problem.

FDA Resources

The FDA, by its own admission, is having problems hiring staff to meet its current responsibilities. Increasing this burden would add to the agency's problems, while potentially affecting patient care. The FDA's lack of resources to execute its existing mission was evident during the COVID pandemic when the agency had to limit the review of COVID Emergency Use Authorization tests to those with a volume greater than 500,000 per week. The inability of the FDA to review new COVID-19 tests raised legitimate concerns about whether the agency has the bandwidth to oversee LDTs, which could conservatively involve the review of tens of thousands of submissions.

For comparison, the Office of In Vitro Diagnostics, which would have oversight of LDTs, received a total of 112 510(k) submissions for the first recent quarter of this fiscal year and 10 PMAs.[15] It is clear the FDA does not have the staff nor resources to review many thousands of additional LDTs.

While ADLM believes that the FDA generally does a good job in evaluating new medical devices that enter the healthcare arena, its process is not perfect and, in fact, needs reform. There are many instances where test kits or drugs have been approved or cleared by the agency only to be later recalled. For example:

---

[14] Zehir A, Nardi V, Konnick EQ, Lockwood CM, Long TA, Sidiropoulos N, Souers RJ, Vasalos P, Lindeman NI, Moncur JT. SPOT/Dx Pilot Reanalysis and College of American Pathologists Proficiency Testing for KRAS and NRAS Demonstrate Excellent Laboratory Performance. Arch Pathol Lab Med. 2023 Sep 30. doi: 10.5858/arpa.2023-0322-CP. Epub ahead of print. PMID: 37776255.

[15] FDA Quarterly Update on Medical Device Performance Goals, MDUFA V CDRH Performance Data, Actions through 31 March 2023, 2nd Quarter FY 2023 MDUFA V Performance Report (fda.gov).

- In 2022, the FDA listed a recall relating to FDA-approved microbiologic susceptibility test plates – which help providers determine which drugs and doses are likely to yield clinical success in treating gram-negative bacterial infections in patients. The faulty plates had been in circulation for 22 months before the recall was released. The information shared with the FDA about the devices was self-disclosed on the part of the manufacturer after a single direct complaint and five medical device reports, consistent with Good Manufacturing Practice. The issue was only detected by clinical laboratory professionals as part of their own Good Clinical Practice measures, in compliance with *existing* regulatory compliance and oversight outlined by CLIA and enforced locally.

- In 2021, FDA-approved COVID-19 home tests were recalled after four months of availability on the market, when false-positive COVID results were reported. The recall was reported to the FDA by the manufacturer after 35 reports of false-positive test findings among users. Another manufacturer initiated a 2021 recall in its FDA-approved COVID PCR kit due to higher-than-expected rates of false *negative* results.

- In 2023, an FDA-approved cartridge-based test for myocardial injury was recalled more than six months after the test had been released to the clinical laboratory market. In this recall, the results were falsely low, increasing the risk of a missed diagnosis. There were 41 complaints to the manufacturer, and no injuries or deaths, which led to the reporting and recall of the devices.

We encourage the FDA to focus its attention on improving its existing review process, rather than seeking to add another area of responsibility that may hinder the agency's ability to meet its current workload.

Health Equity

The FDA states in the proposed rule that "increased oversight may help to advance health equity," through ensuring greater representation of marginalized populations in the clinical studies utilized in developing the test. The agency asserts this will increase the accuracy and usefulness of these tests.

ADLM is concerned that the agency is making policy based on speculative statements without providing scientific evidence to support these claims. Further, we share some of the concerns raised within the agency's cost-benefit analysis of the proposal regarding the potential impact of the proposed rule on underrepresented populations. The FDA analysis states:

"Nonetheless, while the proposed rule may help to advance health equity, we have no specific data showing that increased FDA oversight of IVDs offered as LDTs will necessarily reduce health disparities."[16]

[16] FDA, Preliminary Regulatory Impact Analysis, Initial Regulatory Flexibility Analysis, Unfunded Mandats Reform Act Analysis, Docket No. FDA-2023-N-2177, https://www.fda.gov/media/172557/download?attachment, page 105.

"If laboratories pass-through the cost of compliance to the costs of IVDs offered as LDTs, testing frequency may decrease for areas that rely on IVDs offered as LDTs because of easy, rapid access."[17]

" If laboratories or healthcare facilities respond to increased compliance costs by increasing the price of IVDs offered as LDTs or reducing the availability of IVDs offered as LDTs, there may be an increase in health inequity."[18]

" Vulnerable populations that rely on IVDs offered as LDTs for diagnostic testing may have less access to diagnostic tests in general after the implementation of the rule."[19]

The agency should not be seeking to rush through a proposed rule that could have a deleterious effect on patient access to testing, particularly in economically and racially marginalized communities.

Exemptions

The agency sought input on those entities that should be exempt from FDA oversight. ADLM agrees that academic medical centers provide a unique service, conducting vital research, training healthcare personnel, and often serving marginalized and underserved populations. While we agree these institutions should not be subject to additional oversight, we believe exemptions do not necessarily need to be tied to the institution. CLIA high complexity laboratories performing LDTs should not be subject to additional oversight when:

- there is no FDA-approved test on the market; or
- an ordering physician determines the FDA-approved/cleared test is not appropriate for the patient's needs; or
- an ordering physician determines that a delay in testing could adversely affect patient care; or
- the individual performing the test is a trained medical laboratory scientist or qualified laboratory director under CLIA.

Adverse Event Reporting

The FDA wants to subject clinical laboratories performing LDTs to medical device reporting in phase one. ADLM does not believe the adverse event framework, which was developed for reporting problems involving medical devices, is appropriate for services provided by clinical laboratories. Results from LDTs do not generally result or contribute to the death or severe injury of a patient. During a January 2015 FDA Public Workshop on LDTs, the Mayo Clinic reported that over the previous five years, it had conducted more than 2.5 million LDT-based tests without a single sentinel event (The Joint Commission defines a sentinel event as a safety event that results in death or permanent harm to the patient).

One reason for the overall safety of LDTs is that laboratories implement internal quality controls that detect many analytical and pre-analytical errors and prevent inaccurate results from being

[17] Ibid, pages 105-106.
[18] Ibid, page 106.
[19] Ibid, page 106.

reported. The current CLIA regulatory framework also requires laboratories to identify, document, and perform corrective measures for any laboratory errors, and this would include errors resulting in patient harm if they were to occur. This documentation is reviewed on a regular basis by a CLIA inspector, its accrediting bodies or deemed state agencies. The current CLIA process could be modified to recommend that when a laboratory identifies a testing error it should report that mistake to the appropriate oversight body. This does not require legislative action.

User Fees

The proposed rule would create a new user fee program that would be applied to laboratories performing LDTs. Reimbursement for clinical laboratories is being cut dramatically under the Protecting Access to Medicare Act (PAMA), while at the same time, testing facilities must pay registration and accreditation fees under CLIA, as well as incur the costs of on-site inspections and frequent proficiency testing to demonstrate performance. The regulatory requirements outlined in this measure, along with the additional costs, would ensure that only a few laboratories would continue to offer LDTs. Unfortunately, this outcome would stifle innovation and harm patient care. ADLM believes that LDTs should remain under CLIA and that improvements should occur within the existing process established by Congress.

ADLM is a global scientific and medical professional organization dedicated to clinical laboratory science and its application to healthcare. ADLM brings together more than 50,000 clinical laboratory professionals, physicians, research scientists, and business leaders from around the world focused on clinical chemistry, molecular diagnostics, mass spectrometry, translational medicine, lab management, and other areas of laboratory science to advance healthcare collaboration, knowledge, expertise, and innovation.

Thank you for the opportunity to provide input to the subcommittee on the FDA proposed rule and alternative approaches to improving LDT oversight. If you have any questions, please email Vince Stine, PhD, ADLM's Senior Director of Government and Global Affairs, at [redacted].

November 1, 2023

Chair Bernie Sanders
Senate Committee on Health,
Education, Labor and Pensions
428 Dirksen Senate Office Building
Washington, DC 20510

Ranking Member Bill Cassidy
Senate Committee on Health,
Education, Labor and Pensions
828 Hart Senate Office Building
Washington, DC 20510

Chair Cathy McMorris Rodgers
Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Ranking Member Frank Pallone
Energy and Commerce Committee
2322 Rayburn House Office Building
Washington, DC 20515

Dear Chair Sanders, Ranking Member Cassidy, Chair McMorris Rodgers, and Ranking Member Pallone:

On behalf of the undersigned organizations that represent a diverse and broad community of patient advocates, laboratory professionals, public health laboratories, and clinical laboratories from throughout the United States, we write to express our significant concerns with recently announced plans by the U.S. Food and Drug Administration (FDA) to impose existing medical device regulations on laboratory developed testing procedures (LDTs). LDTs are testing services that hospitals, academic, public health, and clinical laboratories develop and use in patient care. These services are not commercially manufactured and marketed, but rather are designed, developed, validated, performed, and interpreted by board-certified professionals in a single laboratory. LDTs are often created in response to unmet clinical needs and are instrumental for early and precise diagnosis or monitoring and guidance of patient treatment including hereditary disease testing, oncology, infectious disease, and more. As such, FDA regulating them as medical devices would be inappropriate and disruptive to patient care.

We stand united in support of modernizing the oversight framework for high complexity clinical LDTs but primarily through reform of the long-standing Clinical Laboratory Improvement Amendments (CLIA). We believe that the modernization of CLIA requirements could better achieve a sustainable system that fosters innovation and promotes emerging medical knowledge to enable healthcare professionals the ability to offer precise, accurate, and the most up-to-date tests to patients. It is also the most streamlined and cost-effective approach, for both the government and laboratories, and the least disruptive and burdensome approach to ensuring clinical and analytical validity, transparency, and addressing other concerns expressed by interested stakeholders. Modernizing CLIA oversight will support laboratory advances in clinical care as validated discovery and innovation continue to develop rapidly.

Therefore, we urge Congress to direct the FDA to pause rulemaking on LDTs and instead, renew bipartisan efforts to work with stakeholders to pass legislation that would establish a modernized approach within the existing regulatory framework under CLIA.

Sincerely,

Academy of Clinical Laboratory Physicians and Scientists
American College of Medical Genetics and Genomics
ARUP Laboratories
Association for Diagnostics and Laboratory Medicine
Association for Molecular Pathology
Association for Pathology Informatics
Association of Pathology Chairs
Avant Diagnostics, Inc.
Beutner labs
Cancer Advocacy Group of Louisiana
Cedars-Sinai
Coalition for Innovative Laboratory Testing
Damajha Systems
Diamond Medical Laboratories LLC
Elina Labs, LLC
Entvantage Diagnostics, INC
Gene by Gene
GeneMatters, LLC (A Genome Medical Company)
Genomind, Inc.
Igentify INC
Innoterix Labs
Invitae Corporation
IVD Logix LLC
Kaiser Permanente
KSL Diagnostics Inc.
Laboratory Access and Benefits Coalition
Laboratory Nexus LLC
Leading Edge Laboratory Consultants
Lifetime Sciences
Lighthouse Lab Services
Medical Group Management Association (MGMA)
Meridian Diagnostics
Michigan Department of Health and Human Services
MSACL
My geneTx
National Society of Genetic Counselors
Nationwide Children's Hospital
Nebraska Medicine
nuCARE Medical Solutions
Pan American Society for Clinical Virology
Phoenix Laboratory Consulting
Principle Health Systems

Purine Metabolic and Immunodeficiency Lab, Duke University
Society for Pediatric Pathology
Survivor's Cancer Action Network
Teiko Bio
The Foundation for Casey’s Cure
Theralink Technologies, Inc
TriCore Reference Laboratories
University of Chicago Medical Center
University of North Carolina at Chapel Hill Department of Pathology and Laboratory Medicine
University of Rochester Medical Center
University of Wisconsin School of Medicine and Public Health
UW Health
Wisconsin State Laboratory of Hygiene

Statement of Sanford Health for the Committee on Energy and Commerce
Subcommittee on Health of the U.S. House of Representatives
March 19, 2024

Chairs Cathy McMorris Rodgers and Guthrie and Ranking Members Pallone and Eshoo:

Sanford Health ('Sanford Health' or 'Sanford') thanks the Subcommittee for holding this important and timely hearing on the FDA's proposed rule for regulating laboratory-developed tests (LDTs), and we appreciate the opportunity to provide our perspective on this important issue. Sanford Health, the largest rural health system in the United States, is dedicated to transforming the health care experience and providing access to world-class health care in America's heartland. Headquartered in Sioux Falls, S.D., our organization serves more than one million patients through our medical centers, outpatient clinics and acute care facilities. Additionally, Sanford Health has senior living centers, world clinics in nine countries around the globe, and a health insurance plan that serves nearly 200,000 members. Our research arm, Sanford Research, is a premier research institute in the Midwest, focused on innovating health care through cutting-edge science; it is a critical component of our organization's ability to support patients throughout their health care journey.

People living in rural America face unique challenges. They are more likely to have resource constraints around access care, and they experience higher rates of poverty, food insecurity and chronic disease – all of which often lead to poorer health outcomes. At Sanford Health, two-thirds of our patients live in rural communities across America's heartland, and 5 of the top 25 poorest counties in the U.S. are in our footprint. Our promise to those we have the privilege of serving is that their care won't be limited by their zip code. We're committed to removing barriers to access, addressing health disparities, serving our communities and investing in the people and places in our region to improve the quality of life for all – no matter where people live or the health challenges they face.

To ensure our patients receive the best possible care, Sanford Health has significantly invested in LDTs with a test menu of approximately 75 assays. An example of this commitment is Sanford Health's program to offer free pharmacogenomics (PGx) testing to all veteran and active military patients who receive their primary care at Sanford Health. PGx testing, often offered as LDTs, helps provide patients with information on how they process certain medications. This information is very useful for health care providers, helping them make informed decisions about treatment and care plans on behalf of patients. Through this service, thousands of veterans have received information that helps guide an appropriate care plan.

Sanford Health has a devoted laboratory that only processes LDTs; **notably, our medical genetics laboratory is one of two in North Dakota and South Dakota that is both College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified**. The labs are embedded within the communities we serve – from rural and remote portions of the Dakotas to greater Minnesota and beyond – providing both access and proven results.

Through our comments to the Food and Drug Administration (FDA), Sanford Health voiced significant concerns about the effect medical device review would have on our ability to continue providing diagnostic care to rural and underserved population. **Our original estimate of the costs of compliance**

with the FDA proposed rule was approximately $10 million. After further review, our updated cost estimates are closer to $35 million given that test modifications are also subject to submission. Looking ahead, this financial impact will grow as artificial intelligence and innovation for new LDTs would be subject to FDA pre-market approval. Like many laboratories, Sanford Health may not be able to absorb these additional submission costs and be forced to remove tests from our menu, delaying timely access to care and disrupting health care delivery in the rural areas we serve.

The FDA's stated objective from the Proposed Rule, in part, is to "ensure patients are receiving accurate and reliable diagnostic test results regardless of where the tests are made." **This objective is obtainable without imposing medical device review that will have direct and adverse health impacts on patients, amplifying current financial and workforce challenges, and overlapping with already stringent accreditation diagnostic standards.** Sanford Health stands ready to work with Congress, the FDA and other stakeholders on a viable path forward for the landscape of LDTs. Sanford Health encourages that if the committee determines FDA regulation is necessary, the framework should be market driven, recognizing the real challenges that health systems and laboratories face. In particular, Sanford Health urges the focus of any approach to FDA regulation be driven by the following principles:

- A diagnostic regulatory framework that prioritizes analytical and clinical validity and values innovation. Medical device review that relies on safety and efficacy is an inappropriate standard for the practice of laboratory medicine.
- A policy allowing for "grandfathering" of some subset of existing LDTs to avoid a regulatory backlog for submissions to the FDA for market approval. There are likely tens of thousands of existing LDTs in the market, many of which have been safely used for patients for years.
- Flexibility for test modifications without pre-market submission. Clinical laboratories update their tests to make them more efficient, more sensitive and less expensive. Modifications to LDTs that are validated, and that do not have a meaningful effect on analytical or clinical validity should not be subject to pre-market submission.
- A reasonable timeframe for regulatory compliance. The four-year phase-in under FDA's proposed rule is unrealistic and should be extended. Given the breadth of LDTs and the pace of innovation, we recommend an 8-10-year phase-in.
- A regulatory exemption for laboratories that work directly with public health or state agencies must be considered. In alignment with the proposal by the FDA, health systems and laboratories may work collaboratively and hand-in-hand with state public health agencies, even more so in rural states. This relationship, the innovations and LDTs that result must be recognized through a regulatory exemption.

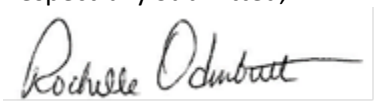
To conclude our statement, consider the below real-life example and the positive effect LDTs have had on health care delivery:

- A young couple suffered five miscarriages within the first trimester over 21 months and no live births. There was no immediate family history of recurrent pregnancy loss, and all other tests were normal. Through LDT genetic testing at Sanford Medical Genetic Lab of both mother and father, providers discovered that the father, through his employment, utilized the chemical 2,4-D – a chemical associated with fertility challenges. The LDT test result, close communication between the provider and lab, and personalized care plan gave the family a full picture of its family planning. Not all commercialized reference labs have the devoted staff and dedicated personnel to follow up on a case such as this. The innovative LDT by Sanford Health and its staff, in this case,

furthered the public health objective of the administration in examining maternal and infant health. Such a test and nimble communication may not exist in a strict LDT regulatory environment.

Sanford Health again wants to emphasize the scope, breadth and tremendous impact the proposed regulation will have on health care delivery – especially in rural areas. We urge Congress to work with the FDA and the clinical laboratory industry to develop a sustainable path forward for LDTs that maintains access to high quality diagnostic care on behalf of patients. Please do not hesitate to contact me at [redacted] if you or your staff would like to discuss these issues in greater detail.

Respectfully Submitted,



Rochelle Odenbrett
System Executive Director – Laboratory
Sanford Health

THE AMERICAN REGISTRY OF RADIOLOGIC TECHNOLOGISTS®

Statement for the Record

of

The American Registry of Radiologic Technologists

House Energy & Commerce Committee Health Subcommittee

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

March 21, 2024

The American Registry of Radiologic Technologists (ARRT) appreciates the opportunity to submit a statement regarding the House Energy & Commerce Health Subcommittee hearing on "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule." While our members are not providers of laboratory developed tests (LDTs), we seek to raise awareness regarding a significant barrier to diagnostic tests and procedures performed by our members as part of the radiology care team. In addition to providing background information about our profession, ARRT appreciates the Subcommittee's consideration of this policy priority as it explores reforms to diagnostic test regulation.

The registered radiologic assistant (RRA) profession was created in 2003 through a partnership of the American College of Radiology (ACR), American Society of Radiologic Technologists (ASRT), and the ARRT to ensure that there is a radiology-specific midlevel provider.1 An RRA is an advance-level radiologic technologist who works under the supervision of a radiologist to enhance patient care by assisting the radiologist. The RRA is an ARRT-certified radiographer who has successfully completed an advanced academic program encompassing a nationally recognized RRA curriculum and a radiologist-directed clinical preceptorship. Under radiologist supervision, the radiologist assistant may perform patient assessment, patient management and assist the radiologist with selected exams, as described below and subject to state law:

- Obtaining consent for contrast agents administered as part of radiology procedures
- Obtaining clinical history from patient or medical record

[1] American College of Radiology, "Registered Radiologist Assistant: Radiologist Assistants are the non-physician providers you shouldn't worry about." (July 8, 2021) Available at https://www.acr.org/Practice-Management-Quality-Informatics/ACR-Bulletin/Articles/Aug-2021/Registered-Radiologist-Assistant.

- Performing pre-procedure and post-procedure evaluation of patients undergoing invasive procedures
- Assisting radiologists with invasive procedures
- Performing fluoroscopy for non-invasive procedures under radiologist supervision
- Monitoring and tailoring selected exams under radiologist supervision (e.g. CT urogram, VCUG, retrograde urethrograms, and preparation and colonic insufflation for CT Colonography.)
- Attempt placement of fluoro-guided naso- or oro-enteric feeding tubes in patients whom the supervising radiologist has determined are appropriate for RRA involvement and under radiologist supervision as part of a radiologist-led team." 2

RRAs do not interpret images, though they create efficiencies within radiology practices by allowing radiologists to focus on interpretations and more complex procedures while decreasing wait times and enhancing patient safety and outcomes. In an effort to ensure that RRAs can practice as envisioned by the profession and consistent with state rules and regulations, in its CY 2019 Medicare Physician Fee Schedule final rule, the Centers for Medicare & Medicaid Services (CMS) finalized 42 CFR Sec. 410.32(b)(3)(4), which states:

> (4) Supervision requirement for RRA or RPA. Diagnostic tests that are performed by a registered radiologist assistant (RRA) who is certified and registered by the American Registry of Radiologic Technologists or a radiology practitioner assistant (RPA) who is certified by the Certification Board for Radiology Practitioner Assistants, and that would otherwise require a personal level of supervision as specified in paragraph (b)(3) of this section, may be furnished under a direct level of physician supervision to the extent permitted by state law and state scope of practice regulations.

While this change has enabled greater patient access to important radiology services, and appropriately defers to state scope of practice regulations to determine physician supervision, CMS has not updated its rules to ensure that such RA services are subject to direct—not personal—supervision for all components of RA-performed diagnostic tests and procedures. Consequently, the radiology practices employing RRAs are unable to submit claims for most RA-performed diagnostic tests and procedures. This barrier prohibits full utilization of the RRA within radiology practices and thereby limits patient access to the high-quality, timely care services RRAs provide.

As a result, multiple RRA academic programs across the country have closed, RRAs have experienced job layoffs, and patient access has decreased. We have been advocating that CMS make the technical fixes needed to stop these unintended consequences and ensure that patients have access to RRA services, including diagnostic tests and procedures, under direct radiologist supervision. ARRT appreciates the Subcommittee's consideration of this significant barrier facing RRAs and the patients we serve. ARRT, working in concert with ASRT and other stakeholders supportive of the RRA role, are pursuing a legislative solution to this challenge and look forward to working with the Subcommittee to advance this desperately needed legislation.

We appreciate the opportunity to raise awareness of ARRT and its members, as well as ongoing concerns regarding RRA ability to perform their duties within the radiology care team. Thank you

[2] American College of Radiology, "ACR Statement on Radiologist Assistant Roles and Responsibilities." Digest of Council Actions (2020).

again for the opportunity to submit this statement for the record, and please do not hesitate to reach out to Liana Watson, DM, R.T.(R)(M)(S)(BS)(ARRT), RDMS, RVT, FASRT, PMP, CAE, at [redacted] if you have any questions.

ASM Statement in Response to Health Subcommittee Hearing

March 19, 2024

Statement from the American Society for Microbiology in response to the Energy and Commerce Health Subcommittee Hearing:
"Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule"

Hearing Date: March 21, 2024

On behalf of our 36,000 members, the American Society for Microbiology (ASM) commends Chairman Guthrie, Ranking Member Eshoo and members of the Energy and Commerce Subcommittee on Health for holding a hearing on the Food and Drug Administration's (FDA) proposed rule to regulate laboratory-developed tests. ASM submitted comments on the proposed rule in Dec. 2023.

ASM remains concerned that the FDA's proposed rule will reduce patient access to high quality and timely infectious disease testing, increase health inequities and limit innovation in developing new LDTs for infectious disease testing. The broad approach taken by FDA doesn't recognize the unique aspects of infectious disease testing, applying standards that will result in the opposite of what FDA seeks to achieve.

ASM members perform testing for the diagnosis of infectious diseases in clinical, commercial and public health laboratories in a range of urban and rural settings. A fall 2023 survey of ASM members showed that laboratory-developed tests (LDTs) are widely used in clinical and public health laboratories for the diagnosis and monitoring of myriad infectious diseases.

LDTs have been at the forefront of clinical innovation in the detection and management of infectious diseases. In many instances, including the 2022 mpox outbreak, LDTs were the first available tests for emerging infectious diseases and were central to the outbreak response. According to the recent ASM survey, 42% of laboratories reported performing more than 10 LDTs. The investment in personnel, time and resources required to obtain FDA approval for existing LDTs will halt the development of novel diagnostics, hindering the innovation and diagnostic progress necessary to keep up with emerging and evolving pathogens.

ASM shares the FDA's goal of protecting public health and ensuring the safety and accuracy of LDTs and health equity. We recognize that there is a lack of information on the current LDTs on the market. To address this, ASM supports registration and listing requirements and severe adverse event reporting for LDTs as a first step toward collecting necessary data and developing a regulatory path for LDTs that is consistent with the realities of how these tests are used in infectious disease care. ASM also supports a risk-based framework, where a low-risk category with enforcement discretion will allow clinical microbiology laboratories to continue with most infectious disease LDTs to serve the most vulnerable communities and serve as sentinel laboratories to local and state public health entities in public health emergencies.

After collecting data and attaining a more accurate and comprehensive picture of the LDT landscape, ASM believes that the FDA, in conjunction with stakeholders and the public, will be better able to determine a more effective approach to regulation of these tests than that outlined in the proposed rule. With knowledge of the universe of LDTs and their applications, as well as more robust adverse event reporting, we believe a risk-based approach that maintains enforcement discretion for low-risk tests will be feasible.

ASM again appreciates the Health Subcommittee's focus on the appropriate regulatory framework for diagnostics, including LDTs. We urge Congress to revive discussions with the goal of finding a path forward that is not one-size-fits-all and considers the realities of how LDTs are used in medical specialties like infectious disease, and we look forward to working with the committee on this important issue.

American Society of Radiologic Technologists

Statement for the Record of

The American Society of Radiologic Technologists

House Energy & Commerce Committee Health Subcommittee

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

March 21, 2024

The American Society of Radiologic Technologists (ASRT) appreciates the opportunity to submit a statement regarding the House Energy & Commerce Health Subcommittee hearing on "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule."

ASRT is the premier association for medical imaging and radiation therapy, representing more than 156,000 members nationwide. It is our mission to elevate the profession and ensure patient safety. As such, ASRT advocates that only individuals who have met nationally recognized education and training standards perform diagnostic medical imaging.

While our members are not providers of laboratory developed tests (LDTs), we seek to raise awareness regarding significant barriers to diagnostic tests and procedures performed by our members as part of the radiologist-led care team. In addition to providing background information about our profession, ASRT appreciates the Subcommittee's consideration of these policy priorities as it explores reforms to diagnostic test regulation.

Priority 1: Access to Radiology mid-level provider

The registered radiologic assistant (RRA) profession was created in 2003 through a partnership of the American College of Radiology (ACR), American Society of Radiologic Technologists (ASRT), and the ARRT to ensure that there is a radiology-specific midlevel provider. A radiologist assistant is an advance-level radiologic technologist who works under the supervision of a radiologist to enhance patient care by assisting the radiologist. The RRA is an ARRT-certified radiographer who has successfully completed an advanced academic program encompassing a nationally recognized RRA curriculum and a radiologist-directed clinical preceptorship. Under radiologist supervision, the radiologist assistant may perform patient assessment, patient management and assist the radiologist with selected exams.

15000 Central Ave. SE, Albuquerque, NM 87123-3909 | 505-298-4500 | 800-444-2778 | Fax 505-298-5063
www.asrt.org

RRAs do not interpret images, though they create efficiencies within radiology practices by allowing radiologists to focus on interpretations and more complex procedures while decreasing wait times and enhancing patient safety and outcomes. In an effort to ensure that RRAs can practice as envisioned by the profession and consistent with state rules and regulations, in its CY 2019 Medicare Physician Fee Schedule final rule, the Centers for Medicare & Medicaid Services (CMS) finalized 42 CFR Sec. 410.32(b)(3)(4), which states:

> (4) Supervision requirement for RRA or RPA. Diagnostic tests that are performed by a registered radiologist assistant (RRA) who is certified and registered by the American Registry of Radiologic Technologists or a radiology practitioner assistant (RPA) who is certified by the Certification Board for Radiology Practitioner Assistants, and that would otherwise require a personal level of supervision as specified in paragraph (b)(3) of this section, may be furnished under a direct level of physician supervision to the extent permitted by state law and state scope of practice regulations.

While this change has enabled greater patient access to important radiology services, and appropriately defers to state scope of practice regulations to determine physician supervision, CMS has not updated its rules to ensure that such RA services are subject to direct—not personal— supervision for all components of RA-performed diagnostic tests and procedures. Consequently, the radiology practices employing RRAs are unable to submit claims for most RA-performed diagnostic tests and procedures. This barrier prohibits full utilization of the RRA within radiology practices and thereby limits patient access to the high-quality, timely care services RRAs provide.

As a result, multiple RRA academic programs across the country have closed, RRAs have experienced job layoffs, and patient access has decreased. We have been advocating that CMS make the technical fixes needed to stop these unintended consequences and ensure that patients have access to RRA services, including diagnostic tests and procedures, under direct radiologist supervision.

Priority 2: Minimum Education and Training Standards

Medical imaging and radiation therapy professionals make up the third-largest group of health care professionals—surpassed in number only by physicians and nurses. The primary responsibility of technologists and therapists is using medical imaging and radiation therapy for diagnostic, interventional and therapeutic purposes. This ranges from creating images of patients' bodies to providing doses of radiation to treat diseases such as cancer. The work of medical imaging and radiation therapy professionals helps patients receive timely and accurate diagnosis and treatment.

An early and accurate detection of any disease or condition is critical to the overall prognosis for a patient as well as the overall cost of a patient's care. By utilizing their education in radiation physics, radiobiology, anatomy and physiology, positioning and processing, and radiation safety, technologists deliver the highest quality images with the lowest dose of radiation possible.

The individuals who perform these procedures are critical members of the health care delivery team. They touch nearly every citizen either personally or through family and friends by providing a critical role in diagnosis, intervention and treatment. Medical imaging and radiation therapy professionals should have a minimum of two years of education from a Joint Review Committee on Education in Radiologic Technology accredited program and pass a nationally recognized credentialling exam.

Unfortunately, there is no enforceable federal minimum of education and training for operators of medical imaging and radiation therapy equipment. This means there is no guarantee that nationally recognized standards are being followed from one state to the next. This creates a significant barrier for medical imaging and radiation therapy professionals to move across state borders as travel technologists, and for patients to receive quality diagnostic care no matter where they live.

With the rapid increase in access to telehealth, as well as the ongoing development in A.I., remote imaging (whereas the patient is in one place, the technologist running the machine is in a secondary location, and the radiologist interpreting the image is in a third) is beginning to become more prevalent.

Because use of technology crosses boundaries, federal minimum standards are more necessary now than ever before. By creating a means of enforcement of the guidelines established under the Consumer-Patient Radiation Health and Safety Act (42 USC Ch. 107) for those operating medical imaging and radiation therapy equipment, the federal government can ensure there are minimum standards across the nation, thereby minimizing poor quality images produced by unqualified individuals, improving patient safety and access to high-quality healthcare, and reducing bureaucratic red-tape for traveling technologists.

We appreciate the opportunity to raise awareness of ASRT and its members, as well as ongoing concerns regarding the significant barriers facing the medical imaging profession and the patients we serve.

Thank you again for the opportunity to submit this statement for the record, and please do not hesitate to reach out to ASRT's Executive Director and CEO, Melissa Pergola, Ed.D.,R.T.(R)(M), FASRT, CAE at [redacted].

Sincerely,

Melissa Pergola, Ed.D., R.T.(R)(M), FARST
CEO and Executive Director
American Society of Radiologic Technologists

Statement for the Record Submitted by the Association of American Medical Colleges to the House of Representatives Energy and Commerce Health Subcommittee: "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule" Submitted March 21, 2024

The Association of American Medical Colleges (AAMC) appreciates the opportunity to submit this statement for the record for the House Energy and Commerce Health Subcommittee's March 21 hearing, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule." The AAMC recognizes the Subcommittee's interest in examining the proposal from the U.S. Food and Drug Administration (FDA) to regulate laboratory developed tests (LDTs), alternative approaches to diagnostic tests developed by academic laboratories, and the resulting impact on patient access to care and medical innovation.

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members are all 158 U.S. medical schools accredited by the Liaison Committee on Medical Education; 13 accredited Canadian medical schools; approximately 400 academic health systems and teaching hospitals, including Department of Veterans Affairs medical centers; and more than 70 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools, academic health systems and teaching hospitals, and the millions of individuals across academic medicine, including more than 193,000 full-time faculty members, 96,000 medical students, 153,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened participation in the AAMC by U.S. and international academic health centers.

Background

For many years, the development and provision of LDTs in the context of clinical care was understood to be outside the scope of FDA regulation, as these tests were designed and used by a single laboratory unlike widely available commercial diagnostic tests, which were regulated by the FDA as medical devices. In October 2014, the FDA released a draft guidance document asserting, contrary to the general understanding of the academic medical center (AMC) community, that LDT oversight was always under the FDA's authority but that the agency had exercised "enforcement discretion" for decades and the agency decided to begin regulating LDTs as medical devices. The LDTs offered by clinical labs at AMCs had not previously been regulated by the FDA through the existing device regulations, and many AMCs considered this repositioning very concerning. Many LDTs would have been newly subject to regulation as a result of the guidance change, and that would present a host of new challenges. According to the FDA, the purpose of the revised framework was to give the FDA oversight of LDTs "based on risk to patients rather than whether they were made by a conventional manufacturer or a single laboratory."

The FDA's novel approach to LDTs was developed and released without the significant expertise of and engagement with the academic medicine community. In response to concerns raised by the academic medicine community and many other stakeholders about the impact on patients of making it more difficult to create and administer these tests, the FDA did not finalize the draft guidance, and subsequently several Congresses drafted and introduced multiple versions of proposed legislation to require FDA oversight of LDTs, with the most recent bill, the VALID Act, being incorporated into the Senate Health, Education, Labor, and Pension Committee's draft FDA user fee reauthorization text, the FDASLA Act of

2022. Ultimately, due to the concerns of many stakeholders, the text of the VALID Act was not included and failed to be incorporated into law as part of the FDA user fee reauthorization.

AAMC Position on Laboratory Developed Tests

The AAMC believes that LDTs used to inform treatment decisions for patients must be accurate and clinically valid. We agree with the FDA that when LDTs are developed and marketed directly to patients outside both FDA oversight and the highly regulated, exacting environment of an AMC, there is the possibility for a public health risk of inaccurate or misleading tests that should be evaluated and addressed. However, we share the concerns of our member AMCs, teaching health systems and hospitals, and clinical laboratories that the FDA's proposed regulatory scheme would have an immediate and detrimental effect on specialized and patient-centric medical care. Additionally, the FDA's proposed regulatory framework would interfere with delivering innovative, cutting-edge medical care, negatively impact patients, mire the development of critical new tests in a costly and laborious regulatory process, and quickly overwhelm the ability of the FDA to efficiently review tests submitted for approval. Rather than identifying problematic tests more quickly, this would overrun the agency with submissions, including the many tests which have been used for years to provide critical information to patients' health care providers.

The AAMC has maintained that AMCs, teaching health systems and hospitals, and the faculty physicians performing LDTs every day on the front line of patient care are best able to determine the most appropriate way to treat patients with important information collected from clinically validated, well-proven, and carefully tailored diagnostic tests. We strongly urge policymakers, including both Congress and the FDA, to partner with academic medicine as it works to deliver timely and innovative patient care, not stifle it.

As the FDA moves to regulate LDTs while Congress considers potential alternatives, the AAMC continues to engage with all stakeholders to find a workable solution and advocate for the continued valuable and critical use of LDTs in the practice of medicine.

Differentiating Academic Medical Center Clinical Labs

Clinical labs in AMCs have unique characteristics that differentiate them from other types of labs that develop and manufacture LDTs. These factors were a large part of why the FDA was comfortable with the development and provision of LDTs in AMCs without FDA regulation for many years.

Key characteristics of academic clinical laboratories (ACLs) include:

- Integration as an integral component of an academic institution which provides direct patient medical care.
- A primary role providing testing and interpretation for the benefit of the patients and clinicians in an affiliated hospital or academic health center as a part of the treatment decision-making process.
- Certification by the Centers for Medicare & Medicaid Services through the CLIA (Clinical Laboratory Improvement Amendments) program to conduct high-complexity tests.

As a function of the ACL's position in an AMC, its activities are already under many levels of internal and external scrutiny. In addition to the laboratory oversight evidenced by CLIA certification, some states, including New York, have additional requirements. Thus, adding another layer of FDA regulation, although it evaluates different characteristics than existing oversight, could limit access to these tests without meaningful changes in the accuracy or validity of the results.

FDA 2023 Proposed Rule

As stated in our December 2023 FDA comment letter, diagnostic testing is a critical element of medical decision-making and, in many cases, commercially available diagnostic tests can provide a health care provider with sufficient information to recommend a treatment plan. However, the patients who come to AMCs often require more tailored, specialized, or specific diagnostic tools. This is where the unique value of LDTs comes into play. These tests, when created in an academic laboratory that is certified for high-complexity testing, meet the needs of patients and providers and fill gaps where commercial products do not, and will never exist. It is only because of these LDTs that many of these patients can receive accurate diagnoses and life-changing medical treatment, including those with rare diseases, genetic and metabolic disorders, emerging infectious agents, pediatric illnesses, and cancer-causing gene mutations.

At academic medical centers, the development of LDTs is exacting, rigorous, resource-intensive, and an essential component of patient care. While LDTs manufactured outside of academic medical centers have been identified with consumer harm and inaccurate results, **a federal response that makes safe, accurate, and needed LDTs unavailable to patients does not promote public health and welfare.** We are concerned that this proposal establishes a broad, disruptive oversight mechanism that will hinder the ability of AMCs to provide care to patients who need it most.

The academic medical center laboratory environment provides a higher level of oversight, regulation, engagement between laboratory and clinician, expertise, and focus on specific patient need than does commercial manufacturers of LDTs and thus warrants continued general enforcement discretion with respect to LDTs developed at academic laboratories. For these reasons, we have urged the FDA to maintain its enforcement discretion for tests that are developed in the highly regulated, specialized academic medical center environment to allow the agency to focus on those tests being marketed directly to patients without the safeguards and oversight which are already an integral part of LDT development at academic medical centers.

The FDA's proposed new regulatory framework fails to recognize that an overly burdensome system to review LDTs could greatly slow the rate of clinical innovation that is critical to keeping our health care system at the forefront of discovery, providing quality care to patients, and responding quickly to emerging public health risks. The extensive time commitment and the economic impact of institutional compliance with the FDA's proposed new regulatory framework for currently administered and newly developed LDTs would be untenable, given the time and cost of guiding even a single test through the FDA premarket approval process. Therefore, institutions will begin to budget for a certain number of LDTs and abandon others, to the detriment of patients. This cost would necessarily lead to institutional decisions that could limit patient access to innovative and targeted diagnostic tests.

Academic Clinical Laboratory Exemption

Given AMC labs integration of the test development and administration into the continuum of patient care, the many other safeguards for patients that these labs are already subject to, and the FDA's retention of the ability to investigate and remove any test from the market regardless of the entity that develops it, **both FDA and Congress must recognize the need to exempt these academic clinical laboratories from an overly burdensome regulatory framework**.

As part of its proposed rule, the FDA has provided for consideration a definition of "academic medical center" for continuing enforcement discretion at these entities. While the AAMC is fully supportive of the

FDA's using general enforcement discretion with respect to tests at academic medical centers, the definition provided is problematic as it would tend to arbitrarily exclude certain organizations that are unquestionably academic medical centers for which general enforcement discretion would be appropriate.

A Path Forward for LDT Regulation

The regulations of all LDTs at AMCs will not address what the FDA posits is a public health risk. Instead, the FDA's overbroad proposed regulation of LDTs will threaten the care patients expect to receive from AMCs. We have suggested to the FDA a tiered enforcement strategy that recognizes the risk mitigation factors present in LDTs developed by ACLs. However, should policymakers and regulators move forward with any form of LDT regulation without providing an exemption for ACLs, such regulatory framework must lessen the burden on ACLs by altering several previous policy proposals in order to make these new regulations less likely to decrease the number of available tests for patient care, potentially negatively impacting patients' health.

The most onerous and resource-intensive aspects of the LDT regulation could be diminished without increased risk to patients or access to care by ensuring that any regulatory framework applicable to labs that are designated as "academic clinical laboratories":

- Grandfather in existing tests that have been successfully used for the benefit of patients at AMCs and exclude them from further regulation.
- Exclude ACLs from any requirement to proactively list all tests that are to be grandfathered. Instead, such labs should be prepared to present evidence of use of the test prior to enactment should a question arise about whether a test was properly included in this exemption.
- Have every test developed by an ACL be designated as low-risk and not subject to the additional requirements for high-risk tests. This would acknowledge the risk-mitigating factors that arise from additional oversight, expertise, and integration into clinical care that ACLs demonstrate, aspects that are wholly different from commercial or reference labs.
- When a test is grandfathered, exempt from premarket review through a technology certification, or approved through premarket review, if that test is developed and administered by an ACL, any changes to the type of specimen used for the test would not be considered a modification that would cause it to be treated as a new test.

Conclusion

The AAMC appreciates the Subcommittee's examining the FDA's proposed rule to regulate LDTs, alternative approaches to diagnostic test regulation at AMCs, and the impact on patient access to care and medical innovation. The AAMC looks forward to continuing to work with policymakers to ensure diagnostic tests are safe and readily available for patient care.

Children's Hospital Association Statement for the Record

Energy and Commerce Committee Hearing, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule"

March 21, 2024

On behalf of the nation's 200+ children's hospitals and the children and families we serve, thank you for holding this hearing, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule." We share the goals of this committee and the FDA of protecting public health by assuring the safety and effectiveness of diagnostic tests, particularly for children with serious or complex medical needs. Therefore, we believe it is essential to understand the unique pediatric considerations of the FDA's proposed rule or any other approaches to regulating laboratory-developed tests (LDT). It is imperative that diagnostic test regulation protect children's access to life-saving tests and timely care.

Role of LDTs in Pediatric Health Care

Children are not just little adults. They are constantly growing and developing, and their health care needs and the delivery system to meet those needs are different from those of adults. Pediatric health care requires specialized medications, diagnostics, tests, therapeutics, and equipment that the nation's children's hospitals provide. LDTs fill a critical gap in the practice of pediatric medicine as they allow for accurate, timely, accessible, and high-quality testing for many pediatric conditions for which no commercial test exists or where an existing FDA-approved test does not meet current pediatric clinical needs. They are critical to children's hospitals' ability to provide timely, cost-effective, and high-quality diagnostics and care for all children, and particularly for children in need of treatment for rare and difficult-to-diagnose pediatric disorders.

LDTs developed and used in pediatric health care settings account for all stages of childhood development, from newborn through adolescence and young adulthood, and address numerous genetic and heritable diseases, pediatric cancers, and acquired conditions that are not well-represented in adult health care practice. FDA itself has recognized four subpopulations within the pediatric population – neonates, infants, children, and adolescents[1]—and the importance and challenges of developing age-appropriate treatments and diagnostics for the pediatric population. For example, tests that are effective in adolescents cannot necessarily be used on neonates without modification. Pediatric-related LDTs provide those age-appropriate diagnostic tools.

Children's Hospitals' use of LDTs

There are numerous FDA-approved tests that could potentially be used for children but are not validated for such use. Children's hospitals' clinical laboratories either develop tests from scratch that are needed by their patients or perform the extensive validation work needed to demonstrate that an FDA-approved test for adults can safely and reliably be used for children. Those in-house tests (LDTs) offer precise and accurate results and they are a critical component of lifesaving treatment plans designed for children.

[1] See, e.g., Pediatric Medical Devices, FDA.

Children's hospital laboratories offer several hundred in-house LDTs or modified FDA tests. These tests are all developed and validated following requirements specified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) in laboratories tightly regulated and further accredited under CLIA and by their states, the College of American Pathologists, or the Joint Commission—in accordance with the CLIA regulation. These existing regulatory measures ensure the quality of this testing, which is usually developed in partnership with pediatric clinical providers to meet well-defined clinical needs.

These pediatric-related LDTs include tests for diseases/diagnoses that are related to infancy or childhood; tests that are approved for adults but must be altered or modified for pediatric use; tests for pediatric rare and orphan diseases; tests that cannot be done—or are not done—by adult-focused laboratories; and tests that are run in hospitals for immediate pediatric patient care.

For example, pediatric LDTs are used when there are no FDA-approved alternatives available for time-sensitive tests to enable pediatric specialists to make immediate clinical decisions for children. These include the test used to diagnose childhood leukemia, which may be individualized within different children's hospital laboratories for the specific child. The curative treatment for children with leukemia is bone marrow or stem cell transplantation, and the genetic test used to monitor the health of the bone marrow transplant after it happens is also an LDT.

There are also numerous situations in which the instructions for use for an FDA-approved test do not include the parameters needed to use the test in the pediatric population. These include tests with instructions for use that exclude pediatric age ranges. Therefore, children's hospitals routinely develop different reference ranges to inform age-appropriate clinical decision-making. For example, the test used to determine bleeding risk in pediatric surgical patients is an LDT because there is no FDA-approved test available for use in patients under the age of 18 years.[2]

Furthermore, adult-focused laboratories often do not have the pediatric-specific instrumentation to care for children of varying ages. LDTs allow children's hospital laboratories to serve pediatric patients of all ages (newborns, infants, small children, and even older children) through the use of age-appropriate equipment—such as extremely small sample sizes and equipment such as microtainer tubes for testing low birthweight preterm newborns.

Impact of Proposed FDA Rule

We believe the proposed FDA rule on LDTs will have serious implications for children's hospitals' ability to provide timely diagnostics for the nation's children. We are particularly concerned with the disproportionate impact that the proposed rule will have on children – especially those enrolled in Medicaid—and their access to the vital testing, screening, diagnostics, and care that they need. Medicaid is the largest insurer of children in the U.S. and, on average, covers one-half of children's hospitals' patients. For some children's hospitals, closer to three-quarters or more of its patients are enrolled in Medicaid. Between one-third and one-half of Medicaid-covered children have

[2] For additional examples of pediatric-related LDTs, see CHA Comments on FDA Laboratory Developed Tests Proposed Rule.

special health care needs.[3] These children frequently face higher disease exposure risks and are more likely to depend on LDTs for their specialized pediatric health care.

It is important to note that, though children's hospitals account for only 2% of hospitals in the U.S., they account for about 45% of all hospital days for children on Medicaid. As a result of the heavy reliance on Medicaid, which often under-reimburses for costs of care, the budgets of children's hospital laboratories are tight and the financial resources and staff needed to pursue the large number of complex reviews under the proposed rule will be in addition to resources already used to meet the stringent regulatory and accreditation requirements under CLIA, the College of American Pathologists, the Joint Commission, state standards, etc.

Furthermore, as we note above, we know that the for-profit sector has not—and likely will not—step in to make tests for pediatric and orphan diseases as the market is too small to be profitable. Similar to the development of new pharmaceuticals, which are usually developed for adults, children are often left behind in the development of commercial testing, given the small market and highly specialized nature of pediatric diseases. As a result, many needed tests for children, including those with rare, uncommon and often life-threatening, diseases will no longer be available with significant negative implications for their overall health and wellbeing.

Given the critical and unique role that LDTs play in pediatric health care, we believe that any regulatory or congressional action affecting pediatric-related LDTs must continue to protect children in need of these life-saving diagnostics. Therefore, we have recommended to the FDA that its final rule continue general enforcement discretion approach for all hospital and health system LDTs, and at a minimum, enforcement discretion for pediatric-related LDTs.

Additional Considerations

While we are not opposed to congressional or regulatory action to give special consideration to LDTs developed by academic medical centers (AMCs), we remind the committee that there are pediatric-specific LDTs that are developed or modified by children's hospitals that are not affiliated with an AMC. Therefore, we believe that consideration must specifically be given to those tests that are developed to meet the specific needs of infants, children, and all those impacted by pediatric diseases—regardless of where the tests are developed.

We also believe that, at a minimum, currently marketed pediatric-related LDTs must be grandfathered in any regulatory structure to ensure that children continue to have access to the specialized clinical diagnostics and care that children's hospitals provide. In the absence of a grandfathering provision, it is likely that some, if not many, children's hospital laboratories will be unable to make the substantial administrative and financial investments that would be required to prepare submissions for FDA review for the range of LDTs currently in use. As a result, they

[3] Medicaid Access in Brief-Children and Youth with Special Health Care Needs (macpac.gov); Children with Special Health Care Needs: Coverage, Affordability, and HCBS Access | KFF.

would have to make extremely difficult decision to consider abandoning existing effective pediatric-related tests putting their child patients at risk.

However, a grandfathering provision will **not** fully ensure that children have access to the tests and health care they need. In addition to a measure to protect tests currently in use, measures must be put into place to support the ability of children's hospitals to continue to develop—and innovate with—new diagnostics that are safe and clinically effective and drive pediatric cures and treatment.

Thank you for the opportunity to highlight the unique implications of the regulation of LDTs for pediatric health care. We know this committee shares our commitment to ensuring that children continue to have access to life-saving diagnostics and timely care. We also join with the committee and the FDA in supporting appropriate regulatory oversight of LDTs in the commercial marketplace and in ensuring that all diagnostics and safe and effective. We look forward to continuing to work with you to meet the health care needs of the nation's children.

March 20, 2024

The Honorable Brett Guthrie
Chairman
House Committee on Energy and Commerce
Subcommittee on Health
2123 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member
House Committee on Energy and Commerce
Subcommittee on Health
2123 Rayburn House Office Building
Washington, DC 20515

Re: House Committee on Energy and Commerce Subcommittee on Health hearing titled, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule"

Dear Chairman Guthrie and Ranking Member Eshoo:

The Medical Group Management Association (MGMA) thanks the Subcommittee for holding this important hearing examining the Food and Drug Administration's (FDA) proposed rule (88 FR 68006) to regulate laboratory developed tests (LDTs) and alternative approaches to diagnostic regulation. MGMA recognizes the FDA's efforts to ensure the safety and effectiveness of LDTs through the proposed oversight framework. However, we have serious concerns that regulating LDTs as medical devices could inadvertently limit patient access to critical clinical testing.

With a membership of more than 60,000 medical practice administrators, executives, and leaders, MGMA represents more than 15,000 medical groups comprising more than 350,000 physicians. These groups range from small independent practices in remote and other underserved areas, to large regional and national health systems that cover the full spectrum of physician specialties.

For years, MGMA has advocated for a robust clinical laboratory infrastructure to support the delivery of routine patient care. Medical groups rely on LDTs to provide essential diagnostic and testing services to patients. MGMA requested a pause in rulemaking in response to the FDA's proposed rule.

The FDA is proposing to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the *Federal Food, Drug, and Cosmetic Act*, including when the manufacturer of the IVD is a laboratory. The proposed rule phases out the FDA's general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory would fall under the same enforcement approach as other IVDs. The proposed oversight framework includes premarket review requirements. FDA's stated intent in proposing this phaseout is to better protect public health by helping to ensure the safety and effectiveness of LDTs.

While MGMA supports ensuring the safety and effectiveness of LDTs, we remain concerned the proposed premarket review requirements may delay or deter modifications to existing tests and the introduction of new ones, hindering laboratories' ability to keep pace with scientific advances and clinical practice guidelines. The increased administrative and financial burdens of the proposed

framework would exacerbate existing cuts in laboratory reimbursement. These compounding impacts could force laboratories to narrow or cease test offerings, further restricting patient access.

The rollout of the European Union's In Vitro Diagnostic Medical Device Regulation (IVDR) offers important lessons for diagnostic regulation. The IVDR, enacted in 2017, aimed to bring all diagnostics under a uniform regulatory scheme by 2022. To avoid widespread shortages, regulators postponed deadlines and granted grace periods for certain tests.[1] According to the European medical device industry association (MedTech Europe) without these delays, 22% of marketed diagnostics could have been pulled from the market during the transition.[2]

Given the concerns outlined above, MGMA urged the FDA to not finalize the proposed rule. Instead, we recommend Congress examines a less burdensome approach to diagnostic regulation that is tailored to meet the specific needs of clinical diagnostics, promotes innovation, and integrates existing Clinical Laboratory Improvement Amendments (CLIA) requirements. CLIA regulations currently provide quality and safety oversight for LDTs. Any update to the oversight of laboratory testing is incomplete and potentially duplicative without integrating CLIA requirements.

In 2023, the *Verifying Accurate Leading-edge IVCT Development Act* (VALID Act) was reintroduced. This legislation would create a risk-based framework for regulating LDTs that resembles the existing approach FDA takes toward other medical devices. MGMA and over 100 other organizations expressed concern in response to this legislation, highlighting that certain provisions were duplicative of existing CLIA and state requirements. The VALID Act's provisions on quality systems, adverse event reporting, and laboratory inspections are all requirements that exist within CLIA. Should Congress once again consider the VALID Act as a legislative pathway for the regulation of diagnostic tests, we urge the Subcommittee to consider these concerns.

MGMA looks forward to working with the Subcommittee in developing an alternative approach to diagnostic regulation that supports group practices as they care for patients. Should you have any questions, please contact James Haynes, Associate Director of Government Affairs, at [redacted] or [redacted].

Sincerely,

/s/

Anders Gilberg
Senior Vice President, Government Affairs

Cc:

The Honorable Cathy McMorris Rodgers
The Honorable Frank Pallone

[1] Huanjia Zhang, *IVDR Rollout Brings New Hurdles for Clinical Labs, Smaller Diagnostic Firms in Europe*, 360Dx, Sept. 18, 2023.
[2] Susan Reilly, *EU to Delay Portions of the IVDR Rollout*, MEDIcept, Feb. 7, 2022.

March 20, 2024

The Honorable Brett Guthrie
Chair, Health Subcommittee
House Committee on Energy and Commerce
2434 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member, Health Subcommittee
House Committee on Energy and Commerce
272 Cannon House Office Building
Washington, DC 20515

The Honorable Cathy McMorris Rodgers
Chair
House Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
House Committee on Energy and Commerce
2322A Rayburn House Office Building
Washington, DC 20515

Dear Chair Guthrie, Ranking Member Eshoo, Chair McMorris Rodgers and Ranking Member Pallone,

On behalf of the more than 30 million Americans living with one of the over 10,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the House Committee on Energy and Commerce's Health Subcommittee for holding a hearing focused on oversight of diagnostic testing that could have a profound impact on the rare disease community NORD so proudly represents.

NORD is a unique federation of non-profit and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded over 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of affordable, comprehensive health care, including access to safe and effective therapies.

Many people living with a rare disease struggle to obtain an accurate diagnosis, have limited treatment options, and grapple with access to health care providers with expertise in their condition, and to afford the often high out-of-pocket costs associated with their treatment and care. The medical needs of those living with a rare disease are complex, as are the policies necessary to enable rare disease patients to thrive. NORD is grateful to the Subcommittee for holding today's hearing examining how best to regulate diagnostic tests without threatening access for patients with rare diseases.

Rare disease patients, families and health care providers need practical and feasible legislative solutions that are risk-based, data-driven, and that consider the unique challenges around rare diseases. The delay in reaching agreement on oversight of lab developed tests (LDTs) has diverted considerable resources and perpetuated substantial and inherently harmful uncertainty for rare disease patients that largely depend on LDTs. We urge Congress to find a solution now that prevents bad tests from harming patients while ensuring continued access to diagnostic testing for rare disease patients – our patients and the future of rare disease therapies depend on it.

<u>The stakes are high for the roughly 1 in 10 Americans living with a rare disease</u>:

1. **LDTs are central to the medical care of rare disease patients – and the economics of developing diagnostic tests for rare diseases are fundamentally different from other disease areas**. As many as 80% of all rare diseases have a genetic component; many genetic tests in clinical use today are LDTs.[1] Similarly, most newborn screening tests administered by publicly funded and run newborn screening programs across the country are LDTs, as are many companion diagnostics such as biomarker tests central to the safe and effective use of many rare disease therapies, particularly in the oncology space.[2]

2. **Rare disease patients need and deserve accurate, reliable diagnostic tests <u>and</u> timely access to them.** In many cases, an incorrect diagnostic test result can cause more harm for the patient and family than no diagnostic test at all. Yet, treatment delays also harm patients; many rare disease patients already face a long 'diagnostic odyssey.'[3] Perhaps most importantly, an increasing number of innovative rare disease therapies have narrow treatment windows. Any delay in diagnosis can – and does – exclude rare disease patients from clinical trials, or from receiving FDA-approved therapies. Given the limited alternative treatment options for many rare diseases, such delays are often devastating for patients and families. Similarly, timely access to companion diagnostics such as biomarker tests,[4] which provide vital information about the safe and effective use of a corresponding drug or biologic, often determines if and when rare disease patients access life-altering therapies.

3. **Not all diagnostic tests are created equal or carry the same risks for patients.** It is not feasible – or desirable - to require the same level of oversight over all tests regardless of how they are used or what risks and benefits they pose to patients. Companion diagnostics such as biomarker tests in particular play an increasingly important role in rare disease drug development, and delays in the approval or clearance of a companion diagnostic can lead to devastating delays in drug approval or biologic licensure.

4. **The existing regulatory framework for devices was not made for LDTs and will not work well for rare disease LDT; careful, deliberate implementation of any sweeping changes to the LDT sector is vital for success.** Data on the use and performance of LDTs in rare diseases (and more broadly) to guide implementation are very scarce. This makes careful, deliberate implementation of

---

[1] Richardson, L., Dobias, M., Akkas, F., Younoszai, Z., & McAndrew, E. (n.d.). *The Role of Lab-Developed Tests in then Vitro Diagnostics Market*. The Pew Charitable Trusts. https://www.pewtrusts.org/-/media/assets/2021/10/understanding-the-role-of-lab-developed-tests-in-vitro-diagnostics.pdf

[2] Id.

[3] *Barriers to Rare Disease Diagnosis, Care and Treatment in the US*. (2020, November 19) National Organization for Rare Disorders.. https://rarediseases.org/wp-content/uploads/2020/11/NRD-2088-Barriers-30-Yr-Survey-Report_FNL-2.pdf

[4] Center for Devices and Radiological Health. *Companion Diagnostics*. (2023). U.S. Food and Drug Administration. https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics#:~:text=A%20companion%20diagnostic%20is%20a,corresponding%20drug%20or%20biological%20product.

any sweeping changes to the LDT sector particularly important. It also reinforces the need for ample input from ALL parts of the impacted communities.

The rare disease community needs Congressional leaders to come together in a bipartisan manner on this topic; we need legislative solutions that can adequately address the unique challenges and needs of all patients including the 30 million Americans living with rare diseases. We hope the upcoming hearing will build on the similar hearing almost 10 years ago.[5]

- We recognize a key question this week – as 10 years ago - will likely be whether FDA should oversee LDTs at all, or whether they are better regulated by modernizing regulations under the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA). FDA and CMS issued a joint statement in January of this year stating "[…] CMS does not have the expertise to assure that tests work" and "[…] the complementary FDA and CMS frameworks are both critical to assuring patients can rely on the clinical accuracy of their test results."[6] Given CMS's strong and recent view on the issue, we worry further discussions of this issue will likely prove of limited practical utility.

- As in 2014, FDA sketched out a new proposal to regulate LDTs in the fall of 2023 – the latest chapter in a long string of unsuccessful regulatory attempts dating all the way back to 2006.[7,8,9] When the public comment period closed last December, the agency had received more than 6,700 public comments, many expressing concerns about the proposed rule.[10] The resulting final rule is currently under Office of Management and Budget (OMB) review. NORD, as well as many other stakeholders, have serious concerns about the proposed rule and the potential unintended consequences associated with its practical implementation, similar to concerns NORD raised almost 10 years ago.[11,12] The final

---

[5] *21st Century Cures: Examining the Regulation of Laboratory-developed Tests*. (2024, March 20). https://www.congress.gov/event/113th-congress/house-event/LC39273/text

[6] Center for Devices and Radiological Health. (2024, January 18). *FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made.* U.S. Food and Drug Administration. https://www.fda.gov/medical-devices/medical-devices-news-and-events/fda-and-cms-americans-deserve-accurate-and-reliable-diagnostic-tests-wherever-they-are-made

[7] Congressional Research Service. *FDA Regulation of Laboratory-Developed tests (LDTs).* (2022, December 7). https://crsreports.congress.gov/product/pdf/IF/IF11389

[8] Center for Biologics Evaluation and Research (CBER). *Framework for Regulatory Oversight of Laboratory Developed Tests.* (2014, October 3). U.S. Food and Drug Administration. https://www.fda.gov/media/89841/download

[9] Covington and Burling, LLP. *HHS Issues New LDT Policy, Rescinding FDA Premarket Review Policies.* (2020, August 25). https://www.cov.com/en/news-and-insights/insights/2020/08/hhs-issues-new-ldt-policy-rescinding-fda-premarket-review-policies

[10] Federal Register. *Medical Devices; Laboratory Developed Tests.* 88 FR 68006. (proposed 2023, October 03). https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

[11] *NORD Supports Lifting the HDE Cap.* National Organization for Rare Disorders. (2015, September 15). https://rarediseases.org/assets/files/policy-statements/2015-09-21.NORD-Supports-Lifting-the-HDE-Cap.pdf

[12] *NORD Comments on Proposed LDT Rule.* National Organization for Rare Disorders. (2023, December 04). https://rarediseases.org/wp-content/uploads/2023/12/NORD_comments_LDT_proposed_rule_2023_final.pdf

rule is likely to raise many (or more) of the same concerns. Unfortunately, similar to 10 years ago, the forthcoming FDA regulatory proposal from FDA is unlikely to generate practical, tangible solutions.

We simply cannot continue this fruitless debate indefinitely. We urge Congress to come together in a bipartisan manner to find a practical solution now that prevents bad tests from harming patients while ensuring continued access to diagnostic testing for rare disease patients – our patients and the future of rare disease therapies depends on it.

NORD is grateful for the Subcommittee's attention to these critical issues and looks forward to working with the Subcommittee to better support the rare disease community. Please do not hesitate to reach out to Karin Hoelzer at [redacted] when NORD can be of assistance to the Subcommittee's important work.

Sincerely,

Karin Hoelzer, DVM, PhD
Director, Policy and Regulatory Affairs
National Organization for Rare Disorders

Statement for the Record
Nationwide Children's Hospital

U.S. House Energy and Commerce Committee
Health Subcommittee Hearing: “Evaluating Approaches To Diagnostic Test Regulation And The Impact Of The FDA’s Proposed Rule”

March 21, 2024

As one of the top ten pediatric hospitals in the country, we at Nationwide Children's Hospital (hereafter referred to as NCH) are deeply concerned about the adverse impact of the proposed rules regarding Laboratory Developed Tests (hereafter referred to as LDTs) put forth by the FDA. We would like to share with you the basis for our concerns, in the hope that we can effectively advocate for our patients who will be severely affected by lack of access to LDTs developed in our hospital, which is an academic medical center (AMC), and in other academic medical centers in the country.

Though we are a Children’s Hospital, our patients includes adults, who are often followed from childhood for congenital diseases, or as in the case of Clinical Immunology, are seen due to a common specialty training for both pediatric and adult patients. Our clinical laboratories within the Department of Pathology and Laboratory Medicine at NCH provide diagnostic testing for our hospital (inpatient and outpatient) patient population as well as our reference laboratory practice. Thus, we are similar to other AMCs, whose patient population includes patients of all ages.

The FDA is proposing to regard all LDTs as medical devices, and as such, to follow a burdensome regulatory protocol to get these tests approved. NCH has 528 LDTs, and in 2022 alone, these were used to provide >75,000 laboratory tests for more than 58,000 patients. Among the patients we serve are several with rare and complex diseases, including genetic disorders, immune disorders, cancer, and more. NCH is both a primary and tertiary care medical center that provides inpatient and outpatient care to tens of thousands of patients each year, from central Ohio and around the country. There are over 7000 rare diseases recognized clinically and the care of these patients, which are individually rare but collectively common (affecting 25 to 30 million Americans), is mainly provided by large and advanced academic medical centers (AMCs), such as NCH. The ability to provide cutting-edge diagnosis and treatment is inherently dependent on the ability of academic medical laboratories, such as ours, to innovate and nimbly and effectively deliver care to patients regardless of race, class or income.

The proposed rules to classify LDTs as medical devices will essentially curtail all advanced LDT access at NCH and most other AMCs, effectively abrogating our ability to deliver high-quality care for the patients who come to our medical center. No commercial reference laboratory can take the place of LDTs offered via AMCs because the development, validation and interpretation of these tests requires a high level of scientific and clinical expertise, often not available in commercial enterprises. LDTs developed in AMC laboratories often fill a void in the markets where FDA-approved in vitro diagnostic (IVD) kits are not available. An example would be the identification of novel lymphocyte subsets that were determined to be present in blood only by the use of LDTs, which often include multiple markers of cell subsets in recognition of the enormous heterogeneity and complexity of the immune system. Currently, only AMCs have the ability to identify and advance clinical care and facilitate the elucidation of the biological relevance of these novel cell subsets in different patient populations. Further, many AMCs offer their LDTs as part of a reference laboratory practice to make advanced diagnostic and monitoring test available to all Americans, regardless of where they reside in the country.

It is relevant to note that AMCs are developing LDTs under very strict criteria, previously formulated by CMS through CLIA for analytical validation of such tests, and these tests are interpreted by board-certified pathologists and/or laboratory scientists in different specialties. Further, most LDTs are seldom interpreted in isolation but in context of multiple laboratory tests and clinical phenotype. These sorts of correlative diagnoses cannot be performed in commercial reference laboratories as they lack access to patients and clinical information to develop the necessary clinical correlations. Also, many LDTs are not independent diagnostic tests but rather used contextually, based on the clinical circumstances of each patient. It is also relevant that the FDA has indicated that CLIA will continue its oversight role for analytical and quality standards, including competency of personnel, proficiency testing and other regulatory requirements.

A recent survey conducted by Lighthouse Lab services of 209 respondents demonstrated that 58% regarded the proposed rules as having a significant adverse impact on the ability of labs (including AMCs) to operate (which means negatively affecting patient care). It is also worthwhile to note that there is an inherent conflict of interest for large commercial operations who have the financial wherewithal, but not the academic and clinical expertise, and who would likely eliminate competition from AMCs offering LDTs through the proposed rules. AMCs invest considerable time, financial, personnel expertise and other resources in developing and offering LDTs, even for rare diseases, which would not meet the financial threshold in many commercial laboratories. The significant financial burden posed by PMA and yearly fees would significantly slow care for complex patients, potentially harming them in the process. There are already multiple layers of rigor built into the LDTs offered by the large AMCs who also serve as reference laboratories for rare disease testing.

Ultimately, the implication of the proposed rules is that there will be limited-to-no accessibility for patients with rare diseases to the necessary complex testing in multiple specialties, This will likely increase morbidity and mortality, and perhaps force families to look for care outside of the United States -- increasing inequitable outcomes for families who cannot afford travel. An analysis

from the Everylife Foundation for Rare Diseases has shown that the economic impact of a delayed diagnosis for a rare disease is more than $500,000 in avoidable costs. The report issued by the Foundation indicated that it takes more than six years and 17 doctor visits, hospitalizations and other costs to receive a rare disease diagnosis after onset of symptoms. The U.S. is a global leader in health care, but there is significant inequity in the accessibility and distribution of services. This is especially true for rare diseases, in part because the specialized testing needed is not easily available. The proposed FDA rule will hobble diagnostic laboratories at AMCs, and this gap in healthcare equity will only grow larger.

Medical education will likely see a negative impact as well. As stated in the proposed rule, AMC laboratories are involved in "medical residency training program(s) or fellowship program(s) related to test development, application, and interpretation." Because AMC laboratories are already operating on small margins with low reimbursement rates, the financial strain created by this proposed rule would force many AMC laboratories to halt offering low-volume tests (e.g. tests for rare diseases) or shut down altogether. This will affect training programs and the future workforce of board-certified laboratory personnel in this country. The proposed FDA rule would ultimately harm our ability to train new laboratory professionals to address clinical needs.

Limitations in the ability of an AMC to support an affiliated laboratory also have downstream effects on training programs for physicians and scientists providing direct patient care, such as those affiliated with Medical Genetics, Genomics and Medical Biochemical Genetics. The Accreditation Council of Graduate Medical Education (ACGME) milestones for these training programs specifically require proficiency in selecting tests, interpreting results and integration of these into patient management. Therefore, the proposed FDA rule has broad-reaching impact to residency and fellowship training programs, with the potential to severely limit training opportunities, particularly among underserved specialties providing care to patients with complex diseases.

It is also relevant for us to point out that NCH is located in an under-served area of a metropolitan area, like the majority of pediatric hospitals in the country. More than 50% of our patient population has health care coverage through Medicaid. Despite this, the hospital's mission and commitment to patient care ensures that all patients receive a thorough evaluation based on their clinical condition. This includes the use of all appropriate and relevant diagnostic testing, which is made accessible because of our status as an AMC and a non-profit hospital. This also means that patients with complex diseases can come to NCH and centers like ours for medical care regardless of their income or social status.

We would like to provide an impassioned plea to the FDA to urgently ensure that AMCs are granted an exemption to continue to innovate and develop new LDTs that support a tertiary care medical practice. As an example, many cellular immunology tests are extremely cumbersome to develop and are often performed manually and cannot be "fully automated" because of their

analytical and interpretive complexity. Any change in the current LDT paradigm, which already falls under CAP (College of American Pathologists) and other regulatory purview, would impose a tremendous financial and resource burden, which would be unsustainable.

Further, we would request the FDA continue to engage in dialogue with AMCs to fully understand the unique nature of our practice, the demographics of the patients we serve across the U.S., and why the ability to develop and deliver advanced medical care through LDTs is the cornerstone of medical practice in the 21st century, which has often been touted by various federal administrations as the era of personalized medicine. It is impossible to deliver precision or personalized medicine without access to LDTs, and additional financial and regulatory burdens will effectively render these advances inaccessible or cost-prohibitive for most patients. This will only deepen the public health crisis in the U.S. related to health care equity. We would welcome the opportunity to have further discussions with the FDA, which would ensure that the FDA's concerns can be addressed without permanently damaging the health care landscape in the U.S., particularly for rare and multifactorial diseases.

Thank you for your kind consideration of this letter. We hope you find these comments helpful as you consider this proposed rule and its potential impact on pediatric and adult patients that rely on LDTs. If you have any questions or comments please contact Charlie Solley, Vice President of Government Relations, at [redacted]

Sincerely,

Rustin Morse, MD [redacted]

Shamlal Mangray, MBBS [redacted]

Key Leaders in Administration and Clinical Departments at NCH as listed below support this letter

Rick Miller
Chief Operating Officer

Timothy C. Robinson
Chief Executive Officer

Oluyinka Olutoye, MD, PhD
Surgeon-in-Chief

Stacy P. Ardoin, MD
Chief, Rheumatology

William Barson, MD
Chief, Infectious Diseases

Timothy P. Cripe, MD, PhD
Chief, Hematology & Oncology

Scott Hickey, MD
Interim Chief, Genetic & Genomic Medicine

Manmohan K. Kamboj, MD
Chief, Endocrinology

Nicolas D. Yeager, MD
Section Chief, Hematology & Oncology

Amy L. Dunn, MD,
Director, Pediatric Hematology

University of Colorado
Anschutz Medical Campus

March 21, 2024

The Honorable Brett Guthrie
Chair, Subcommittee on Health
Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member, Subcommittee on Health
Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

Dear Chair Guthrie and Ranking Member Eshoo,

On behalf of the University of Colorado Anschutz Medical Campus (CU Anschutz), we would like to submit the following statement for the record regarding the Energy and Commerce Health Subcommittee hearing, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule."

CU Anschutz is a world-class medical destination at the forefront of transformative science, medicine, education, and patient care. The campus encompasses the University of Colorado health professional schools, more than 60 centers and institutes, and two nationally ranked independent hospitals - UCHealth University of Colorado Hospital and Children's Hospital Colorado - that treat more than two million adult and pediatric patients each year. Innovative, interconnected, and highly collaborative, the University of Colorado Anschutz Medical Campus delivers life-changing treatments, patient care, and professional training and conducts world-renowned research fueled by over $704 million in research grants.

At the Anschutz Medical Campus, our collective facilities include a multitude of Clinical Laboratory Improvement Amendments (CLIA)-accredited clinical laboratories that offer Laboratory Developed Tests (LDTs) in order to quickly diagnose our patients with potential illnesses and effectively provide them top-quality care and treatments. In coordination with our clinical partners at UCHealth and Children's Hospital of Colorado, CU Anschutz-affiliated labs conduct over 100,000 tests annually, providing patients from Colorado and neighboring states with fast, high-quality, and safe lab results so our providers can provide them with appropriate care.

The Food and Drug Administration's (FDA) proposed rule to regulate LDTs would create a burdensome and expensive regulatory process for academic labs, which could increase costs and delay timely care to patients. Labs at academic medical centers such as CU Anschutz care for a disproportionate amount of Medicare, Medicaid, CHIP, and uninsured patients who need affordable access to high-quality care. The increased regulatory burden, as proposed by the FDA, will impact our ability to care for these populations.

Additionally, CU Anschutz and other academic medical centers are local and regional referral centers where patient care is escalated for challenging or unusual clinical situations. Regional

referral care often includes escalation of care for underserved community members and rural populations. The proposed rule does not take into account the full breadth of areas that academic medical centers serve. It would create a scenario where patients who do not have easy access to their hospital would not be able to receive potentially life-saving tests.

As Congress and the Administration continue to consider potential changes to regulating LDTs, we strongly encourage you to consider the unique nature of labs at academic medical centers such as CU Anschutz to ensure all patients have swift access to safe, affordable, and timely laboratory tests. If you have further questions, please contact Brett Roude, Assistant Vice President of Federal Relations and Health Policy, at [redacted] or [redacted].

Sincerely,

Donald Elliman
Chancellor

John Reilly, Jr. MD
Vice Chancellor for Health Affairs
Dean, School of Medicine

Written Statement for the Record
American Association of Bioanalysts and
National Independent Laboratory Association
House Committee on Energy and Commerce
Subcommittee on Health
Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule

On behalf of the American Association of Bioanalysts and the National Independent Laboratory Association, thank you for the opportunity to provide this statement for the record for the Subcommittee on Health's hearing on *Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule.*

NILA represents regional, community, and specialty clinical laboratories across the United States that perform laboratory testing for physicians, hospitals, skilled nursing facilities, and other health care professionals. NILA members serve a wide variety of communities and patient populations, and many of those communities are not served by large national laboratories. Community, regional, and specialty clinical laboratories play a vital role in providing testing services to patients in rural areas, underserved urban areas, mid-and small-sized cities, congregate facilities, and critical access hospitals. Founded in 1956, AAB members are clinical laboratory directors, managers, supervisors, technologists, and technicians. AAB, like NILA, is dedicated to serving community, regional, and specialty clinical laboratories. Many of our collective member laboratories offer a variety of laboratory developed tests to provide clinicians and diverse patient populations with essential laboratory and diagnostic services that they might not otherwise be able to access.

NILA and AAB strongly object to FDA's approach to the regulation of LDTs as outlined in the proposed rule and cannot support the rule in its current form. The proposed rule asserts that LDTs are medical devices and should therefore be regulated under the same framework as all other medical devices. LDTs are **not** medical devices and should not be regulated as such. Our organizations submitted public comments to FDA that provide greater detail about the expected impact of the proposed rule on community and regional clinical laboratories. In short, the proposed regulations will place undue administrative and financial burden on laboratories at a cost that will stifle innovation and will jeopardize certain aspects of patient care. The proposed regulatory requirements will cause many laboratories to drop tests from their test menus, leaving a gap in patient access to testing at a time when the availability of clinical laboratory testing is essential for patients.

The proposed rule is duplicative and unnecessary given the existing robust regulatory framework already in place. Laboratories conducting complex clinical testing are already under the stringent regulatory requirements of the federal Clinical Laboratory Improvement Amendments (CLIA). State-level regulations and professional society guidelines further ensure that laboratories maintain high standards. This multi-layered regulatory environment guarantees that patients receive accurate and reliable laboratory testing services.

Many LDTs fall within the purview of existing CLIA and state-specific guidelines, effectively overseeing the analytical validity of each test. One such example of this is CLIA'S proficiency testing requirements. CLIA mandates this process for laboratories, which is a critical external quality control measure. This process involves analyzing unknown samples and having the results graded by an HHS-approved proficiency testing program. This ensures the validity and accuracy of LDTs in real-world scenarios. In cases where external proficiency tests are

unavailable, laboratories are required to develop alternative methods to validate their tests. Additionally, all CLIA-based laboratories are required to have quality management systems (QMS) that ensure effective quality assurance, including corrective action programs, when tests fall out of validated limits. These factors ensure the validity and accuracy of most LDTs in real-world scenarios. Prior to releasing any LDT result, laboratories are required to establish the test's analytical validity within their specific environment. This validity is also reviewed biennially by CMS or an agency acting on CMS' behalf, ensuring continuous quality assurance and improvement. A detailed examination of the CLIA testing process, along with state processes (such as those conducted by The New York State Department of Health), illustrates the thoroughness of existing regulations. Additionally, CLIA assessment administered through CLIA-approved accrediting agencies, such as the College of American Pathologists (CAP), COLA, and the Joint Commission, must account for clinical validity. In addition, laboratories whose tests are approved by the New York State Department of Health have the requirement to address both clinical utility and validity. These existing frameworks render additional FDA oversight redundant.

LDTs play an irreplaceable role in patient care and in the detection of diseases and harmful substances. They identify new and dangerous substances during the current opioid crisis, identify emerging infectious diseases, and provide myriad other clinically important information needed in the interest of public health. For many LDTs, there is no comparable IVD test kit—and contrary to the assertion made by the FDA in the narrative of the proposed rule, the changes proposed will not spur innovation from traditional medical device manufacturers to fill those gaps. **NILA and AAB have called on FDA to withdraw the proposed regulation, and instead collaborate with stakeholders and policymakers to develop a solution that works for everyone, acknowledging the unique nature of LDTs and prioritizing patient care.**

While we do not support the rule in its current form, we recognize the importance of collaboration between stakeholders and policymakers to forge a sustainable path forward and offer a number of recommendations that we believe would improve FDA's proposal.

First, any changes should be based on a true risk-based framework. LDTs are not medical devices and should not be forced through a regulatory system that equates them as such. Any imposed regulation of LDTs requires a separate risk-based framework that clearly distinguishes LDTs based on the risk to the patient. NILA and AAB support a risk-based approach to LDT regulation that focuses on tests with the greatest potential to cause harm—not a blanket regulation of all LDTs. We understand that greater regulation may be necessary for the small category of LDTs that provide profit-incentivized, direct-to-consumer tests with higher risks to the patient. However, we disagree with the FDA's proposal to use the existing medical device risk classification system to fill that role. Our concern lies in the FDA's approach to broadly regulate all LDTs by applying sweeping measures that do not align proportionately with the associated risk of the tests to patients.

FDA must also allow existing LDTs to remain on the market. In the proposed rule, the FDA asks whether the current enforcement discretion approach should be applied to tests already on the market, which is grandfathering of tests already in use. NILA and AAB support the grandfathering of LDTs currently in use, unless there are known adverse event reports surrounding those tests. Whatever solution is borne out by the rulemaking process must not be disruptive to patient care. Providers, clinicians, and patients rely on LDTs currently in use and are already under the enforcement discretion of the FDA.

Next, FDA should allow third party reviewers. It is widely known that the FDA does not currently have the capacity to regulate thousands of LDTs. As such the agency must consider third-party partnerships to assist in the review of high-risk LDTs. Specifically, the FDA sought comment on whether the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP) or laboratory programs within the Veterans Health Administration may be "leveraged," meaning that LDTs under these programs would continue to be subject to enforcement discretion, and therefore exempt from the changes in the proposed rule.

NILA and AAB support the use of third-party review and the use of other regulators to assist the FDA in the approval process for LDTs. The NYSDOH CLEP is an excellent example of a program that could be used by the FDA. Currently, the NYSDOH CLEP has approved thousands of LDTs under their regulatory structure. There may be other third-party reviewers who have, or will establish, similar approval processes. These should all be considered. We believe that if a test has already been through a rigorous approval process, the test should not be subject to a duplicative FDA approval process.

Last, NILA and AAB appreciate that patients and practitioners want access to information about LDTs. For that reason, many community and regional clinical laboratories maintain electronic, internet-based test menus that include much of the information sought by the FDA under the proposed regulations to register LDTs. Overly detailed registration and listing requirements imposed on community, regional, and specialty laboratories would be extremely burdensome and duplicative of existing laboratory resources. NILA and AAB recommend a limited registration requirement for existing tests. Laboratories should be allowed to meet the requirements of registration and listing by maintaining an electronic, internet-based test menu on the laboratory's website and submitting the link to that test menu to the FDA.

NILA and AAB members prioritize a patient-first approach in their work, emphasizing the importance of maintaining patient access to critical testing. Given the drastic negative consequences the FDA's proposed rule will have on patient care, authority to regulate LDTs should be considered by Congress and not the FDA. If Congress intends to further regulate LDTs, NILA and AAB ask that the above solutions be considered and recommend that the cost of these regulatory activities be federally funded so as not to impose a burdensome unfunded mandate on laboratories. Lawmakers should avoid creating duplicative regulations and should consider a true risk-based framework for LDTs, especially those already established as safe and effective.

By minimizing duplicative and unnecessary barriers, especially for established LDTs that pose low risks to patients, NILA and AAB member laboratories can continue to provide patients and clinicians with the tools to develop a diagnosis and treatment plan that works best for each unique case. Congress and the FDA must consider a balanced approach that encourages innovation, maintains accessibility, and recognizes the diverse landscape of laboratory testing. NILA and AAB's recommendations aim to provide a framework that addresses the FDA's concerns while ensuring LDTs continue to play a vital role in health care.

Again, thank you for the opportunity to submit this statement for the hearing record. AAB and NILA are available to serve as a resource as the Subcommittee deliberates on this important issue. If you have questions or wish to further discuss this important issue, please reach out to our Washington representative, Erin Morton, at [redacted]

OPINION COMMENTARY Follow

The FDA's Lab-Test Power Grab

The agency assumed the power to shut down early Covid testing. Now it wants Congress to formalize it.

By Brian Harrison and Bob Charrow

Dec. 15, 2022 6:58 pm ET

PHOTO: GETTY IMAGES/ISTOCKPHOTO

Most Americans have never heard of "laboratory developed tests." Yet they are at the center of a bureaucratic turf war that could harm millions of Americans and leave the country less prepared for future pandemics.

LDTs are medical laboratory tests made and used in a single laboratory to assess human specimens such as blood or saliva. They help answer questions such as whether a proposed course of chemotherapy will work on a specific patient's cancer or whether someone with a cough has Covid-19. Most tests consumers are familiar with aren't LDTs but commercial tests sold to laboratories by medical-device manufacturers.

and Medicaid Services, not the FDA. Bureaucrats at the FDA have tried to ignore this rule even though the Supreme Court in Berkovitz v. U.S. (1988) specifically admonished the agency for ignoring federal regulations.

The Valid Act is a bureaucratic solution in search of a problem. A review of all reported cases in state and federal courts reveals no reported suits filed against a laboratory for an LDT result. The absence of any personal-injury suits is extraordinary in our highly litigious society and attests to the safety and efficacy of these tests.

The FDA's own actions prove there is no need for additional regulation. While for decades it has claimed jurisdiction to regulate LDTs, up until we declared the public-health emergency, the FDA opted not to do so. Unfortunately for the U.S., the FDA couldn't help itself and declared that it would begin regulating all LDTs for Covid-19 the moment a public-health emergency was declared.

While we stopped the FDA from regulating these tests in 2020, the Biden administration demonstrated its disregard for federal law and zeal for harmful federal regulations last November by allowing the FDA to resume regulation of LDTs.

FDA Commissioner Robert Califf recently threatened Congress that if it doesn't enact the Valid Act, he will simply take the authority by regulation. Congress must not bend to this threat. There is no demonstrated need for the Valid Act other than to further enlarge the FDA's jurisdiction. When speed and flexibility are paramount, a large bureaucracy shouldn't be in charge.

If Congress gives the FDA authority to enforce needless regulatory hurdles for laboratory developed tests, it would make the U.S. less prepared for future pandemics by preventing America's best laboratories from detecting the spread of new pathogens. Would you rather rely on laboratory testing from the CDC or from laboratories at Harvard, Stanford and Texas A&M University? The Valid Act could literally cost lives, and it should be rejected.

Mr. Harrison is a Texas state representative. He served as chief of staff at the U.S. Department of Health and Human Services, 2019-2021. Mr. Charrow served as HHS general counsel, 2018-2021.

Alabama

Thuy Phung, pathologist University of South Alabama Alabama

Our institution serves a large African American community in Southern Alabama. We rely heavily on LDTs to provide the best clinical testing for our patients in this underserved region**. Without having LDTs, many of our patients would not be able to have much needed testing done locally but would have to rely on out-of-state large commercial labs to do the testing which would pose significant negative economic impact and reduce quality of care. Local care is the best care for people in this region.**

California

David Frishberg, M.D. Professor and Chair, Department of Pathology and Laboratory MedicineCedars-Sinai Medical Center Los Angeles, California

"While the rule is well-meaning in its intent to curb excesses and poor quality seen in a very few for-profit labs that market directly to patients and practitioners, **nonprofit hospital-based laboratories are subject to quality oversight by numerous entities, including but not limited to the Joint Commission, the College of American Pathologists (CAP), CMS, the FDA (for blood banks), and state agencies. In fact, the CAP alone addresses LDTs in no less than five (5) separate checklists as part of its accreditation process. In this regard, hospital laboratories developing their own tests share the key characteristics of hospital and health system compounding pharmacies, for which the FDA itself has published (https://www.fda.gov/media/97353/download) reasons for proposed exemptions to section 503A of the FD&C Act, specifically:**

- The scope of testing by hospital and health systems is limited, in that the tests are ordered by practitioners who treat patients within the hospital or to related facilities that are generally located within close proximity to the laboratory.

- **When the laboratory and the hospital or health system are connected by common ownership or joint management, they share record keeping systems and oversight that facilitate the identification and investigation of adverse events or quality issues associated with testing**. "

Celeste C. Eno, PhD, FACMG, Director Cytogenetics Laboratory, Associate Director Molecular Laboratory Cedars-Sinai Medical CenterCalifornia

Impact on Academic Genomics Laboratories from the perspective of a boarded, current director of a laboratory**. If the FDA moves forward with the plan to eliminate LDTs, our laboratory would not be in operation, it will immediately lead to the unemployment of many citizens and more importantly, it will result in poor patient care due to the wait times for sending the test and due to the lack of innovation and test development**. Additionally, as I have pointed out two IVD failures below (that were never addressed) in the total of only four tests our lab has offered as IVD (50% failure rate), we envision more test failures and lack of follow up in the future. When one or few institutions/companies have a monopoly on a test, everyone fails, which means patients die. Essentially all of our testing in the Cytogenetics laboratory is LDT. **We are known for the excellent**

prenatal care and early detection of chromosomal abnormalities, which is mostly performed on our LDT chromosomal microarray platform. We provide very quick results for patients to make difficult decisions as early as possible. If we were not offering our LDT, the tests would likely be sent off-site to laboratories, which do not have the clinician interaction to inform results, especially when they are highly complex or difficult to counsel. Having the direct clinician interaction allows us to explain variants of uncertain significance, low penetrance, and variability to ensure accurate genetic counseling. We are able to prioritize cases appropriately to allow for decision making, which is not possible when a sample is sent out. We also work with the clinicians to determine if they have an appropriate amount of sample for testing and if there is little sample, we will try the testing unlike many send out laboratories which outright reject samples. **Our laboratory routinely receives oncology samples which would be rejected by send out laboratories; however, we will try any and all testing possible to get the diagnosis.** Additionally, we routinely work with pathologists to get the most appropriate sample and additional samples if needed. **We can prioritize new acute leukemias and routinely report results prior to any send out for similar testing.** If we did not perform our LDT FISH or karyotype, we would not be able to offer answers which may make the difference in therapeutic decision making and lead to poor patient care. An example of a failure of an IVD is the ALK rearrangement FISH probe. There have been multiple publications demonstrating that a specific pattern, which is technically considered negative is a false negative and can lead to patients not accessing vital therapeutics. The company responsible still has not updated its paperwork to include this false negative rearrangement possibility. This issue highlights the need for allowing testing/reporting to be individualistic and flexible to quickly adjust given confirmed public knowledge of alteration patterns that deviate from the FDA reviewed and accepted standards. **Molecular Genetics: Most of our testing in the molecular genetics laboratory is LDT. We provide an extensive Cystic Fibrosis panel which is now recommended by professional societies because the previous IVD test only covered 23 variants which are mainly associated with Caucasian population. Additionally, the IVD test used at most institutions falsely reported a certain variant, and this was reported to the company by multiple institutions without ownership of the mistake.** This incident highlights the need for the reporting laboratory to be able to access all data and understand the test fully, which is best done through extensive validation required for an LDT. PML::RARA STAT tests in which clinicians rely on accurate results must be able to maintain LDT status. As the validation provides insights for the laboratory operating the test into how the test may fail or procedures resulting in errors. We prefer our LDT version of this test since we need the flexibility to review all data prior to releasing the results. As seen in other IVDs, if the full test is essentially a black box, we can envision situations in which the test fails or produces erroneous results, and the patient perishes while we are working with the company to determine the route cause. Very few IVD next generation sequencing tests are available on the market. Those tests are expensive and can be overly expansive, yet not covering the pertinent biomarkers or covering at the necessary depth to pick up all clones. **We have a rapid NGS panel, which is used in cases of acute leukemias. This panel has resulted in correctly identifying key biomarkers for therapeutic decision making, which is necessary to do prior to decision on chemotherapy regimens. We have given the diagnosis prior to even a sample being received by send out laboratories. Our clinicians find it imperative to be able to converse with our team to rush a sample through processing, which does not occur in cases of send out.** Our MPN screening

panel has detected results for BCR-ABL1, JAK2, CALR and MPL even when it was unexpected. By running all these biomarkers on one test, we are efficient and able to diagnosis without step-wise testing. Lymphoid malignancies are newly being clinically sequenced to a high scale. Because of this, publications are routinely being released with new insights (e.g. biomarkers for therapy, diagnosis, and resistance mechanisms). By allowing for LDTs, laboratories can more quickly adjust to these new discoveries instead of waiting for a company to design a new panel.

Shaun Yang, PhD, D(ABMM), MLS(ASCP), Director, Molecular Microbiology and Pathogen Genomics (MMPG) Laboratory Associate Medical Director, Clinical Microbiology Laboratory Associate Clinical Professor UCLA Health California

The rule as proposed by the FDA and the use of the medical device regulatory pathway would have significant and negative consequences for infectious disease testing. The rule does not take into account the practical realities of how these important diagnostics are used when caring for patients and will result in harm by reducing access to high quality infectious disease testing for many populations.

Please consider the following:

• **There are infectious disease tests for patients with conditions for which there are no commercial equivalents, or where an FDA approved assay must be modified to serve a patient population**. For example, we developed and validated next-generation sequencing (NGS)-based bacterial and fungal species identification test to identify clinical isolates that are not able to be identified by conventional methods or any FDA-approved assays. **Our institution serves many immunocompromised patients who are prone to infections caused by unusual or emerging pathogens that are often challenging to identify. Not having these laboratory-developed molecular tests will make these patients lose the access to the only available tests that can precisely identify the exact cause of their infections, and thus severely harm the patients.**

• **Over-regulating LDTs hinders our response to outbreaks. During the 2022 Mpox outbreak, LDTs are the first available tests for an emerging infectious disease and are central to outbreak responses.** Our laboratory developed and validated rectal swab as one of the acceptable sample type and used it to diagnose a patient with Mpox infection but without any lesions, who tested only positive in the rectal swab by our LDT https://pubmed.ncbi.nlm.nih.gov/37866092/. **Taking away the option of LDTs will adversely affect clinical laboratories' capability to choose the medically appropriate sample types for timely diagnosis and exacerbate the outbreak.**

• **Many infectious diseases already disproportionately impact minority communities, low-income people and other vulnerable populations. Limiting access to testing will worsen these disparities.** For example, patients of immigrants from the endemic areas turned to get hypervirulent Klebsiella pneumoniae (hvKp) infections, which is hard to diagnose. Our laboratory developed and validated an LDT to identify hvKp https://pubmed.ncbi.nlm.nih.gov/36312975/ and helped a patient emigrated from Mexico who suffered a hvKp uterine abscess that mimicked ovarian tumor: https://pubmed.ncbi.nlm.nih.gov/35899277/ . In another example, our laboratory's whole-genome sequencing based MTB drug susceptibility test helped optimize the treatment for a patient emigrated from India who was initially treated with toxic second-line and third-line drugs due to erroneous phenotypic drug susceptibility results:

https://pubmed.ncbi.nlm.nih.gov/34745885/. In another example, Mycobacterium abscessus particularly affects transplant patients and cystic fibrosis (CF) patients, and is notoriously resistant to anti-microbial drugs, causing high mortality. Our laboratory developed and validated a cutting-edge whole-genome sequencing based test for clarithromycin and amikacin resistance prediction and subspecies identification of Mycobacterium abscessus https://pubmed.ncbi.nlm.nih.gov/34454109/, and showed its clinical utility in guiding treatment in a CF patient with chronic M. abscessus infection https://pubmed.ncbi.nlm.nih.gov/35369567/.

Holli M. Mason, MD Director, Pathology and Clinical Laboratories, LA County DHS Harbor-UCLA MC and Olive View-UCLA MC (lab director) Los Angeles, CA

A recent survey of ASM members highlighted that clinical microbiology laboratories rely heavily on LDTs for improving patient care. **Over 90% of labs, including academic medical centers, community hospitals, reference laboratories, public health laboratories and consolidated laboratories use LDTs and over 80% have noted that they would consider discontinuing most LDTs if this proposed rule passes. By requiring all tests to go through a costly, pre-market review process initially designed for commercial entities, the rule will have the unintended effect of causing microbiology laboratories operating on a thin financial margin to cease offering many tests, which will reduce access for some of the most vulnerable populations in the U.S., including minorities, children and rural communities.** This rule will have a significant impact on our clinical microbiology laboratory for these reasons. Instead of proceeding with the regulatory pathway as proposed, **we urge you to first collect additional data through registration and severe adverse event reporting.** Registration, listing, and reporting requirements should be streamlined and account for the very limited human and financial resources of clinical microbiology laboratories, most of which are in not-for-profit entities and located in academic medical centers and community hospitals. **After attaining a more accurate and comprehensive picture of the LDT landscape, the FDA in conjunction with stakeholders and the public will be able to determine a more effective, data driven approach to regulation of these tests than the one outlined in this proposed rule.** We believe that a risk-based approach that maintains enforcement discretion for low-risk tests will be feasible and allow clinical microbiology laboratories to continue to serve the most vulnerable communities.

David N. Bailey, M.D. Distinguished Professor of Pathology and Pharmacy Emeritus, Vice Chair for Education and Academic Affairs, Deputy Dean of the Skaggs School of Pharmacy & Pharmaceutical Sciences University of California San Diego

The FDA proposed rule to regulate laboratory developed tests (LDTs) would be devastating to our central laboratories, which develop and provide diagnostic testing in the area of molecular genetics, molecular microbiology, and molecular virology. We would be forced to send tests out to reference laboratories as great expense to our patients and with delays in test turnaround time as a result. This would impact patient care severely!

Colorado

Mark Brissette, M.D. University of Colorado Anschutz Medical Center Colorado

Laboratory developed tests (LDTs) are essential for modern medical care. Lab accreditation agencies (such as the College of American Pathologists) already have stringent standards for LDTs. **Excessive federal regulation will stifle innovation, slow down laboratory responses to new diseases and cancer, and impact patient care negatively**.

Dr. Kurtis Davies - Assistant Professor University of Colorado Colorado

The United States has been the unequivocal worldwide leader in precision medicine advancements. This field, which has dramatically improved the care of millions of patients, absolutely relies upon a dynamic molecular testing environment that can rapidly adapt to scientific advancements. This proposed excessive regulation of LDTs would irreversibly stymie medical advancements in this country, removing the US as the worldwide torchbearer, and ultimately harm patient care.

Dan Merrick, MD University of Colorado Colorado

Our LDTs provide diagnostic tools for a variety of unique tissue sources and in a variety of disease processes. LDTs greatly expand the benefit we can provide for patients with serious diseases.

Connecticut

Chen Liu Yale University School of Medicine New Haven, Connecticut

As an academic pathology department, our primary missions encompass delivering exemplary patient care, conducting innovative research, and educating the next generation of pathologists and clinical laboratory professionals. Integral to achieving these objectives is our ability to develop and utilize Laboratory Developed Tests (LDTs). These tests - **LDTs are essential for accurate and timely patient diagnoses, advancing personalized medicine, and offering valuable educational experiences for our trainees. The proposed FDA regulations** on LDTs raise significant concerns for us. They **threaten to curtail our capacity to develop these critical diagnostic tools by imposing stringent and potentially burdensome requirements. Such constraints could delay essential medical advancements and restrict our educational programs.**

David Rimm MD-PhD, Anthony N. Brady Professor of Pathology Yale University School of Medicine Connecticut

College of American Pathologists oversight, including checklists and surveys for CAP/CLIA lab accreditation do a better job monitoring LDTs than could ever be done by the FDA.

Florida

Theresa Boyle, Director Molecular Solid Tumor Moffitt Cancer Center Florida

As an NCI-designated cancer center, we play a vital role in offering a diverse range of molecular diagnostic tests or procedures, many of which are tailored to the specific needs of the patient population we serve. Almost all of them are laboratory developed tests or procedures that encompass a series of processes coupled with professional services, that are

managed with extensive in-laboratory quality control processes. We routinely test thousands of cancers each year with the results interpreted and reported internally by our faculty member molecular pathologists (MD, PhDs) and precision medicine teams (PharmDs) in coordination with our anatomic pathologists and clinicians. The results guide diagnoses, therapies and clinical trial matching. The proposal to end the FDA policy of enforcement discretion for LDT's will shut down both our routine and our innovative molecular testing at Moffitt, such as our philanthropy-funded pre-screening test for clinical trial matching, which we invested years of time to validate and launch to improve patient care. This proposal will likely lead to an exodus of molecular professionals that serve patients at cancer centers and academic centers to industrial corporations that can afford the FDA price tag for generic limited assays that are too expensive to update. Patient samples, data, and molecular pathology expertise will then reside at corporations instead of at cancer centers and academic centers with limited communication about the results to the physicians caring for the patients and minimal incentive for innovation.

Merce Jorda, MD, PhD, MBA Chair of Pathology & Laboratory Medicine University of Miami Miller School of Medicine Miami, Florida [redacted]

The University of Miami Health System, like many other academic medical centers, has greater than 100 tests currently offered which would be classified as an LDT under the FDA proposed rule change. These LDT's including modified FDA approved assays, assays for therapeutic drug monitoring, toxicology, immunohistochemistry, cytogenetic analysis, next generation sequencing with RNA and DNA mutation evaluation, new emerging pathogens, and coagulation assays, were developed and implemented by our Pathologists and Laboratory professionals in order to addressunmet clinical needs. These tests – **"LDTs" are essential in making determinations in routine and complex cases, where this information is required to construct an appropriate treatment plan. If allowed to be enacted, the current FDA proposal would make it impossible for our health systems to maintain our existing testing menu by creating not only an impossible financial strain, but also an undue staffing burden on an already depleted workforce to complete FDA filings. The removal of these tests, many of which have no FDA approved equivalent, would result in a lower quality of laboratory services and presents an immediate safety risk to patients.**

Illinois

Sally Campbell Lee, MD Interim Head, Department of Pathology University of Illinois at Chicago Chicago, Illinois

The practice of Pathology is focused on patient safety. **If the proposed FDA rule for regulation of LDTs is implemented, there will be a significant risk for harm to patients who receive treatment at academic medical centers. Academic medical centers house the majority of the 72 NCI designated Cancer Centers, which deliver cutting edge therapy that often requires LDTs.** The proposed rules will negatively impact testing ranging from genomic testing for cancer diagnosis to microbiology testing for immunocompromised cancer patients.

Iowa

Nitin Karandikar, MD, PhD Professor and Chair of Pathology University of Iowa Iowa City, Iowa

As the only academic medical center in the state of Iowa, we have a huge responsibility to provide access to ground-breaking care to the people of Iowa and beyond. A big part of this is the ability to develop and validate cutting-edge laboratory testing whose results would determine the management of our patients. We offer a large number of LDTs that are required for patient care. **The FDA rule to regulate these tests would create significant burdens on academic labs (that are already stressed in terms of budgets and staffing).** There would be negative impacts on the effectiveness, efficiency and timeliness of testing and resultant patient care.

Kentucky

Eyas M Hattab, MD, MBA AJ Miller Professor and Chair University if Louisville KY

For decades, academic medical centers' laboratories have served as the bedrock for our nation's healthcare system providing innovative and affordable care to the sickest of patients. **If the FDA's proposed rule is adopted, it will greatly interfere with our ability to deliver what is considered the standard of care in the diagnosis of cancer and other diseases. It will inflict undue burden on our ability to provide timely, accurate and affordable laboratory testing, further inflate our healthcare costs and drive our labor challenges to the brink of collapse.**

Massachusetts

Vijay Vanguri MD, Associate Professor and Vice Chair of Pathology UMass Chan Medical School / UMass Memorial Health Care Massachusetts

Our pathology laboratory provides stellar care for patients in central Massachusetts with better diagnostic yield, faster turnaround time, and lower cost than commercial assays because of well-designed laboratory-developed tests (LDTs). These bureaucratic changes will slow development, restrict innovation, and increase the cost burden on our medium-sized academic medical center.

Missouri

Midhat Farooqi, Director of Molecular Oncology Children's Mercy Hospital, Kansas City Missouri

I am a board-certified clinical pathologist and molecular pathologist. **I perform genetic testing, plus interpret genetic test results, for pediatric patients with cancer each and every day. This involves looking at the tumor sample from patients for genetic variants that critically affect cancer diagnosis, prognosis, and therapy, as well as a patient's normal sample to look for hereditary cancer predisposition risk. This is crucial, not just for the patient, but also their siblings and family. There is no FDA-approved test, not a single one, to do this comprehensively for a child with cancer. As a physician, I can attest that this proposed (and misguided!) FDA regulation would significantly harm patient care.**

Midhat Farooqi, Director of Molecular Oncology Children's Mercy Hospital, Kansas City Missouri

Last year, we developed and launched paired tumor-normal genetic sequencing as an LDT designed specifically for children with cancer. We did so because no such FDA-approved test currently exists for kids and knowing whether certain mutations are present in tumor cells can help guide pediatric cancer diagnosis, prognosis, and therapy. Our LDT also evaluates for inherited predisposition to cancer by looking for genetic mutations in a child's normal cells. Thus, it **helps the 200 kids who are newly diagnosed with cancer by our hospital each year. If this test was removed from our lab, it would prevent children with cancer from receiving leading-edge precision medicine.**

New York

Eldad Hod, MD Vice Chair and Director of Laboratory Medicine Columbia University Medical Center New York, NY

Our clinical laboratories would not be able to afford premarket review and would be forced to discontinue LDT testing, preventing us from taking care of the special populations we serve at our large academic medical center serving a predominantly underserved population. We also believe patients in rural and other underserved areas will be disproportionately affected by this regulatory change and that this will exacerbate health disparities. We disagree with the premise that the need for the rule exists and support modernization of existing CLIA regulations to address test performance as a more cost effective and efficient way of addressing any quality concerns with LDTs.

Christa Whitney-Miller, MD Chair, Dept of Pathology & Lab Medicine University of Rochester School of Medicine & Dentistry Rochester, NY

We estimate 50-75 of the tests our labs are permitted to perform (roughly 5% of our testing volume) would be considered LDTs under the FDA's proposed rule. **If the rule is finalized as proposed, UR Medicine would have to scale back its laboratory services, which would have a detrimental impact on the tests we use to diagnose disease and determine the right course of treatment for our patients, improve outcomes, and advance the next generation of personalized care. We ask the following be considered: Consider New York State as a model for LDT regulation; the Unique characteristics of academic medical centers; grandfather existing tests**.

Kenneth Shroyer, MD, PhD Professor and Chair, Department of Pathology Stony Brook UniversityStony Brook, NY

The clinical laboratorians of Stony Brook University strongly urge the FDA to delay the implementation of the October 3, 2023 proposed rule to regulate LDTs as Medical Devices, in order to better articulate the process of implementation and LDT approval pathways, and for academic medical centers to better prepare their healthcare ecosystems for the significant impact such a rule will undoubtedly have.

Jonas Heymann, M.D.New York-Presbyterian Hospital-Weill Cornell Medicine New York

Our molecular laboratories rely on LDT's, interpreted by Board- and New York State certified academic pathologists to provide our patients with high quality comprehensive cancer care with rapid turnaround time, competitive pricing, integration into the electronic medical record. We do not have the resources to comply with additional FDA regulations. Our patients will be forced to rely on expensive tests from commercial laboratories staffed by pathologists with less (and sometimes no) academic experience.

North Carolina

Russell Broaddus, MD,PhD Distinguished Professor and Chair University of North Carolina School of Medicine - Chapel Hill Chapel Hill, NC

Academic pathology clinical diagnostic laboratories have a documented history of stepping up with the development of novel LDTs that help large patient populations. Because the hospital we support with our testing is a safety net hospital for the entire state, our lab will never have the staffing required to support seeking FDA approval of these LDTs.

Ohio

Jennifer Baccon, MD, PhD, MHCM Chair of Pathology and Laboratory Medicine Akron Children's Hospital Akron, OH

The proposed rule from the FDA regarding LDTs will negatively impact patient care. The core intent of the FDA is to protect patients and ensure high quality laboratory testing. **Unfortunately,** the proposed rule will do the opposite; if implemented, **the rule will make care more costly, laboratory tests will be less accessible, and test results will be less timely**. The laboratories in academic medical centers and community hospitals across our country are run by trained laboratorians, physicians and PhD scientists with deep expertise in developing and providing laboratory testing. **Our existing regulatory framework through the Clinical Laboratory Improvement Amendments currently ensure that certified laboratories are providing quality testing. The proposed rule would stifle innovation, take away the ability of the ones who know the most about laboratory tests to provide care in their hospitals, and levy an immense cost of additional regulation to society; a cost that in most cases will be too large to sustain.**

Nives Zimmermann, M.D., Associate professor of pathology and laboratory medicine University of Cincinnati Ohio

As a physician practicing pathology and laboratory medicine at an academic medical center, I have serious concerns with the proposed regulation of laboratory-developed tests (LDTs) and its likely negative impact on access to tests and innovation in testing.

LDTs are currently used by laboratories for a variety of reasons. LDTs are utilized when no FDA-approved assay is available for a given analyte or condition. **At UC Health there are nearly 50 LDTs that provide thousands of results every month. Some examples include Mycobacterium tuberculosis testing in lower respiratory tract specimens, fentanyl screening, mass**

spectrometry for immunosuppressant drug level monitoring, flow cytometry for malignant cell diagnosis or characterization, tissue characterization by immunohistochemistry, next generation sequencing of solid tumors and body fluid testing including total protein and albumin. Offering this testing in-house significantly reduces test turnaround time, allowing patient treatment to be optimized more rapidly. The FDA's propose rule does not adequately address the number of LDTs that would fall into this category, and therefore, does not provide a realistic plan or budget for regulating LDTs.

Academic medical center-based clinical labs are unique in several aspects. First of all, we serve a broad population of patients, ranging from common diseases to rare disorders. **It is testing for these rare diseases that would be particularly vulnerable if proposed regulation is implemented because these tests are in general not profitable, are thus usually only available in academic labs, and we don't have the venture capital and other funds to take on the burden of extra work that would be required. While each rare disease is rare, please keep in mind that rare diseases as a group affect an estimated 25-30 million Americans** (rarediseases.info.nih.gov). Importantly, **patients with rare diseases already suffer from delayed diagnosis, and barriers to testing would only worsen this impact.**

In summary, the proposed FDA regulation of LDTs as medical devices will seriously hamper the ability of laboratories to offer critical testing to the patients they serve. While some rare LDTs lack clinical validity, most that are in use play a critical and irreplaceable role in patient care, and many have been used for years and are supported by significant scientific literature.

Dani Zander, MD Mackenzie Professor and Chair, Dept. of Pathology and Laboratory Medicine University of Cincinnati College of Medicine/UC Health Cincinnati, OH

The proposed FDA regulation of LDTs as medical devices will seriously hamper the ability of laboratories to offer critical testing to the patients they serve. **While some rare LDTs lack clinical validity, most that are in use play a critical and irreplaceable role in patient care, and many have been used for years and are supported by significant scientific literature. Modernization of CLIA'88 is an alternative route that would use the robust system already in place for regulating laboratories to strengthen LDT oversight without adversely impacting patient access to necessary testing**.

Pennsylvania

Paul Edelstein, Emeritus Professor Perelman School of Medicine, University of Pennsylvania

We had to develop and use LDTs to provide testing that was critical for our immunocompromised patients that was not available in a FDA-cleared test. This included sensitive molecular testing for Legionnaires' disease, rapid identification of fungi and other bacteria, and rapid identification of mycobacteria that included markers of drug resistance. Each test underwent extensive validation per CLIA, taking anywhere from six months to a year to determine that it worked correctly before being used on patients. These LDTs are superior to newer FDA-cleared tests. Limiting LDTs by imposing ponderous and sometime inexpert review by FDA will limit innovative leading-edge medical testing and care, apart from requiring a vast

increase in FDA funding. There is a world of difference between commercial testing using poorly validated methods and LDTs designed to help patients in an academic medical center laboratory.

Rhode Island

Eleanor Lewin, MD Providence VAMC (not speaking on its behalf) Rhode Island

This restriction will harm patients by delaying or prohibiting testing and will not have significant benefit.

Texas

R. Prasad Koduru UT Southwesstern Medical Center Texas

Without LTD innovations or developing new diagnostic tests from the new scientific knowledge is not possible, and it will put US way behind even the developing/underdeveloped countries in providing state of the art testing to our patients.

Utah

Peter Jensen, MD Professor and Chair University of Utah Salt Lake City, Utah

University of Utah Department of Pathology provides clinical laboratory services to the University of Utah Health system. We also provide national testing services through ARUP Laboratories, an enterprise of our department and the nation's largest nonprofit clinical reference laboratory with customer hospital laboratories in all 50 states. **With over 100 faculty, 20 pathology residents, and 30 clinical fellows, our department is focused on providing outstanding clinical service, education, and research across all aspects of pathology and laboratory medicine. As such, test development is essential to the care we provide and the overall advancement of medicine in the U.S. The FDA's proposed rule would have a profoundly negative impact on patient care and diagnostic innovation across clinical laboratories and health systems.** As a department, we support the previous comments and concerns submitted by ARUP Laboratories during the public comment period on the proposed rule (https://www.regulations.gov/comment/FDA-2023-N-2177-5561). **We urge the FDA to withdraw its proposed rule and to engage more closely with the clinical laboratory community in considering a future regulatory framework that supports the provision of clinical laboratory diagnostics in the practice of laboratory medicine**.

Vermont

Debra G.B. Leonard, M.D., Ph.D. Chair and Professor, Department of Pathology and Laboratory Medicine University of Vermont Health Network; Robert Larner, M.D. College of Medicine at The University of Vermont Burlington, VT

This rule, as written, would be among the largest shifts in regulation for clinical laboratory testing, particularly for Laboratory Developed Tests (LDTs). **This prosed rule would have dramatic negative consequences on patients' access to high-quality testing and create a significant financial burden to most laboratories. This financial burden will subsequently impact the cost of testing, or even decrease the availability of testing when laboratories choose to stop performing testing due to the increased regulatory burden, and further limit patient access to affordable care.**

Virginia

Christopher Moskaluk MD, PhD Chair of Pathology, CLIA Director of Medical LaboratoriesUniversity of Virginia Charlottesville, VA

The proposed rule will significantly impact our patient care and laboratories' operations such that our patients will no longer have access to essential, high quality in-house testing, including patients in need of immediate test results for their care. The increased regulatory burden and associated expense of FDA oversight of the hundred LDTs we offer will make it untenable for us to continue to offer/develop such tests. Many of these tests already run at a financial loss to the institution given they are tailored for a small number of affected individuals or are administered infrequently. As a result, our patients, whether they are seeking treatment at our institution because of our specialized expertise (cancer, pediatrics, transplantation, infectious diseases, etc) or in need of emergency or routine care, **could suffer missed or delayed diagnoses and result in worse patient outcomes.**

Washington

Daniel E Sabath, MD, PhD, Professor, Laboratory Director University of Washington

Our laboratory-developed tests allow our patients to benefit from the latest scientific discoveries in precision medicine. If we did not provide this service, our patients would not have access to the state-of-the-art care they expect and deserve.

Wisconsin

Alana Sterkel, Associate Director of Communicable Diseases Wisconsin State Laboratory of Hygiene Wisconsin

Erik Ranheim MD PhD Professor and Chair University of Wisconsin School of Medicine and Public Health Madison, WI

LDTs in academic medical centers are currently subject to extensive internal and external validation and review. **Requiring FDA validation for our existing LDTs would deeply strain an already challenging workforce and fiscal situation. Simply put, we will not be a able to provide high quality laboratory diagnostics to our patients if this additional and unnecessary regulatory burden is placed on our labs and will not be able to respond to COVID-19 like crises in an effective manner.**

March 21, 2024

The Honorable Cathy McMorris Rodgers
Chair, Energy and Commerce Committee
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Brett Guthrie
Chair, Subcommittee on Health
Energy and Commerce Committee
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

RE: Subcommittee Hearing: "Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule"

Dear Chair Rodgers and Chair Guthrie,

On behalf of the LUNGevity Foundation, we appreciate the opportunity to submit comments into the record for the Subcommittee on Health hearing entitled "Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule."

Attached are our comments submitted to the FDA Commissioner in response to the Agency's proposed rule on regulatory oversight of laboratory-developed tests, or LDTs (Docket No. FDA-2023-N-2177). Therein, we outline our concerns on certain aspects of the proposed rule and reiterate our preference for a legislative approach to LDT oversight, such as the Verifying Accurate, Leading-edge IVCT Development (VALID) Act.

Please feel free to contact me at [redacted] with any questions.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
LUNGevity Foundation

December 1, 2023

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

RE: Medical Devices; Laboratory Developed Tests, Docket No. FDA-2023-N-2177

Dear Commissioner Califf,

On behalf of the LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each year[i] and over 600,000 Americans living with the disease,[ii] we appreciate the opportunity to submit comments in response to the proposed rule: Medical Devices; Laboratory Developed Tests, Docket No. FDA-2023-N-2177. LUNGevity submits these comments specifically from the perspective of patients with lung cancer, for whom the accuracy and reliability of diagnostic tests used to direct their treatment is of paramount importance.

Treatment of lung cancer is at the leading edge of precision medicine, with several biomarker-driven treatment options. Approximately fifty percent of patients with non-small cell lung cancer (NSCLC, the most common type of lung cancer) harbor a biomarker with a corresponding FDA-approved targeted therapy.[iii] Targeted therapies are typically linked to FDA-approved companion diagnostics: tests used to identify patients most likely to benefit from that particular treatment. However, the one-drug-one-test paradigm is not reflective of real-world clinical practice, where in-house, multi-analyte laboratory-developed tests (LDTs) are frequently used to direct treatment decisions.

Since the regulatory framework for medical devices was established under the Medical Device Amendments of 1976, the FDA has exercised enforcement discretion regarding LDTs. Over the past decade the Agency has made several moves to bring LDTs under its oversight, recognizing that the number, complexity, and breadth of use of LDTs has increased dramatically since it began its policy of enforcement discretion. In addition to issuing guidance documents and a discussion paper, FDA most recently worked with Congress and engaged with stakeholders, including patient advocates, to develop legislation which created a framework specifically for LDT (or in vitro clinical test (IVCT)) regulation. Despite enjoying support from many in the diagnostics community, this legislative approach to ensuring FDA oversight of LDTs stalled and the Agency has now moved forward with notice-and-comment rulemaking to end enforcement discretion for LDTs.

While LUNGevity understands FDA's rationale for pursuing this course of action, **we support an approach to LDT oversight that balances the dual priorities of patient safety and continued innovation in test development and question whether the current medical device regulatory framework is suited for that purpose**. Herein we lay out concerns that should be addressed in the final rule and/or through subsequent guidance.

Regulation of LDTs should not hinder patient access to accurate, reliable biomarker tests

In lung cancer, where biomarker testing is necessary for determining the most appropriate treatment option, LDTs are frequently used for biomarker detection even when FDA-approved tests exist.[iv,v] The Agency should carefully consider whether the proposed timeframe for phasing out enforcement discretion is adequate for clinical laboratories to prepare application packages for all of the tests they offer, and if submission for **all** tests is necessary. Clinical labs may not have sufficient staff or regulatory expertise to fulfill the proposed new regulatory requirements. If the fees, resource demands, and timelines are prohibitive, labs may cease offering high-quality lung cancer biomarker tests because of onerous requirements, to the ultimate detriment of patients.

In addition to the economic and administrative burdens the proposed rule may place on test developers, we are concerned about the FDA's capacity to review the number of applications it expects to receive in a timely manner. It may be necessary to increase the duration of the phase-out period for enforcement discretion for premarket review, and/or to consider grandfathering of certain LDTs, to ease the burden on both the Agency and labs and ensure the rule does not disrupt patients' access to accurate biomarker testing. **We suggest that the FDA allow grandfathering for existing LDTs that have demonstrated concordance with FDA-approved companion diagnostics** (see, for example, Torlakovic et al.[vi])

Regulation of LDTs should incorporate flexibilities for test modifications

As diagnostic tests often require modification to improve performance and address changing clinical needs, **we encourage the FDA to provide opportunities for developers to make certain modifications to diagnostic tests without unnecessary regulatory hurdles**. The FDA has previously expressed openness to the submission of prospective change protocols, wherein test developers outline anticipated modifications and the procedures they would use to implement them.[vii,viii] If approved, modifications made in accordance with the change protocol would not require a new submission, with only changes significantly altering the intended use or performance specifications requiring review. Change protocols or similar mechanisms allowing flexibilities for modifications should be included and detailed by the Agency in future guidance.

LUNGevity supports a legislative approach to LDT regulation reform

We believe that a legislative solution to diagnostics reform could strike a better balance between promoting patient safety and ensuring regulatory flexibilities for both test developers and the FDA than the proposed rule does. Furthermore, legislation can clarify and codify that FDA has both the authorities and resources necessary to effectively oversee the development and marketing of diagnostic tests.

For example, LUNGevity supported the Verifying Accurate, Leading-edge IVCT Development (VALID) Act of 2022, which established a new category of products (i.e., IVCTs) encompassing all *in vitro* diagnostics, including LDTs, along with a new, fit-for-purpose regulatory framework. Additionally, VALID outlined flexible pathways for marketing diagnostic tests, such as technology certification, to accelerate the delivery of innovative diagnostics to patients without unnecessary regulatory hurdles. Incorporating these kinds of innovations—which would improve the ability of test developers to keep pace with scientific advancements—into current regulations is only possible through legislation as it would require Congressional approval.

In addition to supporting the bill itself, we appreciated the extensive engagement among various stakeholders involved in shaping VALID. **LUNGevity encourages FDA to continue engaging with all stakeholders in the diagnostics community to pursue a legislative option for regulation of LDTs in parallel with rulemaking.**

We appreciate the opportunity to provide these comments in response to the Agency's proposed rule. Please feel free to reach me at [redacted] or at [redacted] with any questions.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
LUNGevity Foundation

---

[i] Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.
[ii] Centers for Disease Control and Prevention. United States Cancer Statistics. Available at https://gis.cdc.gov/Cancer/USCS/#/Prevalence/.
[iii] Thai AA, Solomon BJ, Sequist LV, et al. Lung cancer. *Lancet* 2021; 398(10299):535-554.
[iv] Audibert C, Shea M, Glass D, et al. Use of FDA-approved vs. lab-developed tests in advanced non-small cell lung cancer. *Journal of Clinical Oncology* 2016: 34(15) suppl.
[v] Mino-Kenudson M, Stang NL, Daigneault JB et al. The International Association for the Study of Lung Cancer Global Survey on Programmed Death-Ligand 1 Testing for NSCLC. *Journal of Thoracic Oncology* 2021; 16(4):686-696.
[vi] Torlakovic E, Lim HJ, Adam J, et al. ""Interchangeability" of PD-L1 immunohistochemistry assays: a meta-analysis of diagnostic accuracy. *Modern Pathology* 2020; 33(1):4-17.
[vii] U.S. Food and Drug Administration. Discussion Paper on Laboratory Developed Tests (LDTs). 2017 Jan 13. Available at https://www.fda.gov/media/102367/download.
[viii] U.S. Food and Drug Administration. Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI.ML)-Enabled Device Software Functions: Draft Guidance for Industry and Food and Drug Administration Staff. 2023 Apr. Available at https://www.fda.gov/media/166704/download.

8260 Greensboro Drive Suite A-30 McLean, VA 22102 | 571.418.4824

Written Comments of Oral Alpan, MD

House Energy & Commerce Committee, Subcommittee on Health

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

Thursday, March 21, 2024
10:00 a.m. ET

Chair Cathy McMorris Rodgers, Chair Brett Guthrie, Ranking Member Frank Pallone, and Ranking Member Anna Eshoo, thank you for accepting my comments on the Food and Drug Administration's (FDA) proposed rule to regulate Laboratory Developed Test procedures.

We have a very serious issue at hand. The proposed FDA rule on the regulation of Laboratory Developed Tests (LDTs) will undoubtedly impact patient care. However, a key group of stakeholders most affected by this change are notably absent from the discussion: the treating physicians, especially those with specialized in-office laboratories. Modern medical practice relies heavily on the development of LDTs tailored to specific patient needs for diagnosis and treatment. There are numerous medical practices around the country, across many specialties; immunology, cardiology, otolaryngology, internal medicine, obstetrics and gynecology, and countless others, that has incorporated specialized diagnostics in patient care. I have spoken to many of them, and none of their voices have been heard. These are practitioners that any American can make an appointment to see to get help for their medical problems. With the proposed FDA regulations such care will come to an end. No medical practice in the country can afford the millions of dollars that require FDA approval. These medical practices, along with American citizens will be collateral damage to a power struggle between government agencies and big business. This will affect many lives.

As a board-certified clinical immunologist in Northern Virginia with nearly three decades of experience, trained at the National Institute of Allergy and Infectious Diseases, I serve the Washington D.C./Maryland/Northern Virginia metropolitan area. My practice, Amerimmune, with eight locations, is the largest provider of clinical immunology services in terms of geographic coverage and patient volume in the Washington metropolitan area. Amerimmune is

also the designated referral center for the confirmation of newborn screening for Severe Combined Immunodeficiency in Virginia through our in-office laboratory. Thirteen years ago, we established this laboratory to meet the unmet need for LDTs, which were previously unavailable in Virginia. These LDTs, vital to patient care, have evolved with our growing patient population's diagnostic and therapeutic needs. Such tests, not provided by large national laboratories, are critical for ongoing care. The absence of these LDTs would halt patient care in my practice which serves thousands of patients. The LDTs are part of the medical care provided to patients in my medical practice, Amerimmune. They serve to diagnose conditions that range from severe immune compromise in babies to life threatening food allergies in teenagers.

With thousands of patients under my practices care, the potential FDA regulation raises concerns about patient safety and the continuity of care. My practice, like many across the country with in-office laboratories providing similar services, lacks the resources and funds to undergo FDA approval processes.

We are not a national corporation with billions of dollars; we are a physician practice fully trained, licensed and certified to do the tests our patients need. We cannot hire a phalanx of regulatory experts to meet the FDA rule, which treats lab testing – the practice of medicine – as if it were a device. Frankly, it is unlikely that the FDA will be able to hire enough people because they will be competing with the largest national labs.

I implore your committee and Congress to exert all efforts to prevent this FDA action, as it would inflict irreparable damage on practices like mine, affecting not only business operations but, crucially, patient care and health. The FDA itself notes in the proposal that, "the proposed rule is likely to have a significant economic impact on a substantial number of small laboratories that manufacture IVDs offered as LDTs. The agency fails to acknowledge the existence of in-office physician laboratories as well as that a significant impact on practices like mine also entail a significant impact on the patients we serve. I urge Congress to collaborate with the structure of CLIA and other regulatory bodies such as College of American Pathologists (CAP) to modernize the LDT landscape

Regards,

Oral Alpan, M.D.
CEO,
Amerimmune
[redacted]
www.amerimmune.com

U.S. House of Representatives
Energy & Commerce Committee
Subcommittee on Health

Hearing:
Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule

March 21, 2024

Statement for the Record
American Academy of Dermatology Association

Chairman Guthrie and Ranking Member Eshoo, on behalf of the more than 17,000 U.S. members of the American Academy of Dermatology Association (Academy), thank you for the opportunity to submit a Statement for the Record in response to your hearing, *Evaluating Approaches to Diagnostic Test Regulation and the Impact on FDA's Proposed Rule* held on March 21, 2024. As the leading society in dermatological care, the Academy is committed to excellence in the medical and surgical treatment of skin diseases; advocating for high standards of clinical practice, education, and research in dermatology and dermatopathology; and driving continuous improvement in patient care and outcomes while reducing the burden of disease.

The Academy appreciates the Health Subcommittee examining the FDA's proposed rule, Medical Devices; Laboratory Developed Tests [Docket No. FDA-2-23-N-2127], which would amend regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug and Cosmetic Act, including when the manufacturer of the IVD is a laboratory, and phase out its general enforcement discretion approach for laboratory developed tests (LDTs). The Academy appreciates the FDA's efforts to update, clarify, and strengthen regulations to improve the safety and effectiveness of IVDs, but we have some concerns.

CORRESPONDENCE
PO Box 1968
Des Plaines, IL 60017-1968
EMAIL: mrc@aad.org
WEB: aad.org

ROSEMONT, IL OFFICE
9500 W Bryn Mawr Avenue, Suite 500
Rosemont, IL 60018-5216
MAIN: (847) 330-0230
FAX: (847) 240-1859

WASHINGTON, DC OFFICE
1201 Pennsylvania Avenue, NW, Suite 540
Washington, DC 20004-2401
MAIN: (202) 842-3555
FAX: (202) 842-4355

Academic Medical Centers

While we recognize the FDA's efforts to carve out exemptions for unique circumstances regarding LDTs, we are concerned by the narrow scope by which the FDA singles out Academic Medical Centers (AMCs) for their use of LDTs in direct patient care. We agree that AMCs provide important care to patients but so do community health care delivery systems and independent laboratories. The FDA does not provide a definition of AMCs but rather defines them broadly with two of the main qualifications being 1) the laboratory must be certified under CLIA and 2) the use of the LDT is integrated into direct medical care to the patient, including specimen collection, testing, interaction with treating provider and, if necessary, patient treatment.

Dermatopathologists work in laboratories that are certified under CLIA and use LDTs to conduct immunohistochemistry (IHC) tests and cutaneous immunofluorescence testing, among others, providing direct medical care to their patients. The only identifiable difference between these locally offered LDTs and AMCs is the lack of associated residency or fellowship program. No evidence is provided indicating that AMCs' LDTs are more rigorously studied or more accurate than the locally offered LDTs tested and conducted in non-AMC, CLIA certified labs.

Additionally, locally offered LDTs that are developed by the clinical laboratory actively involved in patient care serve as a mitigating factor for the LDT's risk since the LDT is used by dermatopathologists to confirm the physicians' diagnostic hypothesis. This dialogue between dermatopathologists and physicians allows for better understanding of the strengths and weaknesses of LDTs and addresses a clinically unmet need in a timely manner. In responding to the proposed rule, the Academy urged the FDA to consider expanding their exemption beyond AMCs to include laboratories that develop LDTs in small volumes and serve their local communities, intended for use in diagnosing rare disease or other local population needs using well-characterized standard tests.

We are also concerned that this policy, if finalized, may unintentionally impact continuing medical education. For example, if a non-AMC health system has an LDT that has been submitted to or approved by the FDA it may make that entity, by definition, an ineligible company as defined by the Accreditation Council for Continuing Medical Education (ACCME). That means such an entity would be ineligible to provide accredited education or engage in joint providership. The owners or employees might not be eligible to speak at an accredited CME

program unless the content was unrelated to the test. In responding to the proposed rule, the Academy urged the FDA to collaborate with ACCME to ensure its policies do not lead to any unintended consequences.

1976 – Type LDTs

The FDA also identifies 1976 – Type LDTs as having the potential to be "grandfathered in," thus not required to go through FDA approval, but again, we are concerned by the narrow scope and manual technique requirement. IHC tests are specifically mentioned as an example, but only if they are manually done. Additionally, the FDA notes that many of today's LDTs rely on high-tech or complex instrumentation and software to generate results and clinical interpretations, are used in laboratories outside of the patient's healthcare setting and are often manufactured in high volume for large and diverse populations. However, this is not the case for IHCs used by dermatopathologists and Mohs micrographic surgeons.

IHCs are one of the most common tests performed by dermatopathologists and they play an increasing role in Mohs surgery. Almost all of them are conducted using automated staining. The automated staining process has helped access to care by streamlining the dermatopathologist's workflow and allowing dermatopathologists to make consistent diagnoses and improve patient care. In addition, for each case (e.g., IHC) quality is assured, as the dermatopathologist manually reviews the controls and the corresponding non-IHC slides before making the diagnosis. In responding to the proposed rule, the Academy urged the FDA to allow for the use of automated techniques, using components legally marketed for clinical use and performed by a dermatopathologist or Mohs surgeon, to remain under the FDA enforcement discretion policy.

Impact on Access to Care

We are concerned about the potential impact the proposed rule will have on the practice of medicine. The proposed rule has the potential to delay access to care, stymie innovation, and potentially cost lives. Additionally, requiring FDA approval for LDTs will impose a significant and potentially overwhelming administrative and financial burden on practices, specifically small or solo practices that may lack the additional resources needed to achieve compliance, and in addition will delay care.

For background, numerous dermatologists and dermatopathologists operate in small or solo practices and face daily challenges tied to reporting and documentation requirements. Further, staffing shortages, along with rising inflation and annual Medicare payment reductions, have reached a critical level, making it challenging to absorb additional costs while continuing to provide patient care.

As currently written, practices will be required to go through the FDA approval process, which requires a substantial amount of paperwork and forms along with fees, in order to continue the use of LDTs. Dermatopathologists will be required to divert valuable time and resources away from providing patient care to complete lengthy forms, thus reducing patient access to care. We are also concerned that as a result of this rule, there will be an influx of LDTs submitted for review, slowing down the approval process, thus leading to further delays in care.

Additionally, smaller practices may not be able to afford the costs necessary for FDA approval or have the staff necessary to complete the forms, therefore forcing physicians to outsource to larger companies, increasing the time spent to conducting and reviewing tests, and further delaying patient access to care. In responding to the proposed rule, the Academy urged the FDA to consider the circumstances we highlighted, including the financial constraints and administrative burdens faced by practices and the impact this will have on patient access to care.

Thank you for holding this hearing and providing the opportunity for stakeholders to submit a Statement for the Record. We appreciate your commitment to protect public health while not creating excessive burdens on physicians, especially for small practices that may lead to limited access to and delays in care.

American Cancer Society Cancer Action Network (ACS CAN) Statement for the Record

House Energy & Commerce Committee Health Subcommittee Hearing on Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule

March 21, 2024

The American Cancer Society Cancer Action Network (ACS CAN) advocates for evidence-based public policies to reduce the cancer burden for everyone. As the American Cancer Society's nonprofit, nonpartisan advocacy affiliate, ACS CAN is making cancer a top priority for public officials and candidates at the federal, state, and local levels. By engaging advocates across the country to make their voices heard, ACS CAN influences legislative and regulatory solutions that will end cancer as we know it. ACS CAN has long called for harmonizing and modernizing the regulatory framework for diagnostic tests. We commend the Committee for holding today's hearing and we appreciate the opportunity to provide a statement for the record.

Currently, diagnostic tests undergo widely different levels of oversight depending on whether they are submitted to the U.S. Food and Drug Administration (FDA) or are offered as laboratory developed tests (LDTs), which could – and has – led to the possibility of different test results depending on where the test was conducted. Cancer patients rely on accurate and clinically valid diagnostic tests to optimize their treatment options. Incorrect treatment decisions and patient harm can result if a test result is not valid. Cancer patients and their physicians should be able to trust the information produced by a diagnostic test regardless of where that test is conducted.

ACS CAN's overarching goal for diagnostic reform is to ensure that patients have confidence in the results of diagnostic tests, which have become increasingly critical in the management of cancer. We therefore support the Administration's proposal to begin that harmonization via rulemaking and have submitted comments on the Food and Drug Administration Draft Rule on Laboratory Developed Test Regulation (Docket No. FDA-2023-N-2177) which are attached to this letter. Our preference is for Congress to pass legislation to modernize and harmonize diagnostics oversight, and we have supported the Verifying Accurate, Leading-edge IVCT Development (VALID) Act as a way to achieve that reform. However, until legislation is passed, we believe that taking a regulatory approach to harmonization is appropriate. We encourage Congress to move forward with legislation and look forward to working with you.

American Cancer Society Cancer Action Network
655 15th Street, NW, Suite 503, Washington, D.C. 20005
fightcancer.org | 1.202.661.5700

December 4, 2023

The Honorable Robert Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Comments on Food and Drug Administration Draft Rule on Laboratory Developed Test Regulation (Docket No. FDA-2023-N-2177)

Dear Commissioner Califf,

On behalf of the American Cancer Society Cancer Action Network (ACS CAN), the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, thank you for the opportunity to provide feedback on the Food and Drug Administration's (FDA's) draft rule on laboratory developed test regulation (Docket No. FDA-2023-N-2177).

Cancer patients rely on accurate and clinically valid diagnostic tests to optimize their treatment options, and ACS CAN has long called for harmonizing and modernizing the regulatory framework. ACS CAN's overarching goal for diagnostic reform legislation is to ensure that patients have confidence in the results of diagnostic tests, which have become increasingly critical in the management of cancer. Currently, diagnostic tests undergo widely different oversight depending on whether they are submitted to the FDA for review or are offered as laboratory developed tests (LDTs). This difference opens the door to the possibility that test results for the same analyte may vary depending on where the test is conducted, potentially leading to incorrect treatment decisions and patient harm if a test result is not valid. Cancer patients and their physicians should be able to trust the information produced by a diagnostic test regardless of where that test is conducted.

For the past several years ACS CAN has joined with a broad coalition of stakeholders in calling for legislative reform of the diagnostics space, specifically supporting the Verifying Accurate, Leading-edge IVCT Development (VALID) Act as way to achieve that reform. Our preference is still for Congress to pass legislation to modernize and harmonize diagnostics oversight; however, we also support the Administration's proposal to begin that harmonization via rulemaking. We have focused our comments below on areas of the draft rule that are of the most importance to our organization.

Risk Classification

We strongly support the concept of a risk-based oversight framework, which focuses oversight proportionally on tests based on risk to a patient if a test result is incorrect. A large number of cancer tests would be included in the highest risk tier, and we support the greater level of review proposed.

Implementation

ACS CAN supports the phased implementation of the proposed rule, beginning with registration, listing, and adverse event reporting. We further support the prioritization of high-risk tests as the first category to be brought in for review under the new rule.

As new tests become subject to regulatory requirements, especially pre-market review, FDA will be tasked with a significantly increased workload. The timing of implementation has been designed to align with the next Medical Device User Fee Amendment (MDUFA) reauthorization with an eye toward enabling increased resources for FDA. Securing these resources will be critical to ensuring that the new rule is carried out in an efficient manner that does not hinder test development or patient access.

Conclusion

We continue to support efforts to modernize and harmonize diagnostic test oversight and believe it will not only improve care delivery in the short-term but will also ensure patients continue to benefit from emerging personalized therapies. As you work to finalize and implement the rule, we encourage you to consider our comments and ensure that the final rule ensures patient safety and confidence in diagnostic tests. We look forward to continuing to work with you. If you have any questions regarding our comments, please contact Mark Fleury [redacted]

Sincerely,

Lisa A. Lacasse, MBA
President
American Cancer Society Cancer Action Network

American Hospital Association™
Advancing Health in America

Washington, D.C. Office
800 10th Street, N.W.
Two CityCenter, Suite 400
Washington, DC 20001-4956
(202) 638-1100

Statement

of the

American Hospital Association

for the

Committee on Energy and Commerce

Subcommittee on Health

of the

U.S. House of Representatives

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

March 21, 2024

On behalf of our nearly 5,000 member hospitals, health systems and other health care organizations, our clinician partners — including more than 270,000 affiliated physicians, 2 million nurses and other caregivers — and the 43,000 health care leaders who belong to our professional membership groups, the American Hospital Association (AHA) appreciates the opportunity to comment on the impact of the Food and Drug Administration's (FDA) proposed regulation of diagnostic tests.

Many hospitals and health care systems develop and use laboratory developed tests (LDTs), particularly larger hospitals and academic medical centers. These tests are developed, validated and performed in-house by individual laboratories — they are not commercially distributed. They range from routine tests like blood counts to more complex molecular and genetic tests for cancer, heart disease, and rare and infectious diseases. LDTs provide timely patient access to accurate and high-quality testing for many conditions where a commercial test does not exist or does not meet current clinical needs. They provide physicians with important clinical information to diagnose and treat patients and are essential to the practice of medicine.

The AHA is concerned that the FDA has overreached in its proposal to regulate LDTs as medical devices. We urge Congress to exempt hospitals and health systems from being included in this FDA device framework or help ensure that regulatory oversight of LDTs is modernized in a manner that both supports medical innovation and ensures that these clinical laboratory tests remain accessible, safe and effective.

While we support the need for additional oversight of the development and use of some LDTs and in-vitro diagnostics (IVDs) offered as LDTs, the FDA's proposal to apply its device regulations to hospital and health system LDTs is misguided. These tests are not devices — they are diagnostic tools developed and used for essential patient care. Regulating LDTs under the FDA's device regulatory framework could cause patients to lose access to many critical tests and stifle innovative advances in hospital and health system laboratory medicine.

Hospital and health system LDTs benefit from the many factors that distinguish them from companies that distribute commercially marketed IVDs. These include the integration of laboratory test development and use into the continuum of patient care, the many patient safeguards that laboratories are already subject to, and the FDA's existing ability to investigate and remove any LDT or IVD from the market regardless of the entity that develops it. The AHA has urged the FDA to continue to apply its enforcement discretion to hospital and health system LDTs and defer regulation of these tests mainly to the Centers for Medicare & Medicaid Services' strict Clinical Laboratory Improvement Amendments (CLIA) oversight, the College of American Pathologists accreditation and state law.

Enforcement discretion is particularly important for low- and moderate-risk LDTs, including modifications to FDA-approved IVDs. Modifications improve the performance of approved diagnostic tests on certain patient populations, address problems or issues with FDA-approved devices, and allow the latest research and clinical knowledge to be rapidly incorporated. They are intended to improve testing accuracy and safety. If the laboratory is following the CLIA regulations and is subject to the factors described above, low- and moderate-risk tests, including modifications to commercially marketed IVDs, should be exempt from FDA regulatory oversight.

The AHA also supports continued FDA enforcement discretion for LDTs that are subject to established laboratory evaluation programs, such as that developed by New York State. Many hospital and health system laboratories participate in these evaluation programs for their rigorous validity and quality reviews and even the FDA has accredited the New York State program as a third-party reviewer on behalf of the agency for the premarket clearance process**.**

As highlighted in greater detail in our comment letter to the FDA, we are concerned that this rule — if finalized as proposed — could significantly increase hospital burden and costs and decrease the ability to provide the most effective and appropriate care to patients.

CONCLUSION

Thank you for the opportunity to provide feedback on the FDA's proposed regulation of diagnostic tests. We look forward to working with Congress on this important issue.

March 20, 2024

The Honorable Brett Guthrie
Chairman, Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member, Subcommittee on Health
Committee on Energy and Commerce
2322A Rayburn House Office Building
Washington, DC 20515

RE: Energy and Commerce Subcommittee on Health Hearing on "Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule."

Dear Chairman Guthrie and Ranking Member Eshoo:

On behalf of the American Society for Clinical Pathology's (ASCP) 100,000+ board certified pathologists, other physicians, and laboratory science professionals, I am writing to raise concern about recent proposals to increase the level of federal oversight of laboratory developed tests (LDTs), such as the U.S. Food and Drug Administration's pending Final Rule on LDTs and medical devices. ASCP's members lead the nation's efforts to diagnose and screen for diseases, such as diabetes; breast, lung, and prostate cancer; COVID and more, using laboratory developed tests and FDA-approved diagnostics. ASCP is the world's largest organization representing pathology and laboratory medicine professionals.

First and foremost, ASCP greatly appreciates Congress's interest in ensuring patient testing is accurate and reliable. As a 501(c)(3) dedicated to the needs of quality patient care, we take this mission very seriously. ASCP strongly agrees that all laboratory tests, including LDTs, should provide accurate and reliable results.

While *the overwhelming majority of LDTs have a solid track record of advancing patient care safely and effectively*, some LDTs have suffered from performance issues or may have been marketed inappropriately. Though we agree that enhancing LDT oversight could help address concerns of poorly performing LDTs, we do not agree that this requires the extraordinary level of regulatory oversight outlined in either the U. S. Food and Drug Administration's recent Proposed Rule or the Verifying Accurate Leading-edge IVCT Development Act (the "VALID" Act).

Both initiatives will create significant regulatory challenges that most hospital and academic medical center laboratories will be unable to meet. The result is that these initiatives will adversely affect patients' access to the testing they need. Quality patient care dictates that clinical laboratories should be encouraged to develop innovative testing services, not discouraged.

What are LDTs and how are they regulated?
According to the FDA, LDTs are in vitro diagnostic tests manufactured by and used within a single laboratory. This definition includes those tests fully conceived and designed in a laboratory as well as commercial, FDA-approved tests to which the laboratory has made changes.

Since the FDA gained authority to regulate laboratory tests, it has opted not to do so via enforcement discretion. ASCP is concerned, however, the public debate about LDT oversight has been impacted by misinformation suggesting that LDTs are not subject to federal oversight. In an October 22, 2023 Op-Ed, the Washington Post stated inaccurately stated that that "the federal government regulates [drugs and medical devices] for safety and efficacy, however, it does not provide similar oversight for lab-developed tests; instead the article suggested that laboratories have a "professional responsibility" to ensure their tests work. (See Opinion: How the FDA can help prevent dangerous medical diagnoses)

The truth, however, is that LDTs are closely regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. CLIA sets federal standards for the laboratory testing of human specimens for health assessment or to diagnose, prevent, or treat disease (CDC). Under CLIA, the Centers for Medicare & Medicaid Services (CMS) requires LDTs to provide evidence of the test's analytic validation (the process of determining whether a test can accurately and reliably identify a particular analyte). Clinical laboratories with LDTs may also be required by their CLIA-deemed accrediting agency[1] to provide evidence of a test's clinical validity (the process of determining whether a test can accurately identify a specific clinical condition).

In addition, CLIA requires laboratories to follow specific, extensive, and detailed quality control and quality assurance procedures to monitor the accuracy and precision of a test during the pre-analytic, analytic, and post-analytic phases of testing. Under CLIA, laboratories must demonstrate expertise in each test they offer via mandatory programs of external proficiency testing, including comparisons with peer laboratories, and sanctions (up to and including "cease test" orders) for tests that do not meet statutory proficiency standards. If laboratories are not in compliance with CLIA's standards, CMS and/or its deemed accrediting agencies are empowered to provide corrective remedies.

FDA Proposed Framework
Under the proposed rule, the FDA would expand its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. In conjunction with this

[1] Under the CLIA program, CMS may recognize accreditation agencies to assess whether the clinical laboratories that they accredit are in compliance with CLIA's requirements.

change, the FDA proposes to implement regulatory oversight over LDTs so that IVDs "manufactured" by a laboratory would generally fall under the same enforcement approach as other IVDs, except where meeting certain requirements under CLIA may be leveraged. The FDA is proposing to phase in implementation of its rule in five stages over four years, after which IVDs offered as LDTs generally would be expected to meet applicable requirements.

Why are LDTs important to patient care?
Medical laboratories develop LDTs for a variety of reasons, such as to meet an urgent patient need, identify an emerging infectious disease, or because no suitable commercial FDA-approved test is available. LDTs often frequently represent the first high-quality and effective diagnostics available for infectious diseases and public health emergencies like COVID-19. Certain cancers (including pediatric cancers), like leukemia and lymphoma, may not be diagnosable with commercial, FDA-approved tests. Monitoring of drug levels with narrow therapeutic ranges (to ensure effectiveness and prevent toxicity) in some patients with organ transplants or receiving certain antibiotics would be difficult or impossible in real time without LDTs. When timely diagnosis and treatment is essential, laboratories often rely on LDTs when no clinically appropriate, FDA-approved alternative exists.

LDTs also include commercial, FDA-approved tests that have been *modified* by the laboratory. Test modifications occur for a variety of reasons, such as (1) the test needed to be performed on a specimen type other than that originally approved by the FDA (saliva versus nasal swab), (2) the testing supplies, such as reagents, normally used for the test were not available (a frequent occurrence), (3) the test needed to be customized to the needs of the patient, or (4) the laboratory identified methods to improve the commercial test. Per CLIA, such modifications require laboratories to verify that the changes perform appropriately.

During the COVID-19 pandemic, laboratory supplies shortages were the norm and without the ability to validate alternative testing supplies, laboratory testing—and not just testing for COVID-19—would have been substantially curtailed across the United States; laboratories would not have been able to meet the needs of their patients. Under the FDA's proposal, even the most basic test modifications could require premarket clearance. This would delay treatment with unforeseen consequences. Any initiative, including the VALID Act, that requires pre-approval of test modifications would delay treatment decisions and put patient care at risk.

FDA's Review Capacity and the Scope of the LDT Market
Among our concerns with shifting regulatory oversight of LDTs from CMS to FDA is whether the Agency has the capacity do so. <u>The FDA estimates there are 40,000 to 160,000 LDTs in existence and that 50 percent would require premarket approval (Class III devices). Yet over the last few years, the FDA has averaged fewer than 100 medical devices reviews per year.</u>

Even if the Agency leveraged the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP), the Veterans Health Administration (VHA), and certain

third-party reviewers, it is hard to imagine that the Agency could meet its obligations to timely process all the applications it receives. Moreover, requiring so many new tests to seek FDA approval in such a short timespan would adversely impact the Agency's ability to review other medical devices.

The resulting bottlenecks in securing test clearance and approval would have serious repercussions for patient care. In cases where there are no FDA-approved alternatives, the implications would be particularly troubling. For example, patients with acute leukemia typically present at a late stage of disease, often as a medical emergency requiring prompt diagnosis and treatment, and they are dependent upon testing available only as LDTs. Waiting for tests to be referred to another laboratory for analysis could result in death.

Grandfathering

In the proposed rule, the Agency stated it "expects that some stakeholders will suggest that FDA continue to maintain the current general enforcement discretion approach with respect to premarket review and some or all QS requirements for currently marketed LDTs or a subset of currently marketed LDTs (i.e., what some previously referred to as ''grandfathering'')." The FDA's language here suggests that the Agency is only interested in considering "grandfathering" for those tests it classifies as either Class I or II devices. Presumably, the FDA believes that Class III, and some class II, devices in use prior to the proposed rule must undergo premarket approval. In our opinion, the proposed rule's lack of viable grandfathering does not represent the spirit of discussions ASCP and other laboratory groups had in meetings with FDA about grandfathering and other issues related to FDA's LDT oversight scheme.

ASCP supports grandfathering of all LDTs in use prior to the release of the proposed rule — including those approved by the NYSDOH CLEP or the VHA (including Class III). In addition, ASCP believes that the Agency should allow modifications of "grandfathered" tests without the need for a new PMA/PMN submission. When fully validated, allowing modifications to grandfathered tests would promote quality patient care by incentivizing laboratories to make improvements in the LDTs they offer.

ASCP supports enhanced visibility of LDTs clinically offered in the US, such as through a registry, as well as when adverse events occur with those tests. If the FDA receives data indicating that the performance of a particular LDT may pose immediate patient harm, the Agency should take enforcement action to protect patient health**.**

Leveraging External Partnerships

The FDA states it is "interested in and seeks comment on leveraging programs such as the [NYSDOH CLEP] or those within the [VHA]." ASCP would strongly support reliance on these external partners for any LDT oversight scheme. We note that NYSDOH CLEP requires that laboratories licensed to perform testing for state residents provide evidence of analytic and clinical validity for each registered LDT. ASCP strongly supports the NYSDOH CLEP's allowance

that evidence of clinical validity can take a variety of forms, including published studies in the peer-reviewed literature, the use of clinical guidelines, etc. If the FDA finalizes this rule, we urge the Agency to provide similar flexibility with regard to how laboratories can provide evidence of clinical validity.

The FDA's rule—and the VALID Act—raise the prospect of relying on third party reviewers for the review of 510(k) submissions. Provided the FDA's approach for approving third-party agencies are governed by strict conflict of interest requirements, we do not object to this proposal. Given the size of the LDT market and the number of LDTs the FDA estimates would have to undergo the PMA process, we believe that reliance on additional partners is essential to reduce the significant regulatory challenges and processing bottlenecks we anticipate will undermine patient access to testing.

Methodology Specific Maintenance of Enforcement Discretion

In its proposed rule, the FDA proposed and/or sought input on maintaining or extending enforcement discretion for certain LDTs, such as "1976-type LDTs", human leukocyte antigen (HLA) tests, immunohistochemistry, and tests used solely for forensic (law enforcement) purposes or public health surveillance. Such carve-outs recognize the importance of LDTs to patient health.

1976-type LDTs: The FDA proposes to maintain enforcement discretion for "1976-type LDTs," which the Agency defines as tests that use manual techniques (without automation) performed by laboratory personnel with specialized expertise; use components legally marketed for clinical use; and are designed, manufactured, and are used within a single CLIA-certified laboratory meeting the requirements under CLIA for high complexity testing. ASCP supports maintaining enforcement discretion for 1976-type LDTs.

Immunohistochemistry: Under its proposal, the FDA suggests that immunohistochemistry (IHC) tests that "involve no automated preparation or interpretation" could continue to benefit from its general enforcement discretion approach.[2] IHC tests represent one of the largest methodological classes of LDTs and are absolutely critical to patient care. It is imperative to quality patient care that IHC be covered by the FDA's general enforcement discretion approach. Moreover, while the FDA's proposal of enforcement discretion for IHC tests is greatly appreciated, the vast majority of pathology laboratories providing these essential patient services do not use manual staining and, therefore, their LDTs would not be covered under the FDA's general enforcement discretion approach. It is imperative that *all* IHC testing, regardless of how specimens are stained, are covered under the Agency's general enforcement discretion approach.

[2] The FDA does not propose to extend enforcement discretion to lateral flow tests, as "they do not generally rely on laboratory personnel expertise."

Human Leukocyte Antigen Typing: The FDA proposes to maintain enforcement discretion for these tests (except for blood transfusions), provided they are "designed, manufactured, and used in a single laboratory certified under CLIA that meets the requirements to perform high-complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and 'virtual' HLA crossmatch tests." ASCP appreciates the FDA proposing to provide enforcement discretion for HLA testing. These tests are critical to patient care, particularly for patients being cared for in an acute care facility. As these tests often need to be "customized" to the needs of the patient, requiring premarket approval, or even notification, could prevent patient testing.

Other Test Methodologies:
ASCP notes that there are other types of laboratory tests that the FDA is not proposing to cover under its general enforcement discretion approach that we believe the Agency should also cover under this approach.

Flow cytometry: Flow cytometry tests should be included and for the same reasons as for HLA testing. Flow cytometry is complex testing. It needs to be done locally because patients need timely access to this testing for urgent life-saving situations. Prompt medical care decisions are made based on this testing methodology, so rapid turnaround time (within hours of a patient presenting) is imperative. The vast majority of these tests are LDTs, with many used for Leukemia and Lymphoma, including for pediatric patients, so the need for enforcement discretion here is significant.

Therapeutic Drug Monitoring: Therapeutic drug monitoring is another class of tests we believe should be provided continued enforcement discretion. These tests are only available as LDTs for certain medications. Under the FDA's proposal, transplant patients could have to wait days to establish therapeutic drug monitoring levels. Such a delay could allow rejection of a transplanted organ that could have been avoided with rapid testing.

We anticipate that other types of tests will need to be covered by the FDA's general enforcement discretion approach. To ensure patient access to critical testing, the FDA should not finalize this rule without establishing a process in place to *rapidly* extend enforcement discretion to other kinds of LDTs as needed.

Hospitals and Academic Medical Center LDTs
ASCP believes that LDTs developed by hospital and academic medical center (AMC) laboratories are fundamentally different from those of other LDTs developed in commercial reference laboratories. Traditionally, hospital and AMC laboratories developed LDTs in response to physician requests for assistance with caring and treatment for their patients, and we recognize that LDTs developed in these laboratories are not the driving concern for increasing federal oversight of LDTs. Due in large part to the costs and burdens associated with the FDA's medical

device approval system, some companies opted to develop a laboratory and provide testing services rather than seek FDA approval to sell their devices. It is our understanding that it is this segment of the LDT market that has prompted most of the concern about LDTs. Theranos, for example, which was ultimately stopped by CMS--not FDA--is an example.

Without some sort of regulatory flexibility or exemption for AMCs and hospital laboratories, it is unclear how laboratories at these sites will be able to continue to provide these services to their patients. These laboratories lack the financial resources and personnel necessary to successfully navigate the FDA's medical device regulations. We anticipate the prospect of requiring these sites to undergo the PMA/PMN process is sufficient to cause many of them to discontinue developing and utilizing these testing services. As commercial device manufacturers are unlikely to meet all patient testing needs, the loss of hospital and AMC LDT development and utilization will surely undermine patient access to testing and quality care.

In its proposal, the FDA asked whether there should be a different policy for AMC laboratories. Because of the limitations on hospital and AMC laboratories, these entities would need less resource intensive requirements than the FDA's current medical device requirements. ASCP believes that the FDA as well as any legislative initiatives should maintain enforcement discretion for 510(k) premarket notifications/premarket approvals, quality systems regulation, and labeling requirements in AMC settings, while CMS compiles information on the use of LDTs currently in use in clinical laboratory settings. This could provide the HHS with performance metrics that the Agency could use, on a case-by-case basis, to investigate those LDTs warranting closer examination.

Enhancements of CLIA are also needed, such as requiring all laboratories to document clinical validity of their LDTs. This, we believe, would be complementary to the FDA's oversight of LDTs, particularly those that are under enforcement discretion.

Clinical Validity

One of the issues related to providing additional oversight of LDTs concerns their analytical and clinical validity. The FDA's 2014 draft framework for LDT oversight included a section entitled "Evaluation of Clinical Validity of LDTs" in which the Agency asserted that it "…expects that for many LDTs, clinical validity has already been established in literature."[3] Moreover, the text states that "FDA emphasizes that it is the Agency's practice to leverage such information from the literature in lieu of requiring additional studies to demonstrate clinical validity. In these cases, the FDA may still require studies demonstrating device performance (e.g., analytical evaluations) but generally intends to rely on the scientific literature to support clinical validity if appropriate." The ability to rely on scientific literature to document clinical validity is a matter

[3] Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)
Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories
OCTOBER 2014. U.S. Food and Drug Administration. Accessed Nov. 29 2023.

of vital importance to the laboratory community, but no such statement or assurance is included in the current proposed rule.

Given that many LDTs currently offered or in development may not have a legally marketed device upon which to base a determination of substantial equivalence, the absence of the 2014 assurance raises concerns that the FDA may now plan to require full premarket review for such LDTs. This is very concerning. The clinical trials infrastructure and financial resources required to undertake such studies simply do not exist within hospital, AMC, and smaller regional laboratories. As a practical matter, not allowing laboratories to utilize scientific literature to document clinical validity would lead to an acute shortage of needed testing for their patients.

In the proposed rule, the FDA raises the prospect of leveraging the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP), the Veterans Health Administration (VHA), and certain third-party reviewers, all (or most) of which already require documentation of clinical validity. It is our understanding that NYSDOH CLEP and at least one of the CLIA accrediting agencies that require clinical validation allow evidence of clinical validity to take a variety of forms, such as using published studies in the peer-reviewed literature, the use of clinical guidelines, etc. Whether FDA regulates LDTs under a final rule or by a new statute, we urge policymakers to provide similar flexibility to allow these laboratories to meet patient needs.

Unintended Consequences

ASCP is concerned that the policymakers do not understand the scale of the regulatory burden that the proposed rule or the VALID Act would impose on the pathology and laboratory medicine community. In consulting ASCP's membership about the likely impact of this rule, we have repeatedly heard concerns that few hospital, AMC, or local/regional medical laboratories have the personnel or financial resources to handle the regulatory burden proposed by the FDA. Many of these laboratories will cease to provide LDTs or will drastically reduce their LDT offerings, which will, in turn, greatly restrict patient access to treatment and care.

This impact will not be uniform: rural and underserved communities will be hit hardest. Patients served by smaller laboratories, including those doing larger volumes of LDT testing, may cease operating, and there is no guarantee that commercial diagnostics manufacturers and national reference labs will fill the void with necessary testing solutions. To a certain degree, these impacts may be disease- or condition dependent. For conditions like acute leukemias and aggressive B-cell lymphoma, such as Burkitt lymphoma, patients can currently get same-day diagnostic confirmation and an immediate start to therapy by being served locally. For these and other urgent diagnoses, some patients cannot afford to wait to begin treatment because their test results have been delayed due to being sent to a large reference laboratory.

We expect that this rule will also exacerbate personnel shortages within the pathology and laboratory medicine workforce, as the need within medical laboratories for individuals with

these skills will diminish. To continue working on test development, these professionals may leave the laboratory sector. Moreover, as test development is central to the practice of pathology and laboratory medicine, we are also concerned that this proposal could impact the quality of the practice of pathology and laboratory medicine. Further, as LDT development is central to how residency programs provide training on disease diagnosis, the loss of these tools could diminish the quality of the resident training experience and/or reduce the attractiveness of the pathology profession. This would exacerbate current pathologist shortages. As healthcare personnel tend to seek employment in urban areas, these personnel issues are most likely to be felt in rural and underserved areas.

Moreover, the loss of these skills within pathology and laboratory medicine could also adversely affect medical research. Pathologists and laboratory professionals with expertise in test development are often called upon to develop new tests to identify previously undiagnosable diseases or assess the impact of potential therapies. Diminishing their test development skill set will diminish research, which will slow the pace of medical discovery.

ASCP Recommendations

While we recognize that certain types of LDTs could benefit from additional regulatory oversight, we believe this proposed rule as well as the VALID Act will adversely impact the overall quality of patient care and drastically undermine diagnostic innovation in the United States. The FDA lacks the capacity to quickly and efficiently conduct the number of PMA reviews it is proposing. Even at the low end of the FDA's estimate on the number of LDTs in use, it is hard to fathom that this proposal will not cause massive disruptions for patient access to testing. The loss of access to testing will lead to missed/delayed diagnoses, inadequate treatments, and poorer patient outcomes.

It is highly speculative whether the FDA's estimates on the scope of the LDT market are accurate. CMS does not currently curate a public database of LDTs in current use, so the overall numbers of LDTs, their uses, their performance characteristics, etc., is unknown to the broader public. This "unknown" presents a substantial risk to patient access to testing and quality care should the Agency move forward with this rule. Consequently, we believe that the U.S. Department of Health and Human Services should develop an LDT database to begin the process of evaluating the LDT market for any future regulatory initiatives. This registry should be fully accessible to the public, so that physicians and researchers may be able to better understand the LDT market and how these diagnostics perform relative to other IVDs.

In addition, ASCP believes that the Agency should not require minor modifications of FDA-approved tests (e.g., use serum instead of plasma, allow for dilutions, etc.) to undergo any sort of Agency required filings or review. Given the need for expediency of testing for certain patients, this will cause unnecessary delays in diagnosing and treating patients. We believe that modifications would be better handled under the CLIA framework. We further

recommend that the Agency specifically exclude modifications of FDA-approved tests from its definition of an LDT.

ASCP appreciates the opportunity to provide comments on this important issue. If the Society can be of assistance, please do not hesitate to contact me at [redacted] or Matthew Schulze, Senior Director of the ASCP Center for Public Policy, at [redacted]

Sincerely,

Robert A. Goulart, MD, MASCP
President, ASCP

House panel to discuss FDA proposal to regulate lab-developed tests

Updated: March 21, 2024

Photo: National Cancer Institute - unsplash.com.

Last year FDA proposed better regulation of diagnostic tests as more and more are produced

A key House subcommittee is holding a hearing today to discuss the Food and Drug Administration's proposal to regulate laboratory-developed tests (LDTs). If finalized, FDA's proposed rule would clarify its intent to regulate these increasingly common tests, which have eluded the agency's scrutiny for half a century.

Supporters of FDA's proposed rule, including the nonprofit Center for Science in the Public Interest, say that the agency's proposal would address a major regulatory gap and ensure that patients and doctors are getting accurate and clinically meaningful results.

The 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act gave FDA the authority to regulate all diagnostic tests, regardless of where and by whom they are manufactured. When that law was passed, the agency chose not to use its authority to regulate tests developed and used in a single laboratory, primarily because such tests were simple and used on a small number of patients. Over time, however, lab-developed tests have grown in complexity and number.

Reliable LDTs are critical as false-negative results can lead to undertreatment and false-positive results can lead to unnecessary treatment. Both scenarios are harmful to patients and costly to the healthcare system. Unfortunately, numerous examples of inaccurate tests have been identified by FDA, academics, and the media. Many of these are used in the diagnosis or treatment of serious conditions like COVID-19, heart disease, and cancer, and have caused patients demonstrable harm, according to CSPI.

Absent FDA regulation, laboratories performing clinical tests, including LDTs, are regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments. However, CMS review focuses on laboratory operations rather than test performance. FDA oversight would be much more comprehensive and include review of device effectiveness, manufacturer claims, labeling, and adverse event reporting. Even CMS agrees that FDA has the authority to regulate LDTs and the expertise to do so.

Over a decade has elapsed since FDA proposed regulating LDTs in a 2014 draft guidance that was never finalized due to pressure from industry and Congress. In the years since, Congress has

repeatedly failed to pass legislation that would establish a risk-based regulatory framework for these tests.

"In a Capitol frozen by legislative gridlock, claiming that Congress will 'get it done this time' is not an adequate response to this serious and growing problem," said CSPI president Dr. Peter G. Lurie. "FDA has the clear authority and the will to close this huge gap in its reach with a risk-based approach to regulating these critical products."

Lurie, a former FDA associate commissioner, while at the agency was the lead author of a 2015 report on the public health costs of poor quality LDTs.

CSPI has advocated for the Verifying Accurate Leading-edge IVCT Development (VALID) Act, which would offer a comprehensive regulatory framework for diagnostic tests, including LDTs.

"CSPI supports FDA's efforts to regulate lab-developed tests through rulemaking," Lurie said. "Patients have waited long enough for an assurance that they can rely on the results of their clinical tests. If Congress will not act, FDA must."

The hearing, at 10:00 a.m. EDT, is before the House Energy and Commerce Committee's Subcommittee on Health.

# # #

CONTACT INFO: Lisa Flores, 202-777-8368 or Jeff Cronin, 202-777-8370

STATEMENT

of the

American Medical Association

U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

Re: Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule

March 21, 2024

Division of Legislative Counsel

202-789-7426

Statement for the Record

of the

American Medical Association

to the

Committee on Energy & Commerce, Subcommittee on Health

Re: Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule

March 21, 2024

The American Medical Association (AMA) appreciates the opportunity to submit the following Statement for the Record to the U.S. House of Representatives Committee on Energy and Commerce Subcommittee on Health as part of the hearing entitled, "Evaluating Approaches to Diagnostic Test Regulation and the Impact of FDA's Proposed Rule." The AMA commends the Subcommittee on initiating further discussions around the U.S. Food & Drug Administration (FDA)'s proposed rule regarding laboratory developed tests (LDTs). This is an extremely complex issue that deserves careful attention to ensure that the policies that are adopted are the product of a collaborative approach that is appropriately tailored to meet the shared goals of the FDA and interested parties.

AMA Comments in Response to FDA's proposed rule

In December 2023, the AMA submitted comments in response to the FDA's solicitation for feedback on this proposal and expressed major concerns that the proposal will cause significant upheaval to the laboratory community with detrimental results for patients. While we agree that there is a role for FDA in the regulation and oversight of LDTs, any further regulation of LDTs should appropriately balance the risks and benefits of further regulation and should likely utilize a risk-based system for evaluation that seeks to limit propagation of poorly performing tests while maintaining patient access to critical testing services. We fear the potential that laboratories may cease offering some diagnostic testing services should they come at higher expense or significant administrative burden associated with seeking FDA review of each test and modification. At a most fundamental level, given the existing significant resource constraints, we do not believe FDA will have the necessary capacity to manage the potentially overwhelming volume to ensure continuity of access for patients. Delayed access to treatment and the chilling effect on innovation in the diagnostic space are also potential consequences to this proposal that we find are not insignificant and must be given greater consideration.

The AMA appreciates this Subcommittee's careful consideration of this issue of LDT regulation and the role of the FDA, in any modifications to the existing paradigm. We, along with many of our federation members and colleagues in the laboratory community, share very significant concerns with the proposed approach, and strongly urge to pause any finalization of the proposals for a more deliberate, collaborative approach with interested parties.

ROGEL CANCER CENTER
MICHIGAN MEDICINE

Daniel F. Hayes, MD, FASCO, FACP
Stuart B. Padnos Professor of Breast Cancer Research
Professor, Department of Internal Medicine
Division of Hematology/Oncology
[redacted] / [redacted]
1500 E. Medical Center Dr.
Ann Arbor, MI 48109-5942
[redacted] appointments
[redacted] clinic fax
[redacted] academic office
[redacted] academic fax
[redacted]

March 18, 2024

The Honorable Brett Guthrie
Chair, Health Subcommittee, House Committee on Energy and Commerce

The Honorable Anna Eshoo
Ranking Member, Health Subcommittee
House Committee on Energy and Commerce

The Honorable Cathy McMorris Rodgers
Chair, House Committee on Energy and Commerce

The Honorable Frank Pallone, Jr.
Ranking Member , House Committee on Energy and Commerce

Re: Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule

Dear Chairs Guthrie, Eshoo, Rodgers, and Pallone:

I am submitting my personal support of the recent proposal by FDA to "amend its regulations to make explicit that *in vitro* diagnostic products are devices under the Federal Food and Cosmetic Act" and that it "proposes a policy under which FDA intends to phase out its general enforcement discretion approach for laboratory developed tests (LDTs)." I am writing as a private citizen, and my comments do not reflect either my employing institution (the University of Michigan) or any other private or commercial organizations.

I am the Stuart B. Padnos Professor of Breast Cancer Research and a Professor of Internal Medicine at the University of Michigan Rogel Cancer Center. I am also a past president of the American Society of Clinical Oncology, although I have no current leadership role in this organization. I have more than 40 years' experience as a laboratory and clinical investigator as well as a practicing medical oncologist. I have in the past directed three separate academic breast cancer programs (Harvard's Dana Farber Cancer Institute, Georgetown's Lombardi Cancer Center, and the University of Michigan's Comprehensive (now Rogel) Cancer Center). I have also served as a chair or member of several guidelines and review panels, and I have published extensively regarding tumor biomarker test (TBT) development and clinical applications. I have published more than 375 peer-reviewed papers and more than 190 other publications, such as topic reviews, chapters, and editorials, and I have edited 8 books regarding oncology, of which 2 pertain to TBTs.

I have substantial expertise in the field of TBTs and their application in oncology. Forty years ago, I was integral to the development of a widely used blood-based assay to monitor patients with metastatic breast cancer, designated CA15-3[1,2]. Subsequently, I led translational medicine studies of tissue-based HER2[3,4] markers of angiogenesis[5,6], and many others. In addition to my academic involvement in generating and testing TBTs, I have collaborated with industry manufacturers to conduct research regarding TBTs, including the CA15-3 assay as well as the first and subsequent reports of the assays for circulating tumor cells in breast cancer using the CellSearch™ system[2,7-9]. I have served as an external consultant for several TBT manufacturers. I have been a leader in establishing society guidelines for TBT and for standardizing widely performed tumor biomarker assays when generated as LDTs[10]. I have published several widely cited

commentaries regarding assessment of the relative value of and clinical utility of TBTs, including various factors that are needed to demonstrate the clinical utility of TBTs in clinical and translational research[11-16]. Furthermore, I am an established investigator in clinical trials of novel therapeutics[17-19]

Perhaps most importantly, I was an active clinical medical oncologist for over 40 years, providing care for patients with malignancies, particularly breast cancer.

Taken together, these areas of expertise make me uniquely positioned to comment on the status of LDTs for TBTs. As a clinician, I have trusted that FDA approval implied that the drugs I prescribed were "safe and effective." However, one cannot depend on this maxim for TBTs, since the FDA elected to make the enforcement discretion decision regarding the LDTs many decades ago. At that time, this discretion decision was appropriate, due to the influx of newly developed tests based on the discovery of monoclonal antibodies. The decision was bolstered by the perception at that time that the assays being generated were mostly secondary to making clinical decisions. However, over time, advances in science and technology have resulted in increasingly sophisticated and often multi-parameter TBTs that may be used primarily to determine if a patient should, or should not, receive possibly life-saving but often toxic and expensive treatment. In the modern era, such tests must be considered as important, if not more so, than the therapeutic strategy itself.

The proposal by the FDA to phase out the LDT enforcement discretion decision, using a tier-based system to ensure that existing and widely-accepted assays are not lost while improving regulation of more recently developed and highly complex assays is appropriate. Clinicians and their patients cannot be secure that such assays, if performed as LDTs, are analytically accurate or have sufficient predictive value that the tests can be relied on to make such live-changing decisions.

Several arguments have been made against the FDA's proposal to amend the enforcement discretion decision. One argument is that LDTs must be performed in laboratories that have received approval from the Centers for Medicare and Medicaid Services according to the Clinical Laboratory Improvement Amendments (CLIA) of 1988. Although CLIA approval of laboratories is an important component of demonstrating good laboratory practices, CLIA does not specifically conduct strict review or impose regulation of individual LDTs to determine analytical validity or clinical utility

Another argument is that the amendment would dampen innovation. While this is a concern, in fact one can counter that assays that are developed by commercial industry entities and are submitted to FDA for clearance or approval may then be copied by an independent laboratory as an LDT. In this case, the incentive for the commercial company to engage in time-consuming and expensive but important research to demonstrate clinical utility, as is required for a new therapeutic agent, is removed and innovation is actually reduced.

In summary, clinicians and patients depend on the FDA to carefully review the data and render difficult but reliable decisions about whether a drug is safe and effective. They should take the same approach towards diagnostics, especially in oncology. I have been quoted on several occasions as stating that "a bad tumor biomarker test is as bad as a bad drug." Amending the enforcement discretion decision in a thoughtful and considerate manner is a major step in eliminating this concern.

Thank you for your consideration regarding this incredibly important issue.

Sincerely yours,

Daniel F. Hayes, MD, FACP, FASCO

References

1. Hayes, DF, Sekine, H, Ohno, T, et al: Use of a murine monoclonal antibody for detection of circulating plasma DF3 antigen levels in breast cancer patients. Journal of Clinical Investigation 75:1671-1678, 1985

2. Hayes, DF, Zurawski, VR, Jr., Kufe, DW: Comparison of circulating CA15-3 and carcinoembryonic antigen levels in patients with breast cancer. J Clin Oncol 4:1542-50, 1986

3. Dressler, LG, Berry, DA, Broadwater, G, et al: Comparison of HER2 Status by Fluorescence in Situ Hybridization and Immunohistochemistry to Predict Benefit From Dose Escalation of Adjuvant Doxorubicin-Based Therapy in Node-Positive Breast Cancer Patients. J Clin Oncol 23:4287-97, 2005

4. Hayes, DF, Thor, AD, Dressler, LG, et al: HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 357:1496-506, 2007

5. Guidi, AJ, Berry, DA, Broadwater, G, et al: Association of angiogenesis in lymph node metastases with outcome of breast cancer. J Natl Cancer Inst 92:486-92, 2000

6. Guidi, AJ, Berry, DA, Broadwater, G, et al: Association of angiogenesis and disease outcome in node-positive breast cancer patients treated with adjuvant cyclophosphamide, doxorubicin, and fluorouracil: a Cancer and Leukemia Group B correlative science study from protocols 8541/8869. J Clin Oncol 20:732-42, 2002

7. Cristofanilli, M, Budd, GT, Ellis, MJ, et al: Circulating tumor cells, disease progression, and survival in metastatic breast cancer. N Engl J Med 351:781-91, 2004

8. Paoletti, C, Regan, MM, Niman, SM, et al: Circulating tumor cell number and endocrine therapy index in ER positive metastatic breast cancer patients. NPJ Breast Cancer 7:77, 2021

9. Paoletti, C, Barlow, WE, Cobain, EF, et al: Evaluating Serum Thymidine Kinase 1 in Patients with Hormone Receptor-Positive Metastatic Breast Cancer Receiving First-line Endocrine Therapy in the SWOG S0226 Trial. Clin Cancer Res 27:6115-6123, 2021

10. Nielsen, TO, Leung, SCY, Rimm, DL, et al: Assessment of Ki67 in Breast Cancer: Updated Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst, 2020

11. Hayes, DF, Bast, RC, Desch, CE, et al: Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. J Natl Cancer Inst 88:1456-66, 1996

12. Simon, RM, Paik, S, Hayes, DF: Use of archived specimens in evaluation of prognostic and predictive biomarkers. J Natl Cancer Inst 101:1446-52, 2009

13. Hayes, DF, Allen, J, Compton, C, et al: Breaking a vicious cycle. Sci Transl Med 5:196cm6, 2013

14. Merker, JD, Oxnard, GR, Compton, C, et al: Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 36:1631-1641, 2018

15. Dinan, MA, Lyman, GH, Schilsky, RL, et al: Proposal for Value-Based, Tiered Reimbursement for Tumor Biomarker Tests to Promote Innovation and Evidence Generation. JCO Precision Oncology:1-10, 2019

16. Hayes, DF: Defining Clinical Utility of Tumor Biomarker Tests: A Clinician's Viewpoint. J Clin Oncol 39:238-248, 2021

17. Hayes, DF, Van Zyl, JA, Hacking, A, et al: Randomized comparison of tamoxifen and two separate doses of toremifene in postmenopausal patients with metastatic breast cancer. J Clin Oncol 13:2556-66, 1995

18. Henderson, IC, Berry, DA, Demetri, GD, et al: Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 21:976-83, 2003

19. Rodler, E, Sharma, P, Barlow, WE, et al: Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and BRCA mutation-associated breast cancer (S1416): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 24:162-174, 2023

Taylor & Francis
Taylor & Francis Group

Expert Review of Molecular Diagnostics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iero20

The impact of companion diagnostic testing on medical decision making and IVD regulations

Jan Trøst Jørgensen

To cite this article: Jan Trøst Jørgensen (12 Feb 2024): The impact of companion diagnostic testing on medical decision making and IVD regulations, Expert Review of Molecular Diagnostics, DOI: 10.1080/14737159.2024.2317976

To link to this article: https://doi.org/10.1080/14737159.2024.2317976

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
https://doi.org/10.1080/14737159.2024.2317976

Taylor & Francis
Taylor & Francis Group

EDITORIAL

The impact of companion diagnostic testing on medical decision making and IVD regulations

Jan Trøst Jørgensen

Medical Science, Dx-Rx Institute, Fredensborg, Denmark

ARTICLE HISTORY Received 11 November 2023; Accepted 8 February 2024

KEYWORDS Companion diagnostics; in vitro diagnostics; FDA; EMA; precision medicine

1. Introduction

An increasing number of clinical diagnostic tests are used to inform medical decisions, including the results of companion diagnostic (CDx) testing. In recent years, the importance of these assays has increased, particularly for the treatment of patients with hematological and oncological conditions. By August 2023, more than 60 drugs or drug combinations had an FDA-approved CDx test attached for use [1]. The Food and Drug Administration (FDA) defines a CDx test as an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product [2]. This definition is also reflected in the new In Vitro Diagnostic Regulation (IVDR) for the European Union (EU) and the IVD regulations of several other countries [1,3]. A CDx test is intended to inform drug treatment by directing the physician to choose a certain drug based on the patient's molecular makeup, and here the assay validity can have a decisive impact on the therapeutic decisions. A false positive test result may lead to unnecessary medical intervention with incorrect medication, resulting in delayed treatment with the appropriate therapy. Conversely, a false negative test result may result in disease progression and, in some instances, prevent patients from receiving the appropriate treatment. The consequences of false positive or false negative CDx test results can be substantial and, in some situations, life-threatening [4].

For decades, the safety and efficacy of drugs have been the responsibility of the regulatory medical agencies. In the US, the FDA, and for the EU, the European Medicines Agency (EMA), and the national competent authorities. In contrast, the regulations for *in vitro* diagnostics (IVDs) have been more inconsistent and diverse. In the US, a CDx test manufactured by a commercial company for use by other entities such as laboratories and healthcare providers, is regulated by the FDA. However, for laboratory-developed tests (LDT), the situation is different, as they are not overseen by the FDA; instead, they must meet the requirements of the Clinical Laboratory Improvement Amendments (CLIA) [4]. In the EU, IVDs were regulated by the IVD Directive until 2022, and a CDx test was considered low-risk general IVD that could be distributed without any involvement or review by regulators [5]. Through a self-certification procedure, the manufacturer performed a conformity assessment according to the IVD Directive, after which a CDx test could be CE-IVD labeled and distributed. Owing to the central role of IVDs in the treatment decision process, regulations in both the US and the EU are currently undergoing changes. In this editorial, these changes and their background are briefly discussed.

2. CDx test quality

It is of utmost importance that the CDx tests used for making treatment decisions possess sufficient sensitivity and specificity and that the results generated are reliable with regard to accuracy and precision [6]. Before a CDx test can be used clinically, it must undergo intensive analytical and clinical validation and fulfill strict acceptance criteria. However, this does not appear to be the case for all tests used in the clinic to inform treatment decisions, particularly for some LDTs.

Approximately 25% of all CDx tests are based on immunohistochemistry (IHC), which can be hampered by high error rates [1,7–10]. In clinical trials, patients are often tested locally with an LDT for inclusion, and the paraffin tissue blocks are sent for subsequent central testing to verify the local test results. Disagreement rates between 20% and 30% have often been reported, and in a few cases even higher, when local and central test results are compared [7]. Furthermore, proficiency surveys on HER2 testing have shown that commercial FDA-approved assays have a higher acceptance rate compared to LDTs [7,8]. Based on data from 1703 HER2 tests performed, NordiQC estimated the false negative rate for LDTs to be 25% compared to 11% for FDA-approved tests. Similarly, the false positive rate for LDTs was 5%, whereas it was 0% for the FDA-approved tests [9]. Recently, HER2-targeted therapy has been expanded to include HER2 low breast cancer, which is defined as IHC1+ or IHC2+ and negative for *HER2* amplification [11]. However, the distinction between IHC0 and IHC1+ appears to be a source of difficulty, with a high discordance rate among pathologists, which may lead to misclassification of patients and incorrect treatment decisions [10].

IHC is not the only CDx platform that is burdened by analytical errors. A publication by the FDA reported several

CONTACT Jan Trøst Jørgensen [redacted] Medical Science, Dx-Rx Institute, Baunevaenget 76, Fredensborg, DK-3480 Denmark

cases of inaccurate or unreliable LDTs that could potentially harm patients [12]. In this report, they describe a LDT real-time polymerase chain reaction (PCR) assay to detect HER2 status in women with breast cancer to guide HER2 targeted therapy. However, owing to the poor sensitivity of the assay, a high false negative rate was observed, resulting in patients not receiving treatment with trastuzumab. A second case in the report also involved a PCR assay to detect the *V600E BRAF* mutation in melanoma to identify patients for treatment with vemurafenib. The laboratory claimed that the LDT had a higher sensitivity than the alternatives; however, documentation supporting this claim was lacking, which could result in patients being inappropriately administered vemurafenib [12].

In recent years, several reports have highlighted the high variability of LDT next-generation sequencing (NGS) assays [13–15]. One study focused on the *KRAS* and *NRAS* genes, which are important in selecting colorectal cancer patients who may benefit from treatment with panitumumab and cetuximab [13]. Nineteen different laboratories tested both wet and dry samples, and seven (37%) correctly reported all variants, three (16%) had fewer than five errors, and nine (47%) had more than five errors. Most of the errors were related to false negative test results. Another study examined variability across 16 different local laboratories in the US and Europe, in relation to the use of NGS for measuring tumor mutational burden (TMB) used to identify patients with solid tumors who may benefit from treatment with the immune checkpoint inhibitor pembrolizumab [14]. This study showed that the use of different NGS platforms resulted in substantial variability in TMB among laboratories, potentially leading to incorrect treatment decisions. Finally, a third study found a substantial discordance of more than 70% between two CLIA-certified laboratories when testing identical patient samples for actionable tumor mutations using different NGS panels [15].

3. Regulatory response

The regulatory response to LDTs in both the US and EU has been to tighten regulations for these types of assays, including CDx tests used for patient stratification, even though not all LDTs exhibit the same level of poor performance, as described above [3,4]. In the US, CDx tests manufactured by commercial companies are mainly classified as high-risk Class 3 medical devices and require formal approval through the submission of a premarket approval (PMA) or 510(k). For this type of IVDs, the FDA conducts a scientific and regulatory review of the documentation to evaluate the performance of the CDx tests to ensure that they generate results with high accuracy and precision [2,4]. According to the FDA, an LDT is an *in vitro* diagnostic test that is manufactured and used in a single laboratory [16]. These laboratories are certified by the CLIA program, which means that analytical validity must be documented for the assay. However, there are no CLIA requirements in terms of clinical validity [17]. In the US, LDTs constitute a large part of all CDx tests used in the clinic, and for the HER2 assays, it is estimated that up to 20% yield inaccurate results [12]. To ensure the quality of LDTs, in October 2023, the FDA proposed amending its regulations to include this type of IVDs under the Federal Food, Drug, and Cosmetic Act. The new regulations, if passed by the US lawmakers, will be implemented over a five-year phaseout period and are expected to be in effect by 2028 [4].

As previously mentioned, the process for regulating IVDs, including CDx tests, in the EU has, until recently, been quite different from that in the US. Previously, all CDx tests were classified as low-risk general IVDs, and were not subjected to any formal review by regulators [5]. However, with the implementation of the new IVDR, CDx tests will now be classified as moderate-to-high-risk Class C devices, and their performance documentation must be reviewed by a notified body and EMA or National Competent Authorities before being distributed and used by clinical laboratories [3]. By December 2028, all CDx tests used by clinical laboratories must be CE-IVDR labeled, and LDTs will no longer be an option, except in a few special situations.

4. Laboratory developed tests – pros and cons

Although some LDTs have quality issues, they also offer benefits that should not be disregarded when introducing new regulations. For instance, LDTs provide flexibility in meeting specific patient needs, particularly in relation to experimental treatment and 'off-label' use. Additionally, LDTs can be developed and implemented faster than the FDA-approved assays. However, the downside of this rapid development may be a compromised validation process. Unlike the FDA-approved CDx tests, LDTs do not require clinical validation, which means that there is no assessment of how well the test performs under clinical conditions. Although clinical validation is time-consuming, it is critical for the CDx tests. Furthermore, there might be a tendency for diagnostic companies to update FDA-approved tests more slowly when new improved technologies emerge compared to LDTs, as this will require review by regulators. Additionally, developing and employing LDTs may be more cost-effective than using FDA-approved assays. Finally, it has been stated that the new regulations could impact innovation and research, as developing LDTs allows laboratories to explore new methodologies and diagnostic approaches. However, it is essential to emphasize that the advantages of LDTs must not compromise the quality of the tests, which seems to have been the case in some situations.

5. Conclusion

Although it has been stated that the new regulations would reduce patients access to clinical tests and hinder the development of novel diagnostics, it is important to remember the findings from the US and EU that highlight the inconsistent quality of LDTs, which will lead to stricter regulations for IVD. Given the pivotal role that CDx tests play in treatment decisions for patients with often life-threatening diseases, it is imperative to minimize the occurrence of incorrect test results. The potential harm caused by false positive and false negative test results can be significant, and the coming changes in regulations must be viewed as measures for improving patient safety.

Funding

This paper was not funded.

Declaration of interest

J T Jørgensen has worked as a consultant and advisor for Agilent Technologies, Alligator Biosciences, Argenx, AstraZeneca, Biovica, Visiopharm, and Leo Pharma, and has received royalties from Elsevier. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Jan Trøst Jørgensen http://orcid.org/0000-0001-6255-0006

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Jørgensen JT. Twenty-five years with companion diagnostics. Chin Clin Oncol. 2023;12(6):65. doi: 10.21037/cco-23-96
2. FDA. In vitro companion diagnostic devices. Guidance for industry and food and drug administration staff. 2014 Aug [cited 2023 Oct 29]. Available from: https://www.fda.gov/media/81309/download?attachment
3. European Union. Regulation (EU) 2017/746 of the European Parliament and of the council of 5 April 2017 on in vitro diagnostic medical devices and repealing directive 98/79/EC and commission decision 2010/227/EU. Official Journal of the European Union. 2017 Apr.
4. FDA. Medical devices; laboratory developed tests. A proposed rule by the FDA on 10/03/2023. [cited 2023 Oct 29]. Available from: https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests
   • **FDA proposal for regulation of LDTs.**
5. European Union. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. [cited 2023 Nov 3]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998L0079&from=EN
6. Jørgensen JT Companion and complementary diagnostics as tools of precision medicine. Elsevier Reference Collection In Biomedical Sciences. 2023. [cited 2023 Nov 6]. Available from: https://www.sciencedirect.com/science/article/abs/pii/B9780128240106000423
7. Bogen SA. A root cause analysis into the high error rate in clinical immunohistochemistry. Appl Immunohistochem Mol Morphol. 2019;27(5):329–338. doi: 10.1097/PAI.0000000000000750
8. Vyberg M, Nielsen S. Proficiency testing in immunohistochemistry—experiences from Nordic immunohistochemical quality control (NordiQC). Virchows Arch. 2016;468(1):19–29. doi: 10.1007/s00428-015-1829-1
9. Vyberg M, Nielsen S, Røge R, et al. Immunohistochemical expression of HER2 in breast cancer: socioeconomic impact of inaccurate tests. BMC Health Serv Res. 2015;15(1):352. doi: 10.1186/s12913-015-1018-6
   •• **Socioeconomic impact of incorrect HER2 testing.**
10. Fernandez AI, Liu M, Bellizzi A, et al. Examination of Low ERBB2 Protein Expression in breast cancer Tissue. JAMA Oncol. 2022;8(4):1–4. doi: 10.1001/jamaoncol.2021.7239
11. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in Previously treated HER2-low advanced breast cancer. N Engl J Med. 2022;387(1):9–20. doi: 10.1056/NEJMoa2203690
12. FDA. The public health evidence for FDA oversight of laboratory developed tests: 20 case studies 2015 Nov 16 [cited 2023 Nov 6]. Available from: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf
13. Pfeifer JD, Loberg R, Lofton-Day C, et al. Reference samples to compare next-generation sequencing test performance for oncology therapeutics and diagnostics. Am J Clin Pathol. 2022;157(4):628–638. doi: 10.1093/ajcp/aqab164
14. Vega DM, Yee LM, McShane LM, 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;32(12):1626–1636. doi: 10.1016/j.annonc.2021.09.016
15. Quy PN, Fukuyama K, Kanai M, et al. Inter-assay variability of next-generation sequencing-based gene panels. BMC Med Genomics. 2022;15(1):86. doi: 10.1186/s12920-022-01230-y
16. FDA: Draft Guidance for Industry, Food and Drug Administration Staff, and clinical laboratories on the Framework for Regulatory Oversight of Laboratory developed tests (LDTs). 2014 Oct 3 [cited 2024 Jan 27]. Available from: https://www.fda.gov/media/89841/download
17. Robinson SA, Carter AR, Brindley DA. The changing regulatory landscape for laboratory developed tests. The Regulatory Affairs Professionals Society. Regulatory Focus, 2021 Aug [cited 2024 Jan 28]. Available from: https://www.raps.org/News-and-Articles/News-Articles/2021/8/The-changing-regulatory-landscape-for-laboratory-d
   • **Discussion of the regulatory changes for LTDs.**

FDA and CMS: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made

FOR IMMEDIATE RELEASE
Jan. 18, 2024

The following is attributed to Jeff Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health (CDRH) and Dora Hughes, M.D., M.P.H., acting chief medical officer and acting director of the Center for Clinical Standards and Quality, Centers for Medicare & Medicaid Services (CMS)

Physicians heavily rely on laboratory tests to make critical decisions about their patients' care—roughly 70% of healthcare decisions depend on laboratory test results according to the Centers for Disease Control and Prevention (CDC). For example, results from laboratory tests can be the sole determinant of whether a patient with cancer gets a particular therapy, potentially risking the patient's life with an inaccurate test result. Because of the important role of laboratory tests in healthcare decisions, it is essential to ensure these tests work.

While the U.S Food and Drug Administration (FDA) actively oversees tests made outside laboratories by test manufacturers, tests made and run within a single laboratory, known as laboratory, developed tests or LDTs, are often used without such oversight. The FDA's approach was developed half a century ago when tests made and used in single labs were generally simple, often made to address local individual needs, and mostly manufactured in small volumes. Therefore, the FDA, as a policy approach, generally did not enforce requirements for LDTs. However, since then, LDTs have evolved. Due to the increased risk to patients, it is time to reconsider this approach.

In recent decades, the FDA has identified concerns with a number of LDTs. For example, the FDA is aware of tests offered as LDTs that could have led to patients being over- or under-treated for heart disease; patients with cancer being exposed to inappropriate therapies or not getting effective therapies; and incorrect diagnoses of rare diseases, autism and Alzheimer's Disease.[1,2] Other evidence, including published literature[3,4,5,6,7,8] and the FDA's experience with tests to diagnose COVID-19,[9] suggests that the situation is getting worse. Therefore, in October of this year, the FDA issued a notice of proposed rulemaking to help ensure the safety and effectiveness of LDTs by phasing out the FDA's current approach to LDTs. If finalized, LDTs would generally fall under the same enforcement approach as other tests. The Centers for Medicare & Medicaid Services (CMS) supports the FDA's proposal.

Both CMS and the FDA believe that patients and their doctors need to know that LDTs are valid. The FDA and CMS both provide oversight to help assure the accuracy of test results, however, they have different roles. CMS regulates laboratories that perform testing on individuals in the U.S. through the Clinical Laboratory Improvement Amendments of 1988 (CLIA) by establishing quality standards for all laboratory testing to help ensure the accuracy, reliability and timeliness of patient test results. In 2013, CMS published a fact sheet (https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ldt-and-clia_faqs.pdf) on LDTs, outlining each agency's authority and the complementary roles of the two regulatory schemes. That said, a decade later, in connection with the FDA's notice of proposed rulemaking, we are – together – reiterating that CMS's CLIA program is separate in scope and purpose from FDA oversight.

Some have suggested that concerns with LDTs should be addressed through expansion of CLIA. This is not the answer. As was stated in our 2015 testimony (https://democrats-energycommerce.house.gov/committee-activity/hearings/hearing-on-examining-the-regulation-of-diagnostic-tests-and-laboratory), CMS does not have the expertise to assure that tests work; the FDA does. Moreover, establishing a duplicative system for the oversight of tests by expanding CLIA would create more government bureaucracy and inconsistencies. That makes no sense.

The FDA and CMS have long stood together in mutual support of FDA oversight of the analytical and clinical validity of LDTs. LDTs play an important role in healthcare, but when they perform poorly or are not supported by science, they put patients at risk. The current approach has enabled some tests to enter the market with unfounded claims of innovation. These claims can mislead the public, undermine legitimate competition and disincentivize responsible, science-based innovation. Applying the same oversight approach to laboratories and non-laboratories that manufacture tests would better assure the safety and effectiveness of LDTs and would remove a disincentive for non-laboratory manufacturers to develop novel tests that can be available to and used by many laboratories for many patients.

We are now emerging from a global pandemic that has underscored the importance of accurate and reliable tests. Patients and providers need to have confidence that laboratory tests work. We believe the complementary FDA and CMS frameworks are both critical to assuring patients can rely on the clinical accuracy of their test results.

Related Information:

- Laboratory Developed Tests (/medical-devices/in-vitro-diagnostics/laboratory-developed-tests)

---

[1] See pages 68010- 68012 of FDA's Notice of Proposed Rulemaking (https://www.govinfo.gov/content/pkg/FR-2023-10-03/pdf/2023-21662.pdf).

[2] See "Memorandum to File - Examples of IVDs Offered as LDTs that Raise Public Health Concerns RE: Medical Devices; Laboratory Developed Tests (https://www.regulations.gov/document/FDA-2023-N-2177-0076)"

[3] Pfeifer, J.D., R. Loberg, C. Lofton-Day, et al., "Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics," American Journal of Clinical Pathology, 157(4):628-638, 2022 (https://doi.org/10.1093/ajcp/aqab164) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

[4] Quy, P.N., K. Fukuyama, M. Kanai, et al., "Inter-Assay Variability of Next-Generation Sequencing-Based Gene Panels," BMC Medical Genomics, 15: 86, 2022 (https://doi.org/10.1186/s12920-022-01230-y) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

[5] Vega, D.M., L.M. Yee, L.M. McShane, et al., "Aligning Tumor Mutational Burden (TMB) Quantification Across Diagnostic Platforms: Phase II of the Friends of Cancer Research TMB Harmonization Project," Annals of Oncology, 32(12):1626-1636, 2021 (https://doi.org/10.1016/j.annonc.2021.09.016) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

[6] Offit, K., C.M. Sharkey, D. Green, et al., "Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities," Journal of Clinical Oncology, 41(1): 11-21, 2023 (https://doi.org/10.1200/jco.22.00995) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

[7] Coffey, D., "Blood Test Positive for Cancer, but Is There Really a Tumor?" Medscape, February 17, 2023 (https://www.medscape.com/viewarticle/988431) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

[8] Manrai, A.K., B.H. Funke, H.L. Rehm, et al., "Genetic Misdiagnoses and the Potential for Health Disparities," New England Journal of Medicine, 375(7):655-665, 2016 (https://doi.org/10.1056/NEJMsa1507092) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

[9] See "Memorandum from Elizabeth Hillebrenner to FDA CDRH" (https://www.regulations.gov/document/FDA-2023-N-2177-0121)

MEMORANDUM

DATE: **September 22, 2023**

TO: **Administrative Files:**
Docket No. FDA-2023-N-2177

FROM: **Brittany Schuck, Ph.D.**
Deputy Office Director
Office of In Vitro Diagnostics (OHT7)
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration

SUBJECT: Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests (LDTs) that Raise Public Health Concerns

I. Introduction

FDA is issuing a notice of proposed rulemaking (NPRM) to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer is a laboratory. In conjunction with this amendment, FDA is proposing a policy under which FDA intends to phase out its general enforcement discretion approach for laboratory developed tests (LDTs) so that IVDs manufactured by a laboratory would generally fall under the same enforcement approach as other IVDs.

FDA is proposing this phaseout because that general enforcement discretion approach has led to an oversight scheme that does not best serve the public health. Current information regarding IVDs offered as LDTs raises serious questions about whether patients and healthcare providers can rely on such IVDs. The NPRM describes examples of IVDs offered as LDTs with reported or known issues. These include IVDs offered as LDTs with demonstrated poor or variable analytical and/or clinical performance, tests not supported by sound science, and IVDs that have been reported as problematic. This memo provides additional details regarding examples from non-public sources and some public medical device reports (MDRs).[1] This memo does not include information regarding examples from public sources for which citations are provided in the NPRM.

The problems associated with IVDs offered as LDTs described in the NPRM and further detailed in this memorandum likely do not reflect the full scale of problems associated with IVDs offered as LDTs. Problems with IVDs are difficult to identify, as adverse patient outcomes could be attributed to many factors beyond a potential inaccurate test result. Moreover, under FDA's general enforcement discretion approach for LDTs, FDA generally has not enforced requirements that

[1] While FDA generally makes MDRs available to patients and health care providers through the FDA's public Manufacturer and User Facility Device Experience (MAUDE) database, some reports are not included in the MAUDE database. The MAUDE web search feature is limited to adverse event reports within the past 10 years, and MAUDE may not include reports made according to exemptions, variances, or alternative reporting requirements granted under 21 CFR 803.19.

would otherwise help FDA identify and monitor significant issues with LDTs. FDA is unable to assess fully the extent of the risks to patients from IVDs offered as LDTs until FDA systematically collects information on these tests, such as adverse event reports, in the manner it does for other devices.

FDA has had increasing concerns that poor performing IVDs offered as LDTs pose significant risks to public health. These concerns extend to unvalidated IVDs offered as LDTs, the safety and effectiveness of which has not been demonstrated. The tests described in this memo exemplify in part the concerns that FDA has regarding IVDs offered as LDTs. Though FDA has issued safety communications and taken compliance actions related to some such tests in certain circumstances,[2] more structural change is needed to holistically address problems with IVDs offered as LDTs.

The IVDs offered as LDTs described below, among other things, support FDA's proposal to phase out the general enforcement discretion approach for LDTs.

II. Specific Examples of IVDs Offered as LDTs that Raise Public Health Concerns

This section discusses specific examples of potentially inaccurate, unsafe, ineffective, or poor quality IVDs offered as LDTs that have been identified or described in MDRs, allegations shared with FDA, and FDA's review of marketing and other submissions. In the examples below, the IVDs offered as LDTs either caused or could have caused patient harm. Any follow up by the FDA on the MDRs and allegations described in this memo is not included.

A. MDRs

Although FDA has generally exercised enforcement discretion such that it generally has not enforced applicable requirements with respect to most LDTs, including adverse event reporting requirements, FDA has received at least 29 MDRs for IVDs offered as LDTs that raise questions about whether patients and healthcare providers can rely on such tests.[3] Though no test is perfect, and we expect to receive MDRs for tests whose manufacturers are in compliance with applicable requirements, adverse events are generally underreported in FDA's experience, and the receipt of any MDRs for IVDs offered as LDTs in the current environment (where applicable adverse event reporting requirements have not generally been enforced) suggests that there may be problems

---

[2] *See, e.g.,* "Genetic Non-Invasive Prenatal Screening Tests May Have False Results: FDA Safety Communication," April 19, 2022. Available at https://www.fda.gov/medical-devices/safety-communications/genetic-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication;"FDA Issues Warning Letter to Genomics Lab for Illegally Marketing Genetic Test That Claims To Predict Patients' Responses to Specific Medications," April 4, 2019. Available at https://www.fda.gov/news-events/press-announcements/fda-issues-warning-letter-genomics-lab-illegally-marketing-genetic-test-claims-predict-patients

[3] MDRs were identified by (1) a narrative text query of MDRs in FDA's Decision Management Portal (DMP) database and CDRH Ad Hoc Reporting System (CARS) database, which was conducted in February 2023 (Search terms: "LABORATORY DEVELOP", "LDT", "LAB DEVELOP", %"AB-DEVELOP", "LABORATORY-DEVELOP", "LABORATORY DIAGNOSTIC", "LAB DIAGNOSTIC", "CLINICAL LABORATORY TEST", "CMS", "CLIA", "HOME BREW TEST", "HOUSE DEVELOP"), (2) a query of the DMP database for MDRs using the Laboratory Developed Test product code OQS, which was conducted in March 2023, (3) a search of MAUDE using the OQS product code, which was conducted in August 2018, (4) FDA's investigation into an allegation regarding a particular IVD offered as an LDT, and (5) an MDR query conducted in DMP in January 2022 as part of an investigation into potential genetic non-invasive prenatal screening (NIPS) tests of concern, informed by knowledge of firms that might be offering such tests as LDTs (Search terms: "NIPT", "Prenatal", "Sequenom", "MaterniT21", and the MAO product code).

associated with these tests. We note that FDA has not confirmed the veracity of the information in every MDR.

Non-Invasive Prenatal Screening (NIPS)

FDA received 11 MDRs[4] from patients describing inaccurate results (8 false positives and 3 false negatives) from NIPS tests from across seven laboratories from 2013 to 2023. NIPS tests analyze small fragments of fetal DNA circulating in a pregnant person's blood to determine the risk that the fetus has certain genetic abnormalities. In these MDRs, patients reported numerous adverse events following false results, including anxiety, emotional turmoil, and sleep disturbance, as well as one case of suicidal ideation.

Early Melanoma Detection Test

FDA received a MDR[5] in 2023 from a patient reporting a false positive result from DermTech's melanoma detection test that led to unnecessary biopsy and likely scarring. This test collects skin cells through a sticker, uses gene expression technology to detect early melanoma, and claims to inform the need for surgical biopsy. The MDR cited insufficient evidence to establish a relationship between results from this test and the potential for/risk of melanoma. The MDR also described that the test is not supported as a screening standard and has not been clinically validated for this sample type, that there is insufficient evidence that the test is safe and effective in the clinical evaluation of skin lesions to triage suspicious lesions to biopsy, and that the product is misbranded and falsely labeled.

Lung Nodule Risk Assessment Test

FDA received a MDR[6] in 2021 from a healthcare provider stating that Biodesix's Nodify XL2 test, which is intended to identify the probability of lung cancer in patients with lung nodules, underestimated cancer risk in a large percentage (~40%) of patients. Underestimating cancer risk could provide patients with a false assurance that they are not at risk of cancer, which may lead them to forgo necessary follow-up diagnostic procedures and potentially delay detection of lung cancer, ultimately worsening patient outcomes. The reporter of the MDR also identified a 2022 publication (a draft of which was available online in advance of publication) in the Journal of Bronchology and Interventional Pulmonology that reported that this test incorrectly calculates and applies likelihood ratios, which may lead to falsely low estimates of the probability of cancer, and encouraged physician reassessment for patients that received "reduced risk" results.[7]

---

[4] MW5028444, MW5033207, MW5056359, MW5114346, MW5057632, MW5041599, MW5062480, MW5041668, MW5058670, MW5059350, MW5118392

[5] MW5118236

[6] MW5101029; additional allegation documentation in CTS ((b)(4)

[7] https://journals.lww.com/bronchology/Fulltext/2022/01000/Interpretation_and_Application_of_the_Likelihood.10.aspx

Breast Cancer Prognosis Test

FDA received ten MDRs[8] between 2010 and 2016 for Oncotype Dx[9], offered by Genomic Health (now Exact Sciences). The test analyzes tumor tissue for HER2 gene expression and uses a proprietary algorithm to provide a score related to risk of cancer recurrence and likelihood that chemotherapy will benefit the patient. The test is used to guide treatment decisions for patients with breast cancer. Of these ten MDRs, nine were from the Chief of Pathology at an academic medical center claiming that the test returned grossly inaccurate results that could cause clinical confusion and may result in inappropriate treatment, which could result in premature death. This Chief of Pathology alleged that the test had a false negative rate of 69% and missed 100% of HER2 equivocal cases identified by an FDA-authorized test. The tenth MDR for this test was from a patient with breast cancer who reported misleading and confusing test results that the patient and multiple providers had difficulty interpreting to determine whether to proceed with chemotherapy.

Porphyria Testing

FDA received a MDR[10] in 2019 regarding a false negative result from Quest Diagnostics' blood plasma fractionated porphyrin test. This IVD was offered as an LDT to aid in the diagnosis of certain types of porphyrias, a group of rare metabolic disorders, in symptomatic patients. The report was submitted by a parent with a family history of acute intermittent porphyria, whose son was experiencing symptoms of porphyria and obtained a false negative test result.

Infectious Disease Next-Generation Sequencing (NGS) Tests

FDA received a MDR[11] from a healthcare provider in 2016 reporting that Granger Genetics was offering various infectious disease NGS tests as LDTs without validation, and that medical decisions made with these unvalidated tests could lead to limb loss, women's health issues, and urological issues. The healthcare provider alleged that a series of NGS tests for infectious disease were transferred from one company to another and offered without supporting data for uses that included diagnosing prostatitis, informing the need for amputation, identifying over 100,000 bacteria, and informing which antibiotics would work.

Hereditary Cancer Risk Tests

FDA received a MDR[12] from a physician in 2016 describing a false negative *BRCA1* genetic test result from a hereditary cancer risk assessment test by Gene ID. The patient had a family

---

[8] MW5020797, MW5020803, MW5020806, MW5020809, MW5020846, MW5018398, MW5020799, MW5020801, MW5020807, MW5059937

[9] This test was also included in FDA's 2015 report on problematic LDTs as an example of a test that yields false negatives that would prevent breast cancer patients from receiving appropriate cancer treatment and could lead to cancer progression. FDA, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies," November 16, 2015, available at http://web.archive.org/web/20151122235012/https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf.

[10] MW5091923

[11] MW5066562

[12] MW5061341

history of increased cancer risk and was subsequently diagnosed with breast cancer as well as retested and identified as a *BRCA1* mutation carrier by another laboratory. The test that was the subject of this MDR is currently offered to predict a person's risk of cancer and to inform risk to family members, identify the need for screening and surgical intervention, and provide in vitro fertilization (IVF) and prenatal genetic diagnosis to prevent continuation of risk. Also in 2016, FDA received another MDR[13] from a healthcare provider regarding a different patient who received results from this test that were discrepant with the results from another IVD offered as an LDT.

Proteomic Oncology Blood Test

FDA received a MDR[14] in 2016 from a patient who received a false positive breast cancer result from an ONCOBlot Labs proteomic oncology blood test. The patient alleged that the false positive result led to unnecessary follow-up procedures, including a breast MRI and breast biopsy, as well as emotional anguish and monetary expenses.

Medication Adherence Test

FDA received a MDR[15] in 2009 from a health professional regarding a false positive result from the Ameritox Ltd. Rx Guardian Urinalysis drug test in a patient under long-term pain management. The report alleged that the patient was taking medication that would interfere with the test's results, and that a false positive result led to inappropriate clinical management (by a different healthcare professional), including abrupt medication discontinuation without assistance other than a recommendation for rehabilitation.

B. Allegations

FDA has received multiple complaints and other allegations regarding IVDs offered as LDTs. Though FDA has not confirmed the veracity of the information in every complaint and allegation, collectively this information points to potential problems among IVDs offered as LDTs.

Lead Tests

In 2021, (b)(4) contacted FDA[16] about laboratories using dried blood samples collected on filter paper to screen young children for elevated blood lead levels. Blood lead testing is extremely susceptible to environmental contamination and variability in specimen integrity. There is no scientific consensus that filter-paper based blood collection is an acceptable substitute for liquid blood samples to assess blood lead levels,[17] and use of dried blood samples may compromise the accuracy of lead test results.

---

[13] MW5062390
[14] MW5062882
[15] MW5011950
[16] Source documentation in CTS ((b)(4))
[17] Parsons PJ et al. (2020). A critical review of the analysis of dried blood spots for characterizing human exposure to inorganic targets using methods based on analytical atomic spectrometry, J Anal At Spectrom 35, 2092-2112.

In a separate matter brought to FDA's attention in 2020 by (b)(4) [18], a laboratory repurposed an instrument designed and manufactured for environmental lead testing for clinical use. After reviewing the laboratory's analytical validation data, FDA found them insufficient to establish that the test could accurately and precisely detect lead in a blood sample. There is no safe level of lead in the blood,[19] [20] [21] and chronic exposure to environmental lead may cause serious health problems, including anemia, kidney dysfunction, neurocognitive problems, digestive, cardiovascular, and reproductive issues, and death. Thus, false negative lead test results can have serious health implications.

Oncology Diagnostics for Treatment Selection

FDA received an allegation[22] in 2019 that (b)(4) forged patient reports for tests that inform oncology treatment selection. Due to test failures and lack of confidence in the test results, the laboratory reported all results as negative. In general, patients who receive false negatives may not be considered for targeted therapy from which they may have derived clinical benefit, potentially resulting in the absence or delay of optimized treatment, which could lead to cancer progression and/or death. The complainant also alleged that a lack of a formal standard operating procedure system caused test performance to vary and allowed for errors.

Autism Spectrum Disorder (ASD) Test

(b)(4) reached out to FDA in 2019 with concerns that (b)(4) test was being marketed at the development stage and lacked clinical data supporting its commercial use.[23] (b)(4) was providing funding for the test and assisting the test manufacturer in designing appropriate validation studies. FDA had also received pre-submissions[24] for this test, and the preliminary data provided in the pre-submission was insufficient to support this use. Inaccurate results from tests intended to aid in the diagnosis of autism could lead to unnecessary hardship on the family as well as delays in appropriate treatment.

Gonorrhea Antibiotic Resistance Test

FDA received an allegation[25] from (b)(4) in 2014 expressing concerns about inaccurate results from a test for gonorrhea antibiotic resistance offered by (b)(4) (a reference laboratory). The allegation stated that the test wrongly identified a gonorrhea case as drug resistant and that the test method did not correspond with standard laboratory testing for antibiotic resistance. In the allegation, (b)(4) indicated that the implications of the alleged inaccurate

---

[18] Source documentation in CTS ((b)(4))
[19] https://www.cdc.gov/nceh/lead/prevention/health-effects.htm
[20] https://www.who.int/news-room/fact-sheets/detail/lead-poisoning-and-health
[21] https://www.epa.gov/ground-water-and-drinking-water/basic-information-about-lead-drinking-water#:~:text=EPA%20and%20the%20Centers%20for,to%20health%2C%20especially%20for%20children.
[22] Source documentation in CTS (b)(4)
[23] Source documentation in CTS ((b)(4)
[24] Review documentation in CTS ((b)(4)
[25] Source documentation in CTS ((b)(4)

results include misinformed clinical management and receipt of ineffective antibiotic treatment for the patient. The (b)(4) conducted a subsequent antibiotic susceptibility test to inform patient management before treatment decisions were made in this specific case. Untreated infections can cause vulvovaginitis, salpingitis, pelvic inflammatory disease, infection of the oral or anal cavities, or eye infection, and the original infection may also develop into disseminated gonococcal infection. Inaccurate results can also have broader public health implications when they lead to a patient unknowingly infecting others with antibiotic resistant gonorrhea.

C. Submissions

FDA has gathered information about IVDs offered as LDTs[26] through its review of submissions to the Agency. Although the Agency generally has not enforced requirements for most LDTs, it has received submissions from some laboratories seeking marketing authorization, or exploring the requirements for authorization of, their tests. FDA has received numerous premarket submissions (i.e., 510(k)s, de novo classification requests, Humanitarian Device Exemption (HDE) applications, and Premarket Approval Applications (PMA)), Q-submissions, and investigational use applications for IVDs offered as LDTs. FDA's review of these applications/submissions (referred to as "submissions" throughout) has revealed significant concerns in some cases. Examples of these concerns are set forth below, and we note all examples are IVDs that were offered prior to or during FDA review.

Tests for Rare Diseases

FDA has received multiple submissions for tests offered as LDTs intended to diagnose or inform patient management of rare diseases, where the tests were not validated properly and/or had unacceptably high rates of false results.

In 2020, FDA received (b)(4) application[27] for (b)(4) assay to inform treatment considerations for patients with (b)(4), a rare blood cancer. The application revealed inadequate validation and a concerning false positive rate. The sponsor withdrew the application after feedback from FDA. In general, inaccurate results from tests used to inform cancer treatment considerations may lead to suboptimal patient management decisions.

Also in 2020, FDA received (b)(4)[28] for (b)(4), which is a genetic test that informs (b)(4) treatment eligibility for patients with (b)(4). FDA's review revealed that the submission did not contain sufficient information to determine whether the test accurately and reliably identified patients that would benefit from such treatment. For example, the submission lacked interference testing and sample stability data, the precision study did not assess key gene regions, and accuracy data only covered mutations consisting of a single base pair insertion or

[26] FDA relied on representations made by the manufacturer in identifying IVDs offered as LDTs. This self-identification does not necessarily capture all submissions for IVDs offered as LDTs and does not indicate FDA concurrence that these are LDTs.

[27] Review documentation in CTS (b)(4)

[28] Review documentation in CTS (b)(4)

deletion when the test was intended to detect mutations consisting of insertions and deletions up to 50 base pairs. The sponsor conducted additional validation studies at FDA's request and revised the intended use of the test to align it with supporting data in order to obtain marketing authorization (b)(4). In general, inaccurate results from tests used to determine treatment eligibility may lead to patients receiving drug treatments that may not be effective or missing an opportunity for beneficial drug treatment.

In 2017, FDA received a de novo classification request for (b)(4) test[29] intended to diagnose and monitor disease progression or treatment of Fabry disease. Fabry disease is a rare neurological disease which often presents in early childhood, and can cause early death due to kidney failure, stroke, and heart attack. During review of this submission, FDA identified multiple issues with the test, including insufficient analytical and clinical validation data to support the proposed intended use of the test. For example, the submission lacked: any clinical data demonstrating the ability of the test to aid in the diagnosis of Fabry or monitor disease progression or treatment of Fabry disease; software validation; precision studies evaluating typical sources of variation that could cause imprecision; a linearity study to demonstrate the test can measure the quantity of the biomarker in the types of specimens the test is intended to be used with; and interference testing data to demonstrate there would not be false results when substances reasonably expected to be in samples were present. Further, sample stability data indicated that samples stored in conditions recommended by the laboratory were unstable and could return erroneous results. Moreover, FDA noted a high false negative rate in the data provided, which could lead to failure of the patient to receive treatment, potentially resulting in worsening symptoms, kidney failure, stroke, heart attack, and early death. Inaccurate results for monitoring disease progression could cause the disease to appear stable where it is not, leading to inadequate patient treatment. The premarket submission was withdrawn by the company following FDA's identification of concerns.

In 2014, FDA received (b)(4) applications[30] [31] for two genetic tests offered by (b)(4) to inform treatment eligibility (b)(4). The data provided were inadequate to demonstrate that the tests could accurately and reliably identify patients that would benefit from such treatments. For example, there was a lack of software validation and verification, the analytical accuracy and sample stability studies were improperly designed such that FDA could not tell whether the test worked or not, and the analytical validation studies were conducted with an earlier version of the test such that the data generated from those studies was not applicable to the version that was submitted for approval. (b)(4) addressed FDA's concerns by conducting additional analytical validation testing and updating their labeling. Both tests were eventually approved but had been offered for clinical use prior to completion of sufficient validation.

---

[29] Review documentation in CTS ((b)(4)

[30] Review documentation for (b)(4) in CTS ((b)(4))

[31] Review documentation for (b)(4) in CTS ((b)(4))

Neurological Diseases and Conditions

In 2022, FDA received (b)(4) for (b)(4) (b)(4)[32] intended to aid in the early detection of dementia subtypes, including Alzheimer's (b)(4). Inaccurate results from tests intended to aid in the diagnosis of neurological diseases may lead to a delay in appropriate treatment and clinical management or misdiagnosis and unnecessary treatment.

FDA reviewed a de novo classification request for (b)(4) test[33] offered as an LDT to aid in the diagnosis of Alzheimer's disease (AD) and differentiate AD from other forms of dementia. (AD is the most common form of dementia in older adults). During FDA's review, FDA found that the submission did not include adequate performance data to determine the analytical reliability of the test (e.g., inappropriately designed precision studies, inappropriately designed reference range study with less than a quarter of the recommended number of samples, missing stability and interference studies), and the clinical data presented may not have been accurate because the study population was not representative of the intended patient population in the U.S. The submission also lacked software validation and verification. The IVD is still being offered as an LDT. Many treatable conditions have symptoms similar to AD or another form of dementia. Without sufficient information to demonstrate adequate validation, a test's performance is unknown, which may put patients at risk of harm due to inaccurate results. In general, false positive results from AD diagnostic tests could lead to unnecessary workup and treatment of AD, as well as a delayed diagnosis and anxiety regarding an incorrect diagnosis, and false negative results could delay receipt of available treatment and early planning in the course of progressive disease.

Coronary Artery Disease (CAD) Gene Expression Test

(b)(4), FDA received pre-submissions from (b)(4) for the (b)(4) test to rule out obstructive CAD in stable non-diabetic patients with symptoms suggestive of CAD. Pre-submissions generally do not include data; however, in this case (b)(4) provided the clinical validation data they intended to submit to support a future marketing authorization submission. These data would not have been adequate to support the test was safe and effective since the clinical validation study did not collect data in the intended use population. Information provided by (b)(4) in (b)(4) also indicated that the analytical validation for the test was inadequate.[34] The test was offered for clinical use (b)(4). Without sufficient information to demonstrate that the test is analytically and clinically validated, the performance of the test is unknown, which may put patients at risk of harm due to inaccurate results. Inaccurate results could lead to ineffective patient assessment and treatment decisions for patients with symptoms of CAD. For example, false positive results could lead to unnecessary treatment or medical procedures, and false negative results could lead to failures to prevent serious issues such as heart attacks, potentially resulting in missed or delayed diagnosis and missed opportunity for treatment. (b)(4) and the test is no longer offered.

[32] Review documentation in CTS (b)(4)
[33] Review documentation in CTS (b)(4)
[34] Review documentation in CTS (b)(4)

Tests to Select Multiple Myeloma Treatment

In 2022, FDA received two investigational use submissions[35] to conduct clinical investigations of IVDs offered as LDTs intended to select treatment for multiple myeloma patients as part of therapeutic product clinical trials. These submissions did not contain appropriate analytical validation studies to show the tests were likely to work, which is a critical step in determining whether such therapeutic product clinical trials are safe to proceed. In one case, the precision study did not include samples close to the test's cut-off or negative samples and, therefore, the reliability of the test could not be determined. For the other IVD, the analytical validation studies were performed using two different sample types without data to support that the performance between the two sample types would be equivalent. As such, there was not enough data to determine that the test would be accurate and reliable enough in either sample type. In general, inaccurate results from tests used to guide cancer treatment decisions could lead to suboptimal treatment decisions for patients with cancer.

Tests to Select Treatment Based on Detection of Minimal Residual Disease (MRD)

Between 2018 and 2022, FDA received five investigational use submissions from laboratories to use investigational tests for MRD in clinical trials of a therapeutic product for patients with cancer. The information provided for these tests was inadequate to support a determination that the trials were safe to proceed (e.g., missing accuracy, analytical specificity, precision, limit of detection, and sample stability studies). These labs did not properly design and perform analytical validation, which is a critical first step prior to using a test in such therapeutic product clinical trials. The lack of adequate validation resulted in delay of the clinical trials. In three cases,[36] the sponsor withdrew the unvalidated tests from the clinical studies. In two cases,[37] FDA worked with the labs, which were located at academic medical centers, by providing feedback on the appropriate design of validation studies. One trial was eventually deemed safe to proceed. FDA is still working with the second laboratory on appropriate validation. In the meantime, the performance of the test is unknown, which may put patients at risk of harm due to inaccurate results leading to suboptimal patient management.

Acute Myeloid Leukemia (AML) Test

In 2021, FDA received a 510(k) submission[38] from (b)(4) for their (b)(4) (b)(4) test for monitoring changes in burden of disease in pediatric and adult patients with AML during and after treatment. The submission did not contain adequate analytical and clinical validation studies to show the test worked as intended. For example, the sponsor did not provide any data from interference, detection limit, and reagent stability studies;

---

[35] Review documentation in CTS (b)(4) (b)(4)

[36] Review documentation in CTS (b)(4) (b)(4)

[37] Review documentation in CTS (b)(4)

[38] Review documentation in CTS (b)(4)

did not submit data from precision studies to demonstrate the test is reliable in intended use specimens; only used one specimen to evaluate sample stability rather than the recommendation of at least ten; and included samples in the clinical study that were not the sample type intended for use with the test. The sponsor withdrew the submission after FDA raised concerns with the inadequate validation data. Without sufficient information to demonstrate adequate validation, a test's performance is unknown, which may put patients at risk of harm due to inaccurate results. In general, inaccurate results from tests to monitor disease burden during and after treatment for AML could lead to suboptimal clinical management of patients with AML. The risk of false negative results (i.e., a patient assumed to have a more favorable prognosis based on the false negative result) could potentially result in a reduction in the level of care such as less medication use, subsequent confirmatory testing, and other possible treatment decisions. False positive results (i.e., a patient who is disease free presumed to have a hematologic malignancy based on the positive test result) could result in additional unnecessary testing.

Hereditary Cancers Test

In 2019, FDA received a de novo classification request[39] for (b)(4) (b)(4) a genetic test that identifies certain genetic variants associated with hereditary cancer predisposition syndromes to inform medical management decisions (e.g., increased cancer screening, preventative surgeries, etc.). The submission did not include adequate performance data to demonstrate the analytical accuracy and reliability of the test. For example, the submission did not include sufficient accuracy or precision data for certain types of variants the test was intended to detect. In general, inaccurate results from tests used to inform medical management decisions for individuals with an increased risk of cancer due to a genetic predisposition may lead to increased screening, trials of medications, invasive diagnostic procedures, and possibly surgical removal of organs. The sponsor withdrew the submission after feedback from FDA.

Prognostic Brain (Glioblastoma multiform) Test

In 2022, FDA received a de novo classification request[40] for (b)(4) (b)(4), a test used to aid in management of glioblastoma patients and inform prognoses. The submission did not contain adequate data to support the intended use of the device. For example, the submission lacked clinical data demonstrating that the test could provide meaningful information on the state of glioblastoma patients, lacked data to demonstrate the test was accurate, included precision data that showed the test would not provide reliable results, and lacked cybersecurity documentation. The use of an inadequately validated prognostic test may lead to inappropriate patient management decisions, which could ultimately result in patient harm. The sponsor did not respond to FDA's concerns and the submission was withdrawn.

[39] Review documentation in CTS (b)(4)
[40] Review documentation in CTS (b)(4)

D. Emergency Use Authorization (EUA) Requests

FDA has received and reviewed a significant volume of EUA requests from laboratories. Experience with these submissions has heightened FDA's concerns about the validation of IVDs offered as LDTs. Examples of these concerns are set forth below.

COVID-19 Molecular Diagnostic Tests

FDA conducted an analysis of the first 125 requests for COVID-19 molecular diagnostic tests from laboratories and found that 82 (66%) were not designed or validated appropriately. Please see Memorandum to File from Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs, RE: Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2 (September 22, 2023), available in Docket No. FDA-2023-N-2177, for the full analysis of the 125 molecular diagnostic COVID tests. Without sufficient information to demonstrate that such tests have been adequately validated, the performance is unknown, which may put patients at unreasonable risk of harm due to inaccurate results. In the case of an emergency involving an outbreak, inaccurate tests can lead to greater spread of the disease and poor management of the outbreak due to false results.

COVID-19 Serology Tests

FDA received multiple EUA requests for COVID-19 serology tests from laboratories that either lacked sufficient validation data or included data demonstrating poor performance. For example, one academic medical center laboratory[41] (b)(4) had an unacceptable false negative rate and their EUA request was denied. Another academic medical center laboratory[42] (b)(4) had an unacceptable false positive rate that was noted during triage and was declined for further substantive review. A third academic medical center laboratory (b)(4) submitted two EUA requests. FDA declined to issue EUAs for these tests[43] as both of the EUA requests lacked adequate analytical validation data and sufficient information to understand how the clinical study was performed. The test of a fourth academic medical center laboratory (b)(4) had unacceptably high false positive and false negative rates and their EUA request was withdrawn.[44] This laboratory also developed a test to quantitatively measure neutralizing antibodies against SARS-CoV-2 and identify convalescent plasma donors. The EUA request did not include any clinical data to demonstrate that the test could identify convalescent plasma donors. The request also lacked data from detection limit and linearity studies to demonstrate the test could measure the quantity of neutralizing antibodies. Their EUA request was withdrawn following feedback from FDA.[45] Use of poor performing and inadequately validated tests may lead to inappropriate patient management decisions.

---

[41] Review documentation in CTS (b)(4)
[42] Review documentation in CTS (b)(4)
[43] Review documentation in CTS (b)(4)
[44] Review documentation in CTS (b)(4)
[45] Review documentation in CTS (b)(4)

COVID-19 Antigen Test

FDA received an EUA request for a COVID-19 antigen assay from an academic medical center laboratory ([(b)(4)][46] that lacked data demonstrating the test was analytically and clinically validated. Specifically, the EUA request did not include: data from interference testing to demonstrate that reasonably expected microbial and endogenous substances would not cause false results, sufficient information on how the limit of detection study was conducted, nor clinical study data to demonstrate the performance of the test for asymptomatic subjects (the proposed indication included testing of asymptomatic subjects). The limited data that was submitted showed that the test had an unacceptably high rate of false positive results. If this test were used, people without COVID-19 would be incorrectly identified as having COVID-19 when they were in fact negative.

H1N1 Test

FDA received an EUA request[47] for a test to detect and differentiate the novel H1N1 and seasonal strains of influenza virus during the 2009 H1N1 influenza public health emergency from an academic medical center laboratory ([(b)(4)]. However, clinical data submitted by the laboratory demonstrated that the test could not detect or distinguish novel H1N1 from seasonal H1N1, and the EUA request was withdrawn. If this test were used in clinical practice, patients with pandemic flu would have been incorrectly identified as having seasonal flu. These patients would not have been reported to public health authorities and would not have received the treatment and follow-up instructions appropriate for pandemic flu. Not only could this have adversely impacted the individual tested, it could also have put others at greater risk of disease and misinformed the national public health response.

Brittany W. Schuck -S

[46] Review documentation in CTS ([(b)(4)])
[47] Review documentation in CTS ([(b)(4)])

Addendum

The following paragraph replaces the paragraph beginning "In 2022, FDA received," at the top of page 9 in this memorandum to file, Docket No. FDA-2023-N-2177, re: Examples of In Vitro Diagnostic Products (IVDs) Offered as Laboratory Developed Tests (LDTs) that Raise Public Health Concerns:

> In 2022, FDA received (b)(4) for (b)(4) (b)(4) [1] intended to aid in the early detection of dementia subtypes, including Alzheimer's (b)(4). The request included preliminary data suggesting the accuracy of the test was poor. Inaccurate results from tests intended to aid in the diagnosis of neurological diseases may lead to a delay in appropriate treatment and clinical management or misdiagnosis and unnecessary treatment.

Brittany Schuck, Ph.D.
Deputy Office Director
Office of In Vitro Diagnostics (OHT7)
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration

September 26, 2023

[1] Review documentation in CTS ((b)(4))

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Memorandum

Date: September 22, 2023

To: Administrative Files:
Docket No. FDA-2023-N-2177

From: Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs
Center for Devices and Radiological Health (CDRH)
U.S. Food and Drug Administration

Subject: Summary of 2020 Assessment of the First 125 EUA Requests from Laboratories for Molecular Diagnostic Tests for SARS-CoV-2

In the Spring of 2020, FDA determined that it would be beneficial to assess emergency use authorization (EUA) requests for molecular diagnostic SARS-CoV-2 tests offered by laboratories, many of which were offered prior to authorization, as described in the COVID-19 Test Guidance.[1] The assessment aimed to evaluate whether laboratory manufacturers were offering well designed and appropriately validated tests.

This memo summarizes the analysis that was conducted in 2020. Since that time, some issues identified in this analysis have been resolved by redesign, additional testing, limitations in indications for use, or a combination of those. Forty-seven (47) of the 82 EUA requests previously identified as having major issues have been authorized following these changes.

At the time of the analysis, tests used to diagnose SARS-CoV-2 infection were primarily molecular tests that identify the presence of the virus's genetic material using a technology called reverse transcription polymerase chain reaction (RT-PCR). RT-PCR testing consists of collecting a specimen from the patient (typically with a swab), extracting RNA from inside any virus particles in the specimen, converting the RNA to DNA within the test mixture, amplifying (i.e., making many copies of) the DNA, and determining whether any genetic material that matches the genetic code of SARS-CoV-2 is present. RT-PCR testing is considered a well-established diagnostic method that, when appropriately validated, leads to consistent and reliable results.

Methods

In the Spring of 2020, FDA identified the first 125 EUA requests from laboratories for which review was either completed or sufficient for a preliminary evaluation of the quality of the design and validation of the assay in the original EUA request. Upon completing initial review per standard practice, the lead reviewers of each EUA request provided me with their findings. I confirmed reports in the administrative record (i.e., review memos and correspondence with laboratories) and categorized the findings for analysis.

[1] See FDA, "Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency; Guidance for Clinical Laboratories and Food and Drug Administration Staff," February 29, 2020, available at https://web.archive.org/web/20200229191633/https:/www.fda.gov/media/135659/download (this guidance subsequently was revised in March 2020, May 2020, November 2021, September 2022, and January 2023).

Results

Of the first 125 EUA requests reviewed, FDA identified 82/125 (66%) tests with "major issues" – i.e., validation issues, design/indications for use issues, or both. Forty-three (43) of the 125 (34%) tests had no major issues, meaning that the laboratory did not have to address significant deficiencies or conduct additional validation studies, reanalysis, redesign or relabeling to meet the EUA standard. A summary of the number of issues identified is provided in Figure 1 and Table 1.

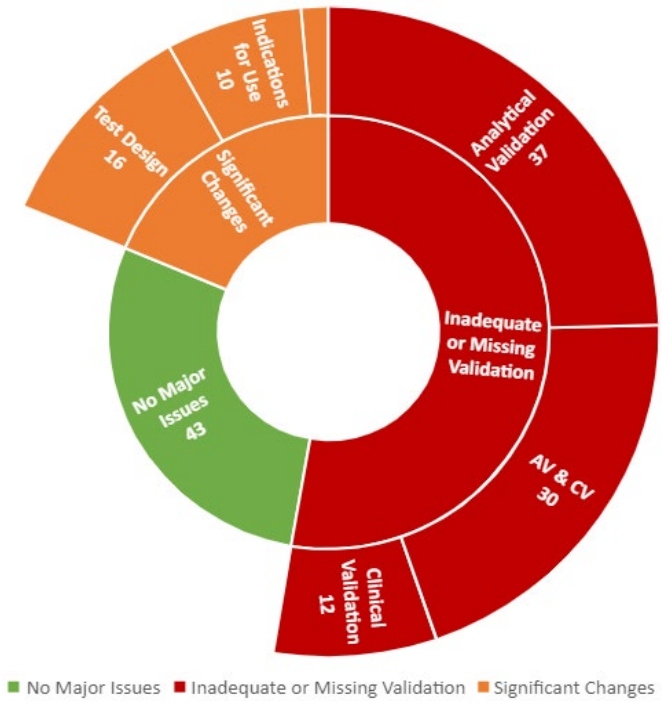


Figure 1. 82/125 (66%) of the tests reviewed included major issues

Table 1. Summary of EUA requests[2]

	Number of EUA Requests	Percent of EUA Requests
No Major Issues	**43**	**34%**
Validation Issues	**79**	**63%**
Analytical Validation Inadequate or Missing	37	30%
Clinical Validation Inadequate or Missing	12	10%
Both Analytical and Clinical Inadequate or Missing	30	24%
Significant Design/Indications for Use Issues	**28**	**22%**
Test Design Issues	16	13%
Indications for Use Issues	10	8%
Both Test Design and Indications for Use Issues	2	2%

For tests where no major issues were identified, FDA may have requested clarification or additional details regarding studies already conducted. In five of these cases, the assays were revalidated because the laboratory changed the design (e.g., to increase throughput) or the indications for use (e.g., to add saliva specimens or home collection), but these changes are not considered "major issues" as they were not done in response to any problems identified.

Of the 82/125 tests identified with major issues, the primary findings included 1) inadequate or missing analytical and/or clinical validation or 2) significant design and/or indications for use issues.

Validation Issues

Seventy-nine (79) tests, representing 63% of those evaluated, had validation issues. This includes inadequate or missing analytical validation data, inadequate or missing clinical validation data, or a combination of the two. Common issues are described below.

Cross-cutting Issues with Validation:

- Some laboratories did not provide minimal descriptive information about their validation studies in the EUA request for FDA to assess the performance.

[2] Note that some tests included in this analysis had multiple issues, which is why the total number of EUA requests with major issues (n=82) is smaller than the total number of issues identified.

- Several laboratories conducted the appropriate types of validation testing, but the results demonstrated poor performance. Some laboratories resolved initial performance concerns through various means such as redesigning their tests or limiting the indications for use of the test; however, others stopped testing and their EUA requests were withdrawn or denied/declined.
- Some laboratories failed to include any analytical and/or clinical validation information in their EUA requests.
- Several laboratories failed to conduct validation of their complete test system, including the collection device and RNA extraction kit. It is important that tests be validated with these components, as different components can impact performance (even those based on the same technologies). The significance of validating a test with the complete test system is highlighted by examples from outside the analysis. For example, FDA observed a COVID-19 test was only capable of detecting the virus when levels were 5-10x higher with one extraction kit as compared to another.

Analytical Validation:

- The most common issue with analytical validation[3] was related to use of synthetic DNA or small fragments of synthetic RNA. Using either may overestimate performance. We acknowledge that viral RNA was difficult to obtain through April 2020, and so FDA had recommended that if synthetic RNA was used, validation should include full length or long strand RNA to closely approximate natural viral RNA.

  Forty-three (43) tests, representing 34% of those evaluated, used synthetic DNA or small fragments of synthetic RNA. Of these, many were redesigned after identifying problems with their test upon revalidation. Using synthetic DNA or small fragments of synthetic RNA precludes evaluation of all key steps in the testing process and therefore can make the assay's Limit of Detection (LoD) seem better than it is.

  - When synthetic DNA is used to evaluate an assay's LoD, the evaluation omits two fundamental assay steps that are part of clinical testing: the step in the assay that extracts the viral RNA from within the virus's protein shell and the step in the assay that makes DNA from the virus's RNA. The assay may be inefficient at performing both steps, but LoD studies using DNA would not be able to reveal this issue. Inefficiencies in extraction and conversion from RNA to DNA would significantly change the LoD, so testing DNA can give better results than would occur in true clinical use.
  - When small RNA fragments are used to evaluate an assay's LoD, the test's targets do not compete with the other parts of the virus's RNA that are present in natural clinical specimens for reaction with the enzymes in the assay. Because the primers, probes and enzymes that react are not distracted by other parts of RNA, they can more efficiently amplify the target RNA and show superior performance. Primer and probe binding is also easier when the target is small.

  Table 2 below shows the differences in LoDs determined for the same assays with synthetic DNA or synthetic RNA fragments versus viral RNA for three tests included in this analysis, for illustrative purposes.

  Table 2: Difference in identification of the lowest level of virus detectable by an assay when different materials are used in the assessment

[3] The assay LoD should be validated by taking specimens from patients who are not infected (i.e., "clinical matrix") and mixing in different known concentrations of viral RNA. The clinical matrix evaluated should match that for which the test is intended to be used, because assays can perform differently with different types of specimens (e.g., respiratory specimens versus saliva). Developers then run their assay on specimens consisting of clinical matrix with different levels of viral RNA to determine the lowest concentration at which 19/20 specimens (95%) test positive with the assay. While alternative approaches, such as creating contrived specimens with synthetic DNA, can be used, particularly in the early stages of an emergency when availability of viral RNA is limited, the limitations of these approaches need to be addressed in the validation. Lower LoD usually translates into better sensitivity in clinical specimens and so therefore is an important assessment.

	LoD based on analysis with synthetic DNA or synthetic RNA fragments	LoD based on analysis with viral RNA	Difference
Example Assay 1	8 copies/µl	55 copies/µl	**7 X**
Example Assay 2	3.1 copies/µl	100 copies/µl	**32 X**
Example Assay 3	1.5 copies/µl	5 copies/µl	**3 X**

- Another common issue with analytical validation was failure to use clinical matrix. In some cases, laboratories did not mix viral RNA with any clinical matrix while others mixed viral RNA with clinical matrix that typically performs better than the specimen type they intended to be used for their test (e.g., using specimens from nasopharyngeal (NP) swabs rather than the intended sputum specimen). In these cases, the assessment did not address the assay's ability to detect virus in the clinical specimens with which it would be used in practice. Table 3 below shows the differences in LoDs determined for the same assays with and without intended clinical matrix for three tests included in this analysis, for illustrative purposes.

Table 3: Difference in identification of the lowest level of virus detectable by an assay when assessed without intended clinical matrix versus in intended clinical matrix

	LoD based on analysis <u>without</u> intended clinical matrix	LoD based on analysis in intended clinical matrix	Difference
Example Assay 1	140 copies/ml*	1230 copies/ml	**9 X**
Example Assay 2	25 copies/ml*	125 copies/ml	**5 X**
Example Assay 3	0.156 copies/µl**	12.5 copies/µl	**9 X**

**LoD based on analysis in neat transport media (i.e., no clinical matrix)*
***LoD based on analysis in clinical matrix from NP swabs rather than the intended specimen type (sputum)*

<u>Clinical Validation:</u>

- The most common issue with clinical validation was due to an insufficient number of samples.

  In one case, an academic medical center originally included validation with only 12 positive samples, showing perfect performance among this limited sample set. FDA requested evaluation of additional specimens to confirm. When an additional 12 samples were evaluated, the cumulative performance dropped to an unacceptable positive percent agreement (PPA) of 71%, and the EUA request was withdrawn.

- Another common issue with clinical validation was use of contrived clinical specimens made with inappropriate concentrations of viral RNA or with DNA. If a laboratory includes too much viral RNA, the evaluation does not assess how well the test performs on specimens near the cutoff used to distinguish positive and negative results. In several cases, the laboratories' calculation errors resulted in testing inappropriately high levels of virus, from which assay performance could not be determined; essentially, a bad test could appear to perform well. Similarly, for the reasons outlined above regarding analytical validation, use of DNA is a less challenging evaluation than use of viral RNA.

  In one case, a laboratory performed new studies at FDA's request, and the new data revealed contamination of reagents and a high signal variability between replicates of the same sample, suggesting issues with the reproducibility of the assay. The laboratory could not identify the root cause of these problems, which can lead to both false positive and false negative results. The EUA request was denied/declined.

Significant Design/Indications for Use Issues

Test Design Issues:

Following FDA review, 18 laboratories changed the design of their test to address concerns with performance or contamination. In some cases, FDA suggested specific design changes to address identified issues. In other cases, FDA requested re-validation with appropriate methods, which enabled the laboratory to identify and address issues with design changes. In all 18 cases, FDA's review and feedback led the laboratories to improve the design of their tests. Examples are provided below:

- One laboratory did not use viral material for its analytical validation and generated false negative results on 3 out of 5 positive clinical specimens. FDA asked the laboratory to consider a change in its algorithm and to redo the validation appropriately to assure the test performed adequately (i.e., that no false negatives were detected in the 5 positive clinical specimens). The new studies showed a contamination issue. In working to address these issues collectively, the laboratory redesigned the assay, including using different types of testing instruments. FDA worked with the laboratory to resolve multiple issues with its test development over time.
- Several laboratories did not include the minimum positive and/or negative control samples[4] needed to ensure their test continues to function properly over time. FDA interactively worked with these laboratories to build those controls into their test design to prevent inaccurate results when the test is used on patient specimens.
- In nine cases, performance data were inadequate to support authorization and the laboratories modified the interpretation algorithm to address the concerns. This included changes to the cutoff (i.e., how the test distinguishes a positive from a negative result), algorithm changes to account for certain quality control results, and algorithm changes to determine the assay output when one target is positive but the other is negative. For example, based on results from revalidation of its test with appropriate methods, one laboratory changed both the test cutoff and positive control to improve performance of the test.
- One laboratory's original test design was not specific to the novel coronavirus and did not perform well. Even though validation was conducted in a manner that over-estimates performance, results indicated it was 200x less sensitive than CDC's authorized assay. Based on FDA's feedback, the laboratory redesigned its test to be specific to the novel coronavirus and revalidated the new version of the test.
- After notifying FDA that its test was validated for clinical use, one laboratory identified a contamination issue, which the laboratory resolved by eliminating one of the test's two targets.

Indication for Use Issues:

While some problems identified through FDA review were addressed with design changes, others were addressed by changes to the indications for use of the test. Following FDA review, 12 of the 125 EUA requests assessed required changes to the indications for use of the test; most changes were based on FDA's identification of limitations in supporting data. For example:

- Several EUA requests included testing with specimen types for which validation was not provided in the EUA request, including saliva, stool, and cerebrospinal fluid (CSF). When FDA requested validation, some laboratories removed these specimen types from indications for use and stopped testing; no data was ever provided to FDA, and it is unclear if the laboratories had validated these specimen types prior to clinical use.
- One laboratory sought authorization for testing asymptomatic individuals; however, the validation data in such individuals was so poor that FDA limited authorization only to symptomatic patients rather than the standard indication for other molecular diagnostics for individuals suspected of COVID-19, regardless of symptom status.
- One laboratory's data demonstrated that when its test was run on NP swab and saliva specimens from the same patients, the results were consistent only 11% of the time. The test had been previously validated with NP swabs

[4] Molecular tests typically include quality controls to ensure problems (e.g., contamination) are detected when they arise. These controls may include positive and negative samples with known results which can be compared to the test's results to monitor performance over time.

and the laboratory considered these data adequate to support testing with saliva samples. FDA requested that the laboratory stop testing with saliva, and the laboratory agreed[5].

- In three cases, laboratories were offering testing for asymptomatic individuals with home specimen collection or drive-through collection sites. One laboratory presented data showing poor performance in tests with these specimens from asymptomatic individuals, missing 35% of positive patients and 19% of negative patients compared to when specimens were collected under the supervision of a healthcare worker. These laboratories changed the indications for use for their tests to be for symptomatic individuals only.
- Six tests were authorized with limited indications based on supportive evidence. Three had a high rate of false negative results with testing of oral fluid, but acceptable performance with other specimen types. Because data showed positive results with oral fluid were accurate, FDA authorized such tests with a limitation requiring the laboratory to confirm all negative results from testing of oral fluid by testing another specimen type. In the other three cases, the indications were limited for different reasons corresponding to the limitations in their respective datasets; one was limited to symptomatic patients, one was limited to specimens from NP swabs, and one was limited to specimens in viral transport media (i.e., not "dry" swabs).
- One laboratory sought authorization for testing dry nasal swabs from asymptomatic individuals; however, the data package included no such samples. The lab provided data on 15 dry nasal swabs from symptomatic individuals and a retrospective analysis of results from NP swabs from asymptomatic nursing home residents. The limited data suggested that the test did not perform as well with dry nasal swabs compared to NP swabs. Further, the asymptomatic data showed the test missed 2 out of the 3 samples that were in the range of viral load most often observed in the general asymptomatic population, which differs from the elderly nursing home population in which it was evaluated. Additional data was not collected, the laboratory narrowed the indications for use of the test, and the test was authorized with limitations.

Discussion

Analysis of 125 molecular diagnostic EUA requests submitted by laboratories for COVID-19 identified 82/125 (66%) with design and/or validation issues. Issues identified included inadequate test validation, need for design changes to address poor test performance and/or contamination, and lack of supportive evidence for the proposed indications. In most cases, these tests were utilized for COVID-19 detection prior to or without authorization. Therefore, tests identified under this report as having serious concerns which could impact accuracy may have been utilized clinically to test individuals suspected of having COVID-19 prior to, or without, these problems being addressed. Since the analysis was completed, FDA worked with the laboratories to address many of the issues. However, even with additional FDA collaboration, 28 tests (34% of the tests with major issues) were denied/declined EUA-authorization and the EUA requests for six tests (7% of the tests with major issues) were withdrawn by the laboratory.

Of the 125 EUA requests from laboratories assessed, 46 were developed by hospital laboratories. Overall, there was no difference in the rate of issues observed in tests developed by hospital laboratories versus commercial laboratories.

FDA recognizes that many laboratories made their own molecular diagnostic tests for SARS-CoV-2 due to the urgent need to test patients. Therefore, some of these laboratories may not routinely make tests for other purposes and may not be experienced with test design and validation. However, many laboratories included in this analysis are well established commercial and academic laboratories that conduct much of the country's clinical testing outside the pandemic. This report provides a snapshot into how various laboratories have developed and validated assays in the context of a public health emergency for COVID-19, as well as insight into how laboratory developed tests are designed, validated, and utilized. The findings from this assessment are particularly concerning because the type of test technology used for diagnosis of COVID-19, RT-PCR, is well established.

[5] At the time of review, there was not sufficient information or data to support primary saliva samples. FDA understands that additional research has been completed since the time of this analysis which supports use of saliva samples.

RELATED TOPICS:
DISEASES | REGULATION | PHARMACEUTICALS | PATIENT TESTING | PATIENT ENGAGEMENT | PANDEMICS

To Protect Patients And Spark Innovation, Codify The FDA's Oversight Of Laboratory-Developed Tests

Eli Y. Adashi, Daniel P. O'Mahony, I. Glenn Cohen

JULY 3, 2023 **DOI:** 10.1377/forefront.20230621.170697

Laboratory-developed tests (LDTs) constitute a class of diagnostic in vitro tests that are designed, manufactured, and used <https://pubmed.ncbi.nlm.nih.gov/35244685/> within a single laboratory. The Food and Drug Administration (FDA) has long viewed the oversight of the safety and effectiveness of LDTs as part of its regulatory mission <https://pubmed.ncbi.nlm.nih.gov/35244685/> . However, the scope of this FDA responsibility has been the subject of continuous evolution and contention during which the agency exercised regulatory discretion.

The issue has come into sharper focus in recent years as, the Congressional Research Service describes <https://crsreports.congress.gov/product/pdf/IF/IF11389> , "genetic testing has become increasingly available for direct purchase by consumers, generally over the internet, often without the involvement of a health care provider and for increasingly complex and common diseases (e.g., cancer)." Furthermore, there is concern <https://crsreports.congress.gov/product/pdf/IF/IF11389> that pharmacogenetic tests offered as LDTs may be relied upon by patients and their health care providers to "make adjustments to medication and/or dosing that could be detrimental to patient health." Given the increasing complexity of LDTs and their growing clinical significance, policy makers must codify the FDA's role in overseeing this diagnostic modality.

It was with this goal in mind that a bipartisan draft version of the Verifying Accurate, Leading-edge, IVCT Development (VALID) Act <https://bucshon.house.gov/uploadedfiles/valid_act_discussion_draft_12.6.18.pdf> was first released in 2018 by Representatives Larry Bucshon, MD (R-IN) and Diana DeGette (D-CO) of the House Committee on Energy and Commerce and by Senators Michael Bennet (D-CO) and Orrin Hatch (R-UT) of the Senate Committee on Health, Education, Labor, and Pensions. Despite repeated attempts during the 116th and subsequent Congresses as a standalone bill or as a constituent of other "must-pass" bills, the VALID Act has not been enacted as of the time of this writing.

disposition thereof.

A New Regulatory Framework

If enacted, the VALID Act <https://www.congress.gov/bill/118th-congress/house-bill/2369> would create a new, flexible, risk-based regulatory framework <https://pubmed.ncbi.nlm.nih.gov/34243115/> for FDA oversight of LDTs—an approach that would apply regardless of where said LDTs are produced and used. The bill thoroughly delineates the FDA oversight process including notification and listing requirements for LDT sponsors. The legislation also lays out other elements of the FDA oversight responsibility such as premarket review requirements, labeling, registration, and listing obligations. More of the same applies to design and quality responsibilities as well as to mandatory reporting of LDT upgrades, discontinuation, and adverse events.

The VALID Act establishes a three-tiered, risk-based system to classify LDTs, an approach recommended by the College of American Pathologists <https://documents.cap.org/documents/cap-may-2022-valid-act-comments.pdf> and other groups, and seeks to ensure that the FDA prioritizes its resources on the highest-risk LDTs that harbor the greatest potential to produce harm. Existing LDTs that have been the subject of historical enforcement are to be deemed exempt from FDA oversight so as to assure continued patient access. The law would also establish a precertification program for lower-risk LDTs that may not require premarket review. This element would make it possible for the FDA to establish standard validity requirements while reducing regulatory burdens in the interest of continued innovation. Low-risk LDTs that have proven responsive to the concerns of the FDA will be deemed certified and eligible for marketing.

Other "humanitarian" test exemptions are to be granted to LDTs that are "intended for use for a disease or condition for which no more than 10,000 (or such other number determined by the Secretary) individuals would be subject to negative or positive diagnosis by such test in the United States per year." In contrast, high-risk LDTs will be required to undergo premarket review of their analytical and clinical validity prior to the granting of marketing approval. The VALID Act also proposes to establish a publicly available electronic database replete with information about all of the marketed LDTs. The law would institute a user fee program to fund the LDT regulation program.

The bill's sponsors attest that by clarifying the FDA's authority, these provisions will allow the regulatory framework to keep pace with the increasing complexity of diagnostic tests and enable practitioners to respond efficiently and accurately when making health care decisions. They point to the outbreaks of COVID-19, MERS, SARS, and Ebola to underscore the importance of reliable testing in combatting contagious diseases. Moreover, in the wake of the Theranos scandal and reports questioning the accuracy <https://www.nytimes.com/2022/01/01/upshot/pregnancy-birth-genetic-testing.html> of noninvasive prenatal testing, the bill could help reaffirm public confidence in medical test results.

Congress Fails To Act—So Far

The Senate Health, Education, Labor and Pensions Committee did make an initial effort to incorporate the VALID Act into the Food and Drug Administration Safety and Landmark Advancements Act of 2022 (S. 4348), also known as the User Fee bill, and then later into the Continuing Appropriations and Ukraine Supplemental Appropriations Act of 2023 (Public Law No. 117–180). But ultimately, both laws were enacted without the VALID Act's provisions. Its exclusion from the Supplemental Appropriations Act was attributable <https://subscriber.politicopro.com/article/2022/12/valid-act-left-out-of-year-end-omnibus-00074748> , at least in part, to opposition expressed by Rep. Cathy McMorris Rodgers (R-WA), currently chair of the House Committee on Energy and Commerce. Concurrent objections were raised by elements of the clinical laboratory sector who deem the proposed FDA oversight process too costly, laborious, and burdensome, and thus antithetical to innovation.

At the time of this writing, indications are that the 118th Congress is unlikely to enact the VALID Act. Staunch supporters of the bill such as Rep. Bucshon remain committed to seeing the VALID Act as public law. However, Sen. Richard Burr (R-NC), another influential advocate, recently retired, markedly compromising the law's path toward ratification. Nevertheless, it is possible that lawmakers will single out the soon-to-be reauthorized Pandemic and All Hazards Preparedness Act as a vehicle for the passage of the VALID Act, given the recognition of lawmakers of the important role played by the LDTs in the diagnosis of SARS-CoV-2 infections during the pandemic. It is in this and related contexts that FDA-approved LDTs have proven to be all but indispensable.

Absent a legislative option for the ratification of the VALID Act, the FDA is expected to engage in rulemaking with LDT regulation in mind. FDA Commissioner Robert M. Califf, alluded to this possibility when he noted <https://www.raps.org/news-and-articles/news-articles/2022/10/califf-fda-may-use-rulemaking-for-diagnostics-refo> that "federal rulemaking—which is always an option for the FDA—is a very lengthy and contentious process … but we also can't stand by." Should the FDA choose to go this route, legal challenges to its statutory authority are to be expected. The agency can also expect to continue grappling with the ongoing lobbying by supporters and opponents of LDT regulation.

<https://www.pewtrusts.org/-/media/assets/2021/01/clinical_lab_tests_need_stronger_fda_oversights.pdf> from the Pew Charitable Trusts stated, “flawed tests can lead to serious harm. If results are not accurate and reliable, patients may receive the wrong treatment for their condition or undergo unnecessary and potentially invasive procedures. They may also experience delays in diagnosis and care that allow a disease to progress to an advanced stage and, if communicable, infect more people.”

Article Metrics

<https://www.altmetric.com/details.php?domain=www.healthaffairs.org&citation_id=150955913>

Related

CONTENT

Pharmaceuticals & Medical Technology

TOPICS

Diseases
Regulation
Pharmaceuticals
Patient Testing
Patient Engagement
Pandemics

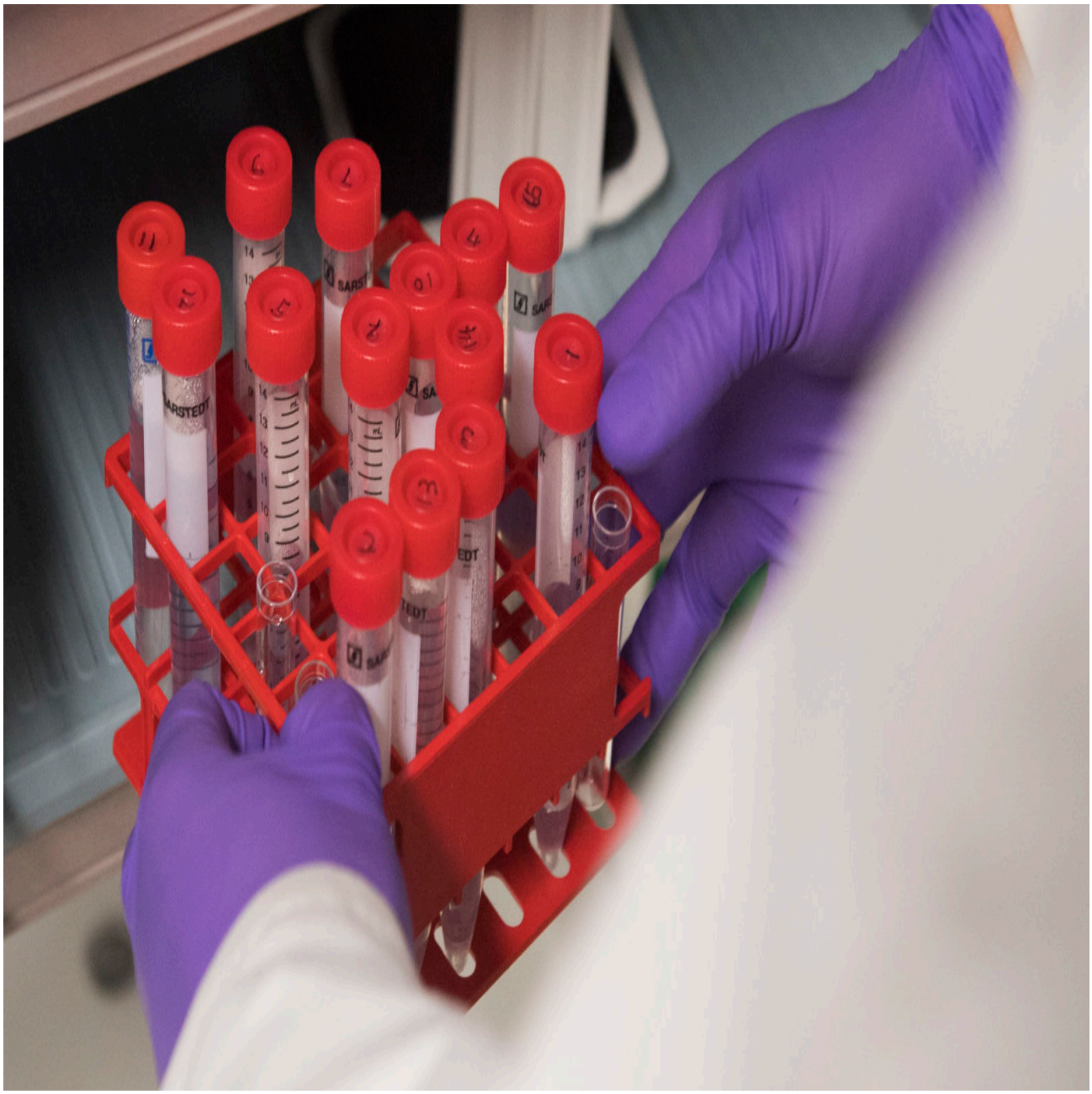
Cite As

"To Protect Patients And Spark Innovation, Codify The FDA’s Oversight Of Laboratory-Developed Tests", Health Affairs Forefront, July 3, 2023.

DOI: 10.1377/forefront.20230621.170697

Better lab test standards can ensure precision medicine is truly precise

By Jeff Allen *and* Lisa LacasseNov. 30, 2022



SAUL LOEB/AFP/Getty Images

Cancer is becoming less deadly in America.

According to the recently released Annual Report to the Nation on the Status of Cancer[2], overall cancer death rates have continued to decline by about 2% per year over the last several years for Americans of all ages, races, and genders. The decline in cancer death rates is clearly welcome news and coincides with a significant shift in cancer treatment through the

development of new targeted therapies and accompanying diagnostic tests that guide their use.

For decades, most cancers have been treated with toxic, cell-killing treatments that had limited ability to distinguish between cancerous and normal cells. While this approach often worked, it came with significant side effects and made treatment difficult to tolerate.

A growing number of new cancer therapies, however, use precision medicine to tailor treatment to the patient and target only cancer cells. But these targeted treatments must be matched to specific genetic markers, which can be detected only with lab tests known as biomarker tests.

Biomarker tests can help determine what an individual's prognosis might be and which drugs would work best to treat their disease. For example, tests that detect certain genetic characteristics in breast, lung, and skin cancer can indicate who should — or should not — be treated with specialized classes of targeted drugs.

With the advent of targeted therapies, the accuracy of a diagnostic test is critical. Yet oversight of such tests has not kept pace with innovation.

The Food and Drug Administration currently regulates and ensures only the accuracy of tests used in multiple laboratories or health care facilities. Those designed for only a single laboratory, known as laboratory-developed tests (LDTs), are left to meet less-stringent standards. That means a growing number of lab tests, including those used to determine cancer treatment for a specific patient, are offered without assurances that they work.

An example of the potential damage of faulty and poorly regulated LDTs is the stunning case of Theranos, a consumer health care startup that claimed

to be able to diagnose countless ailments with a single drop of blood. The company's touted technology never worked, thousands of people received faulty test results for a number of serious conditions. The company's founder, Elizabeth Holmes, was recently sentenced to more than 11 years in prison[4] for fraud.

In an earlier example, from 2008[5], a company claimed a lab test could detect 99% of early-stage ovarian cancers but could, in fact, detect only 1 in 15 (7%) of cases. The remaining 14 women received false positive results and may have pursued unnecessary, invasive, and even dangerous surgeries to remove healthy uteruses, fallopian tubes, and ovaries, which could affect their ability to have children and send them into early menopause.

A recent study[7] published in the American Journal of Clinical Pathology reported that LDTs offered for the same intended use as an FDA-approved test had significant variability in their results. Errors in tests, including false negatives (when the test inaccurately states the genetic marker is not present) may impede patients' access to safe and effective treatments for their cancers.

The VALID Act (S. 2209[8] and H.R. 4128[9]), currently before Congress, provides an opportunity to set a clear, modernized regulatory framework to ensure that any test, no matter where it is developed, meets the same quality and performance standards. It also allows for continued innovation by providing detailed flexibilities that will ensure labs can still meet individual patient needs without delaying patient care.

VALID is a flexible, bipartisan bill that is the result of years of collaborative work between various stakeholders. The bill is good for industry, laboratories, providers and, most importantly, patients. An

individual's best chance to fight cancer should never be affected by something as easily preventable as a faulty diagnostic test. Congress has the opportunity today to do what is right for patients.

Jeff Allen is the president & CEO of Friends of Cancer Research. Lisa Lacasse is the president of the American Cancer Society Cancer Action Network.

First Opinion newsletter: If you enjoy reading opinion and perspective essays, get a roundup of each week's First Opinions delivered to your inbox every Sunday. Sign up here[10].

About the Authors

Jeff Allen

@CancerResrch[11]

Lisa Lacasse

@LLacasseACSCAN[12]

STAT encourages you to share your voice. We welcome your commentary, criticism, and expertise on our subscriber-only platform, STAT+ Connect[17]

To submit a correction request, please visit our Contact Us page[18].

Links

1. https://www.parsintl.com/publication/stat/
2. https://seer.cancer.gov/report_to_nation/
3. https://www.statnews.com/2022/11/03/why-were-not-prepared-for-next-wave-of-biotech-innovation/
4. https://www.statnews.com/2022/11/18/elizabeth-holmes-theranos-sentencing/
5. https://www.nytimes.com/2008/10/09/business/09cancer.html
6. https://www.statnews.com/2022/08/17/synthetic-biologists-try-making-cancer-biomarkers/
7. https://academic.oup.com/ajcp/article/157/4/628/6454342?login=true
8. https://www.congress.gov/bill/117th-congress/senate-bill/2209
9. https://www.congress.gov/bill/117th-congress/house-bill/4128/
10. https://www.statnews.com/signup/first-opinion/?utm_source=applenews&utm_campaign=signup_mr&utm_medium=apple_housead
11. https://twitter.com/CancerResrch
12. https://twitter.com/LLacasseACSCAN
13. https://www.statnews.com/topic/advocacy/
14. https://www.statnews.com/topic/cancer/
15. https://www.statnews.com/topic/congress/
16. https://www.statnews.com/topic/diagnostics/
17. https://connect.statnews.com/
18. https://www.statnews.com/contact/

comments and controversies

Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities

Kenneth Offit, MD, MPH[1,2]; Catherine M. Sharkey, JD, MSc[3]; Dina Green, MA, MS[1]; Xiaohan Wu, MPH, JD[4]; Magan Trottier, MSc[1]; Jada G. Hamilton, PhD, MPH[1,2]; Michael F. Walsh, MD[1,2]; Sita Dandiker, MS[1]; Sami Belhadj, PhD[1]; Steven M. Lipkin, MD, PhD[2]; Thelma Alessandra Sugrañes, MD[5]; Michele Caggana, ScD[6]; and Zsofia K. Stadler, MD[1,2]

abstract

Cancer predictive or diagnostic assays, offered as Laboratory-Developed Tests (LDTs), have been subject to regulatory authority and enforcement discretion by the US Food and Drug Administration. Many LDTs enter the market without US Food and Drug Administration or any regulatory review. The Centers for Medicare & Medicaid Services under the Clinical Laboratory Improvement Amendments focuses on analytic performance, but has limited oversight of the quality or utility of LDTs, including whether patients have been harmed as a result of their use. Increasingly, LDTs for cancer risk or early detection have been marketed directly to consumers, with many LDT developers depicting these tests, requested by patients but ordered by personal or company-associated physicians, as procedures falling under the practice of medicine. This patchwork of regulation and enforcement uncertainty regarding LDTs and public concerns about accuracy of tests given emergency authorization during the COVID-19 pandemic led to the Verifying Accurate Leading-edge IVCT (in vitro clinical test) Development Act of 2021. This pending federal legislation represents an opportunity to harmonize regulatory policies and address growing concerns over quality, utility, and safety of LDTs for cancer genomics, including tests marketed directly to consumers. We review here questions regarding the potential benefits and harms of some cancer-related LDTs for cancer risk and presymptomatic molecular diagnosis, increasingly marketed to oncologists or directly to the worried well. We offer specific proposals to strengthen oversight of the accuracy and clinical utility of cancer genetic testing to ensure public safety.

J Clin Oncol 41:11-21. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on June 27, 2022 and published at ascopubs.org/journal/jco on August 9, 2022: DOI https://doi.org/10.1200/JCO.22.00995

Genomic advances have facilitated hereditary cancer risk prediction and improved molecular diagnostics,[1] resulting in a panoply of tests for inherited disease risk and presymptomatic disease detection (Table 1).[2] From the regulatory perspective, cancer predictive or diagnostic assays are considered Laboratory-Developed Tests (LDTs). Currently, LDTs, provided by an estimated 12,000 laboratories, reach millions and are increasingly offered directly to consumers.[3] With increasing test complexity, the US Food and Drug Administration (FDA) has begun to provide an expedited de novo process for low-risk to moderate-risk devices, exercising regulatory authority and enforcement discretion over the safety and effectiveness of LDTs. Although the FDA approves or clears many tests before they reach patients, a large number of LDTs enter the market without FDA or any regulatory review because they are created and used in the same facility.[3] The laboratories themselves are principally regulated by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). CMS has limited oversight of the quality, reliability, or usefulness of LDTs, including whether patients have been harmed as a result of their use; CLIA focus on analytical validity of tests during inspections that may occur up to two years after an LDT is first performed.[3]

CONTEXT

Key Objective

How can more comprehensive oversight of Laboratory-Developed Tests (LDTs) improve safety of genomic risk assessment and molecular diagnosis of cancer?

Knowledge Generated

There has been a rapid increase in consumer-initiated cancer-related LDTs, which may not be subject to review by the US Food and Drug Administration. The existing patchwork of regulatory oversight of LDTs has raised concerns of harms as well as limited benefits and has led to pending federal legislation, the Verifying Accurate Leading-edge IVCT (in vitro clinical test) Development (VALID) Act of 2021.

Relevance

The VALID Act and similar measures can play an important role in enabling clinicians to assess the clinical utility and safety of tests for inherited cancer risk and presymptomatic liquid biopsies marketed to consumers and cancer care providers.

Recently, marketing of consumer genomic testing (CGT) has focused on patients and the worried well.[4-7] The CGT paradigm extends direct-to-consumer provision of testing to a model where an individual is encouraged to request a specific test from their personal physician or from a health provider employed or contracted by the testing laboratory.[5] Although FDA considers LDTs as medical devices under its jurisdiction, many LDT developers using the CGT paradigm depict these tests, ordered by physicians, as procedures falling under the practice of medicine. The FDA does not regulate procedures falling under the practice of medicine.

This patchwork of regulation and enforcement uncertainty regarding LDTs and public concerns about accuracy of LDTs given emergency authorization during the COVID-19 pandemic, as well as the disgraced laboratory startup *Theranos*, constitute factors driving comprehensive federal legislation to regulate LDTs.[3,8] We review here recent concerns over the accuracy, utility, and validity of some cancer-related LDTs for cancer risk and early diagnosis, increasingly marketed to oncologists or directly to patients and the worried well. We document both risks and harms as well as benefits and offer specific proposals to strengthen oversight of both analytic and clinical validities of cancer genetic testing to ensure public safety. We conclude that amendment and passage of a pending piece of federal legislation, the Verifying Accurate Leading-edge IVCT (in vitro clinical test) Development Act of 2021, offers an opportunity to harmonize regulatory policies and address growing concerns over quality, utility, and safety of LDTs for cancer genomics, including tests marketed directly to consumers.

CURRENT LANDSCAPE OF LDTs IN PREVENTIVE ONCOLOGY

In addition to a public website of commercial laboratories that provides tests for panels of cancer-predisposing genes,[9] an industry website directed to consumers lists more than 120 companies offering ancestry and/or genetic testing services to consumers (Table 1).[10] Of five major ancestry companies that claim to hold DNA samples on more than 26 million individuals,[11] two offer an option for medical tests, one of which remains the only FDA-authorized health report. Of 96 entities listed with sufficient information to evaluate, 85 use a CGT model requiring cash or credit card payment without mention of acceptance of governmental or private insurance. As shown in Table 1, of the tests listed on this website, with the exception of a broad category including nutrigenomics, the highest number of tests reported was for the category of cancer-related testing. In addition, more than a dozen laboratories now offer liquid biopsy tests for circulating tumor DNA (ctDNA) or cell-free DNA for tumor detection, monitoring, or treatment selection using samples of blood, stool, or other fluids, with differences in read depth, regions covered, limits of detection, and methodologies (Appendix Table A2, online only). Marketing of at least one ctDNA assay is following the consumer-initiated, physician-ordered, direct pay model.[12] In 2021, a commercial laboratory announced a collaboration with a large diagnostic company facilitating sample collection for a not yet FDA-approved ctDNA test.[13]

In addition to providing reports and analyses, some CGT companies provide personalized raw data for consumers to download; as shown in Table 1, more than a dozen companies offer reports derived from input of these raw data. Such reports bear on characteristics such as fitness and cancer and heart disease risks. It is estimated that up to 62% of consumers use third-party applications to interpret their raw data and health information,[14] with 40% of genetic variations found and then sent for clinical confirmation resulting in false positives.[15]

REGULATORY CONTEXT

The hallmark illustration of the loophole in FDA regulation of LDTs was the *Theranos* case, in which a company marketed what was later found to be a fraudulent technology that purportedly allowed thousands of multiplexed tests.[16] Establishing important precedents during the pandemic, the FDA gave Emergency Use Authorization to at-home self-collection COVID-19 tests[17-19] and the US Department

TABLE 1. Consumer-Targeted Companies With Health-Related Genetic Testing Products Classified by Indication, Physician Involvement in the Ordering Process, and Potential for Submission of Raw Genomic Data

Number of Tests by Category	Nutrigenomics, Fitness, Beauty, Other Wellness, and Lifestyle	Reproductive and Prenatal Risk	Pharmacogenomics	Cancer Risk	Comprehensive Health Risk	Neurodegenerative and Psychiatric Risk	Longevity and/or Biologic Age Analysis	Cardiac Risk	Other Disease Susceptibility	COVID-19 Susceptibility	Liquid Biopsy cfDNA Cancer Detection[a]
Total No. of tests reported in each category	65	15	16	17	15	9	6	10	8	7	12
Direct-to-consumer testing (CGT without MD involvement)	64	7	6	9[b]	14	8	6	5	6	7	0
CGT with local MD involvement	2	7	9	7	1	0	1	4	1	1	9[c]
CGT with a company-contracted MD	1	2	3	3	1	1	0	4	1	0	1
Analysis of consumer-provided raw genomic data	37	7	6	7	11	6	2	6	5	5	0

NOTE. One hundred twenty-four companies involved in health-related genetic testing were evaluated from DNA Testing Choice[10] and extensive online search. Online search terms used included "Direct to consumer genetic testing + Health," "Direct to consumer genetic testing + Cancer," "At home genetic testing + Health," and "At home genetic testing + Cancer." Companies from health-related CGT reports seen in our clinic were incorporated as well. Twenty-eight companies were excluded as they had discontinued health-related genetic testing, did not have information about genetic tests on their website, or no longer existed at the time of analysis. Twelve companies providing cell-free DNA testing were included (Appendix Table A2). Information is based on publicly available data via company websites, accessed in August 2021. Laboratories that offer multiple mechanisms for test ordering or multiple test types may be counted more than once.

Abbreviations: cfDNA, cell-free DNA; CGT, Consumer Genomic Testing; MD, medical doctor.

[a]Liquid biopsy companies are listed in Appendix Table A2. Technology used by each company varies.

[b]One cancer risk assessment requires pretest counseling with a genetic counselor, but it is unclear if an ordering MD is required for testing.

[c]Three companies have no online evidence of consumer-marketed liquid biopsy product via advertisements or presence in popular media geared toward noninvestors or the nonscientific community.

of Health and Human Services (HHS) determined that the FDA would not require premarket review of LDTs, including but not limited to COVID-19 tests.[20,21] These regulatory exceptions were also applied to cancer genomic testing. In November 2021, HHS reinstated a requirement for FDA Emergency Use Authorization approval for COVID-19 LDTs. Non–COVID-19 LDTs remained under FDA's enforcement discretion, whereby FDA reserves the right to take action when harm occurs or may occur.[22] The regulatory and enforcement uncertainty regarding LDTs and public concerns about COVID-19 laboratory testing and the *Theranos* case have increased the likelihood of comprehensive LDT legislation this year.[3,8,23] Such legislation, introduced in a bipartisan and bicameral manner in the current session of Congress, is represented by the Verifying Accurate Leading-edge IVCT (in vitro clinical test) Development Act of 2021 (Appendix Table A1, online only). At the same time, legislation introduced in the House (H.R. 8845) and Senate (S5051), the Multi-Cancer Early Detection Screening Coverage Act, seeks to mandate Medicare coverage of molecular early cancer detection assays.[24]

MEDICAL CONTEXT FOR REGULATORY OVERSIGHT

In vitro diagnostic tests (IVDTs) use biospecimens to determine the presence or risk of certain diseases. Analytic validity refers to whether an IVDT can measure what it purports to measure (eg, DNA sequence changes), whereas clinical validity is the ability of an IVDT to measure a medical condition or predisposition. Clinical validity can be quantified by the sensitivity, specificity, and predictive value of an IVDT, whereas the most important parameter to the clinician is clinical utility, namely, whether the IVDT and any subsequent interventions lead to an improved health outcome among people with a positive test result.[25] Laboratory-developed in vitro tests (LDTs or home brew tests) were not historically regulated by the FDA; under the Medical Device Amendments of 1976,[26] certain LDTs have been exempt,[27] with the agency using enforcement discretion when there is alleged harm to consumers. According to the FDA, the LDT exemption policy did not routinely apply to direct-to-consumer genetic tests,[28] which it can regulate, pursuant to its enforcement discretion, as medical devices.[29] Only laboratories certified by the CLIA as being high-complexity can develop and deploy LDTs, with an estimated 12,000 of 267,000 such laboratories registered with CMS as of March 2020.[3] Many of these laboratories process thousands of patient samples per day, and because these LDTs are not centrally registered, the number of such tests on the market or their performance as compared with FDA-reviewed diagnostics is not known. As noted in a recent Pew Report, when the FDA was originally granted oversight of medical devices, most LDTs served a limited number of patients living near the laboratories that developed them. Today, LDTs reach millions of people and increasingly, these tests are being offered directly to consumers.[3] However, the FDA has reviewed very few of the LDTs offered via the CGT paradigm[30]; the remaining are unapproved LDTs.

Widespread consumer access to genomic testing has potential benefits such as increased testing accessibility, affordability, and consumer health empowerment[4] and concerns including inconclusive results, false negatives and positives, poor interpretation, and therefore potential for inappropriate medical management.[31] The FDA has pursued divergent approaches to regulate the CGT industry (Fig 1).[32] Perhaps because of deficiencies of the existing review processes[33] or deregulatory trends, the FDA has embraced flexible regulatory paradigms for tests offered through CGT.[33] To reduce the burden on test developers, the FDA accredited the New York State Department of Health as a third-party reviewer of certain LDTs.[34,35] These third-party accreditation programs do not currently include most genetic tests,[36] but entities like the New York Department of Public Health are accredited to review 510(k) submissions of next-generation sequencing–based tumor profiling tests.[35]

Although genetic testing has improved disease prevention and management, most notably for cancer,[37] substantial challenges remain, including the interpretation of results of genomic variants of uncertain significance, incomplete genetic knowledge of health care providers, and disparities in access to personalized genomic services.[1]

SAFETY CONCERNS

Safety concerns of nonapproved LDTs and consumer-marketed testing relate to false-positive and false-negative results because of analytic or interpretative error, incomplete genetic assessment, failure to communicate results or take medical action, and untoward psychosocial effects.[38-42] As documented in Appendix Table A3, online only, we and others have observed cases where we were unable to confirm results of consumer-initiated tests for cancer predisposition (eg, a case of Peutz-Jeghers syndrome), errant interpretation (eg, a patient with a *CHEK2* mutation told that she could have Li-Fraumeni syndrome), and severe psychological sequelae because of absent counseling (eg, a 14-year-old offered testing by her parents for recreational purposes). Consumer risks may also result from pursuing inappropriate medical interventions on the basis of results of third-party raw genomic data interpretation companies, which are largely unvalidated (Appendix Table A3).[43] At present, almost half of consumers seeking clinical confirmation of their genetic testing results from raw genomic data interpretation services could not confirm results, wasting health care dollars.[15] We and others have seen in consultation numerous cases where results of cancer risk testing from CGT companies or those that interpret raw data from self-directed DNA sequencing were not confirmed, and some led to adverse sequelae including scheduling of unnecessary prophylactic surgeries, false reassurance, or undue anxiety (Appendix Table A3).[44] We are conducting an ongoing survey of genetic counselors in the United States seeking to document the occurrence of cases where tests by CGT or raw data interpretation were not confirmed or led to adverse outcomes.[45]

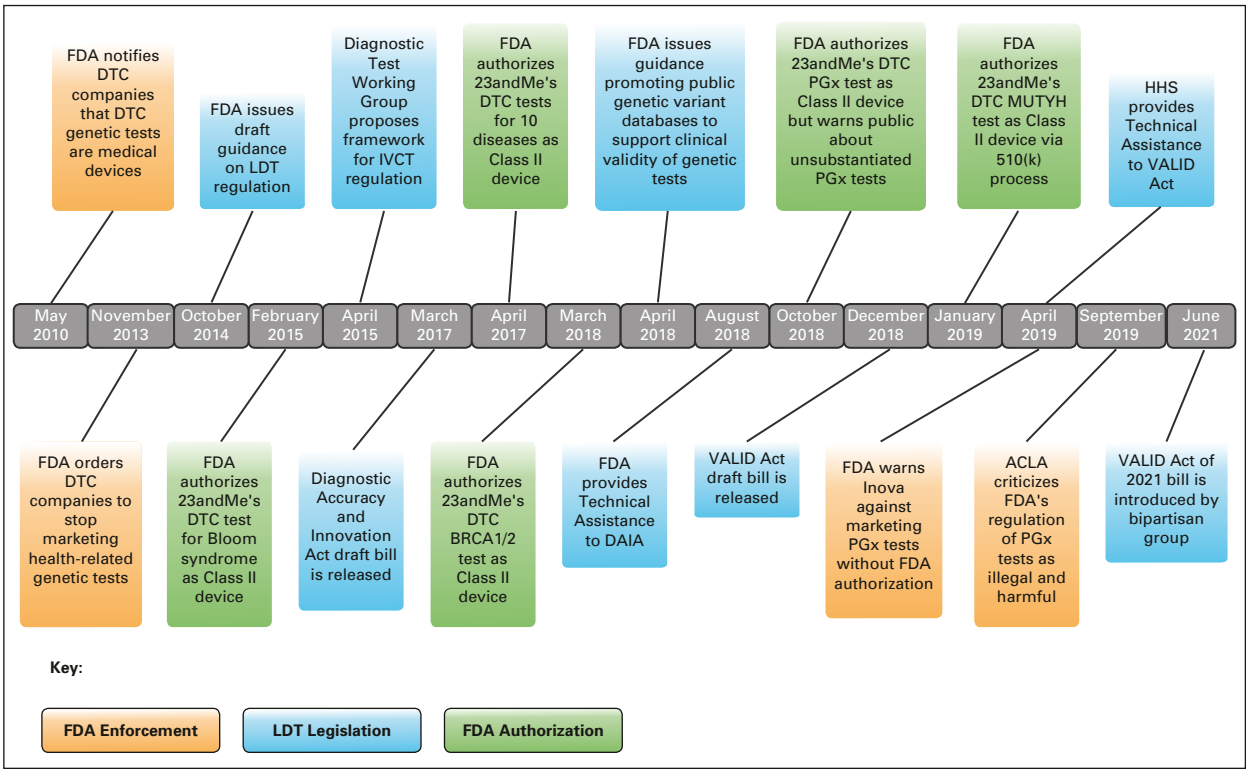


FIG 1. Timeline of FDA authorization of direct-to-consumer and COVID-19 testing. ACLA, American Clinical Laboratory Association; DAIA, Diagnostic Accuracy and Innovation Act; DTC, direct-to-consumer; FDA, US Food and Drug Administration; HHS, Department of Health and Human Services; IVCT, in vitro clinical test; LDT, laboratory-developed test; PGx, pharmacogenomic; VALID, Verifying Accurate, Leading-edge IVCT Development.

Adding to safety concerns, consumer-marketed genetic testing has been shown to be associated with failure to take follow-up action.[38,39,46] Only 27% of patients in one study shared their genetic results with primary care providers[38]; this may lead to misinterpretation of genetic tests and false reassurance or undue anxiety.[43,44,46-49]

Finally, safety concerns also stem from limited FDA oversight and inconsistent reporting of metrics for clinical validity. For example, increasingly marketed as consumer-initiated LDTs, a recently developed ctDNA test for cancer early detection is not FDA-approved. Overall, the sensitivities and specificities of current ctDNA tests vary substantially with lowest sensitivities for some tests observed for early stages of disease (Appendix Table A2) and with false-positive rates of some ctDNA presymptomatic tests recently marketed in the United States ranging substantially depending on how the calculation is made.[50-56] For one methylation-based ctDNA LDT, the positive predictive value, the proportion of actual cancers found after an abnormal test in an asymptomatic population, ranged from $<$ 10% to 45%, depending on how the calculation was performed.[55] These inconsistent metrics are due to differing methodologic assumptions regarding incident rather than prevalent cancer rates in asymptomatic populations, lower test sensitivities in earlier-stage disease, and the presence of noncancer conditions affecting specificity,[53-56] underscoring the need for clinicians and regulators to have access to reproducible metrics of clinical validity. For presymptomatic cancer LDTs, a predictive value of a positive test that is $<$ 50% will have substantial safety implications in terms of risks of resulting invasive diagnostic procedures. Indeed, the number of false positives for one recently marketed ctDNA LDT was noted to be higher than the number of true positives, with many true positives being lymphoid cancers for which early disease detection is of unproven efficacy.[57] For other ctDNA methodologies, inconsistencies have been noted between orthogonal approaches.[58]

STRENGTHENING GENETIC TESTING REGULATORY FRAMEWORKS TO PROTECT PUBLIC HEALTH

Drafted well before the COVID-19 pandemic–focused concern on FDA oversight of LDTs, the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021 was reintroduced into both the House and Senate by a bipartisan group including US Senators Michael Bennet (D-CO) and Richard Burr (R-NC). The Act seeks to modernize regulatory oversight of LDTs by creating a single, diagnostics-specific, regulatory framework under the authority of the FDA (Appendix Table A1).

The VALID Act proposes a new tiered, risk-based system for the regulation of IVCTs, which includes LDTs, that

resembles the traditional approach to regulating medical devices.[59] For high-risk IVCTs, there is an FDA preapproval review, from which low-risk diagnostics are exempt, with a middle tier requiring approval, but without meeting the more stringent requirements of high-risk diagnostics. The Act also allows for grandfathering status for qualifying LDTs that were offered for clinical use before enactment of the legislation and a Technology Certification program for marketing authorization on the basis of documentation of methods, procedures for test development, validation and maintenance, and clinical and nonclinical data used in designing the test (Appendix Table A1). One opportunity to pass the VALID Act in 2022 will be as an attachment to the reauthorization of the Medical Device User Fee Amendments (MDUFA), which funds almost half of the FDA's annual budget.[8]

The approach of the VALID Act would build on the FDA's *risk-based classifications* for specific genetic associations, modeled on the framework for analyte-specific reagents (ASRs).[60] Those ASRs that are Class II or Class III would have additional requirements for their safe and effective use. The FDA's recent regulation of pharmacogenomic (PGx) testing is illustrative of the use of risk-based approaches to labeling and regulation. As the FDA authorized the first and only CGT PGx test, it issued a simultaneous warning letter cautioning the public against adjusting the dose or stopping medication on the basis of PGx tests with unapproved claims.[29] The FDA subsequently demanded another testing company to stop offering physician-ordered PGx tests that lacked evidence of clinical validity, while at the same time, a PGx testing company provided limited consumer access to drug-specific information.[29] In February 2020, the FDA published a list of pharmacogenetic associations that it believes to be supported by evidence.[61]

A counterproposal to the VALID Act, supported by some testing laboratories, the Verified Innovative Testing in American Laboratories Act, would maintain LDTs under CLIA regulation with updates to CLIA to account for modern tests.[62] At the same time, new legislation was introduced into the House (H.R. 8845) and Senate (S5051), the Multi-Cancer Early Detection Screening Coverage Act, to ensure timely Medicare coverage of molecular early cancer detection assays once they are FDA-approved.[24] Such legislation is unprecedented as it would bypass the evidentiary review by bodies such as the US Preventive Services Task Force and professional organizations.

STRENGTHENING THE FDA's RISK-BASED REGULATION

As a matter of public health policy, it seems prudent that risk-based regulatory approaches should apply to all LDTs regardless of whether a test is consumer-initiated or physician-ordered and whether the health-related report is derived from data from an in-house in vitro diagnostic test or raw data from another source. Laboratories marketing consumer-requested germline or somatic (ctDNA) assays should not be permitted to evade review simply because tests are ordered by a prescribing doctor or subcontracted to companies that hire physicians to process CGT requests. In New York, for example, tests ordered by physicians employed by the laboratory performing the test are illegal (Section 238 of Public Health Law) and physicians may not order tests that are not approved by the New York State Department of Public Health. A risk-based approach to oversee all LDTs would serve to avoid regulatory end runs[63] by CGT marketers.

STRENGTHENING THE VALID ACT TO ADDRESS SAFETY CONCERNS OF LDTs

As summarized in Table 2, the VALID Act offers an opportunity for cancer genomic tests to be placed in a high-risk LDT category to ensure that there is premarket review of analytic and clinical validities of tests that will determine medical interventions. Congress should amend the Act to strengthen postmarket protections and reinforce the requirement that health care workers report to FDA cases of test-related patient harm and define specific mandates for FDA collection of user fees from test developers to fund oversight activities.[64] There should be uniform requirements of provision to consumers of counseling resources before inherited risk testing and assurance of access to appropriate medical follow-up after testing. Rules endorsed by professional societies pertaining to testing vulnerable populations (eg, young children who would not benefit from testing at early age) should be incorporated into FDA guidelines. Although the 2016 21st Century Cures Act excluded certain medical software from regulation as medical devices,[65] the VALID Act should clarify that software used to analyze raw consumer–entered genomic data to generate reports that bear on health (eg, cancer-causing mutations) fall within the purview of FDA,[66] regardless of whether the reports are generated for profit or not for profit.[67]

The VALID Act can also address many of the safety concerns stemming from newly developed LDTs including ctDNA assays. It is critical that H.R. 8845 is harmonized with the VALID Act to ensure full premarket FDA review so that ctDNA tests meet benchmarks of other diagnostic tests. The adoption of proposed congressional mandates for CMS coverage of ctDNA would bypass current evidentiary review, increase costs because of false-positive tests, and potentially increase health disparities. It has been shown that even after a genetic test has been performed, there remain substantial disparities in access to and adoption of preventive surgery or radiographic screening, as well as genetically targeted therapies, in historically underserved groups.[68] ctDNA LDTs should also be classified as high risk, and manufacturers should be required to submit to the FDA-standardized reporting of metrics for clinical validity including sensitivity, specificity, false-positive and false-negative rates, and positive predictive

TABLE 2. Potential Enhancements of Regulatory Oversight of Consumer-Initiated Genomic Testing for Cancer Detection and Risk Assessment

Suggested Amendments to the VALID Act of 2021
Define cancer genetic tests as high risk thereby requiring premarket review to ensure analytic and clinical validities of tests that will determine medical interventions
Include companies that issue reports on the basis of consumer submitted raw genomic data that bear on health (eg, cancer-predisposing mutations) as falling within purview of FDA review
Increase postmarket protections and specify mechanisms for health care workers to report cases of genomic test–related patient harm to the FDA
Specify processes whereby the FDA may collect user fees from consumer genomic test developers to fund oversight activities
Harmonize H.R. 8845 and S. 5051, the Multi-Cancer Early Detection Screening Coverage Act, with the VALID Act to ensure premarket FDA review of cfDNA tests to meet benchmarks of other diagnostic tests
Require proficiency testing for laboratories that directly market clinically actionable germline cancer genomic or ctDNA assays
Prohibit regulatory exclusions of tests claimed to be for educational purposes if they are viewed by professional bodies as generating clinically actionable findings
Harmonize provisions of S.1666, the Verified Innovative Testing in American Laboratories Act of 2021, distinguishing the special exigencies of COVID-19 testing compared with non–COVID-19 LDTs such as cancer risk and diagnostic genomic assays
Other Regulatory Enhancements
Provide consumers with assurances of professional proficiency of health care providers ordering and interpreting consumer genomic tests
Mandate participation of commercial laboratories in FDA-supported databases of genomic information (eg, ClinVar and BRCA exchange)
Ensure that the Health Insurance Portability and Accountability Act protections of privacy apply to consumer genomic testing results if these are used for a medical purpose

Abbreviations: cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; FDA, US Food and Drug Administration; IVCT, in vitro clinical test; LDT, Laboratory-Developed Test; VALID, Verifying Accurate Leading-edge IVCT Development.

value. As with physician-ordered PGx tests, the FDA should require that manufacturers of ctDNA LDTs demonstrate clear evidence of clinical validity of tests.

Perhaps the most effective strategy to ensure the quality and safety of genetic testing services has been the effort to promulgate a *proficiency testing* (PT) of laboratories providing LDTs. An example is the PT program for inborn errors of metabolism, involving more than 150 laboratories.[69] Currently, all laboratories certified under CLIA, or its main accrediting bodies, the New York State Department of Health, the College of Pathology, or the Joint Commission, require PT testing.[70] A regulatory requirement for PT should be reinforced by the VALID Act for all laboratories that offer consumer-initiated germline or ctDNA assays. Laboratories should not be permitted to declare that their tests are for educational purposes only, hence not subject to oversight, if the laboratories suggest to consumers that results be discussed with health care providers as they may generate clinically actionable findings. The Act should also provide consumers with information regarding professional training (eg, appropriate board certification) of geneticists or oncologists ordering and interpreting cancer genetic tests and guiding their medical care, who should have fiduciary responsibilities to the patient or consumer and not to the testing laboratory.

CLINICAL VALIDITY AND FDA PARTNERSHIPS

In view of its finite resources, the FDA has recognized the genetic variant information in the Clinical Genome Resource (ClinGen) consortium's ClinGen Expert Curated Human Genetic Data as a source of scientific evidence that can be used to support clinical validity in premarket submissions.[71] Such recognition by the FDA increases safety and availability of information on clinical validity and the pathogenicity of individual genomic variants, made possible by more than 700 ClinGen stakeholders aiming to standardize clinical annotation and interpretation of genetic data.[72] Requirements for clinical validity should be built into FDA approval of high-risk LDTs; these considerations have been applied by the Federal Trade Commission for CGT companies, making unsupported nutrigenetic and dermagenetic claims of clinical utility for products in the absence of randomized clinical trials.[73]

ClinGen and its variant database partner, ClinVar, play a vital role in curating genomic information to support genomic medicine and research.[74] However, this database relies on voluntary contribution of data.[75] The FDA can play a stronger role in encouraging such participation; indeed, it has already expressed its need to request raw data to assess analytical and clinical validities of high-risk IVCTs.[76] The FDA can also require disclosure of proprietary information to the agency, providing incentives to CGT companies like those contained in the Hatch-Waxman Act.[77] As a step in this direction, the FDA is a sponsor of an international data set of genetic variant information for the *BRCA* genes built by the Global Alliance for Genomics and Health.[78] In addition, with HHS, the FDA proposed a Comprehensive Test Information System in its initial comments on the VALID Act.[79]

CONSUMER ACTIVISM

Another driving impetus for regulatory protection relates to privacy considerations resulting from immense private genetic data sets. The DNA of a projected 60 million Americans is expected to be in the possession of commercial laboratories by 2025.[80] Genomic data, without voluntary release, have already been used for forensic purposes, and there is a movement to create large genetic databases to aid law enforcement.[81] The Health Insurance Portability and Accountability Act was modified in 2013 to safeguard privacy and genetic information, but it is unclear if this regulation applies to CGT results if these are used for a medical purpose.[40,77,82] In the realm of genetic privacy, consumer activism will be required to motivate regulatory action and inquiry, as is occurring now in the debate over private and sensitive information sold by social media for commercial purposes.[83]

In conclusion, oncologists and other health practitioners are faced with an increasing number of LDTs to guide preventive, diagnostic, and therapeutic aspects of care. Genomic tests constitute an important subset of biomarkers for cancer risk, diagnosis, and prognosis. To safely and responsibly use new technologies, clinicians ultimately rely on shared performance metrics for these biomarkers, including clinical validity and, most importantly, the clinical utility or actionability of the LDT result. For genomic LDTs, in the absence of uniform regulatory oversight and transparent communication of clinical utility metrics by commercial laboratories, practitioners can rely on guidance of expert bodies such as the National Comprehensive Cancer Centers, the US Prevention Services Task Force, and federally supported efforts such as the ClinGen consortium.[84-86]

More widespread accessibility to genomic tests, facilitated by the direct-to-consumer model, has potential benefits: it can increase consumer awareness of the importance of genetics and preventive health, improve access to genetic information not provided by clinicians or insurance companies, lower costs, enhance the convenience of sending of samples from home, and make data available to companies for research. Potential drawbacks of consumer-initiated genetic testing include questionable reliability of results, failure to take into account other cancer risk factors, incomplete translation of test results to preventive action without input by clinicians, and concerns about security and privacy of consumers' genetic information.[31] On a societal level, commercial profitability of a new LDT is determined by the sheer volume of tests performed, whether positive or negative. In some cases, CGT approaches could be cost-effective when comparing the costs of the test and resulting interventions relative to the amount of benefit that they yield. Such would be the case for widespread testing, for example, of founder mutations of susceptibility genes for breast, ovarian, prostate, and colon cancers in defined populations. However, cost-effectiveness also takes into account the burden of false negatives and positives, including costs of un-needed diagnostic procedures, or missed diagnoses because of false-negative tests. Randomized cohort studies, particularly for emerging liquid biopsy tests, may be required to provide the evidence base needed to derive both medical efficacy and societal cost-effectiveness compared with other strategies of cancer screening. In the absence of these data and uniform regulatory oversight of CGT, consumers and clinicians will need to assess test results in the context of individual personal and family histories of cancer and other risk factors and existing professional guidelines.

Although clinicians can be assured that the majority of testing laboratories are committed to the highest quality and meet current regulatory requirements, safety concerns resulting from the recent proliferation of consumer-initiated cancer genomic testing create a need for the FDA to assume full oversight of LDTs for cancer and other diseases. The VALID Act's requirement of the FDA to use a risk-based approach to regulate quality and safety of LDTs seems a necessary and important first step. The Act should be amended so that self-directed genetic tests and commercial laboratories that produce personalized health reports on the basis of genomic data have the same regulatory oversight as other high-risk tests. Barriers should be put in place to avoid regulatory end runs[63] by companies hiring physicians to order genetic tests. Passage of an amended VALID Act will uphold the FDA's mission to protect public health by ensuring that laboratory-developed presymptomatic and diagnostic genetic tests marketed to consumers are safe and effectively used to guide medical care and disease prevention.

AFFILIATIONS

[1]Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Weill Cornell Medical College, New York, NY
[3]New York University School of Law, New York, NY
[4]The University of California, Berkeley School of Law, Berkeley, CA
[5]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
[6]Wadsworth Center, New York State Department of Health, Albany, NY

CORRESPONDING AUTHOR

Kenneth Offit, MD, MPH, Clinical Genetics Service, Memorial Sloan Kettering Cancer Center, New York, NY 10021; e-mail: [redacted].

DISCLAIMER

K.O. and S.M.L. are cofounders of AnaNeo Therapeutics. The views expressed do not represent those of affiliated institutions or sponsors.

SUPPORT

Supported in part by the Robert and Kate Niehaus Center for Inherited Cancer Genomics, the Breast Cancer Research Foundation, the Sabin Family Research Foundation, the Sharon Corzine Foundation, and the D'Agostino Foundation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00995.

AUTHOR CONTRIBUTIONS

Conception and design: Kenneth Offit, Catherine M. Sharkey, Xiaohan Wu, Jada G. Hamilton, Michael F. Walsh, Steven M. Lipkin, Michele Caggana
Administrative support: Kenneth Offit, Sita Dandiker
Provision of study materials or patients: Dina Green, Magan Trottier
Collection and assembly of data: Dina Green, Xiaohan Wu, Magan Trottier, Michael F. Walsh, Sita Dandiker, Sami Belhadj, Thelma Alessandra Sugrañes
Data analysis and interpretation: Kenneth Offit, Catherine M. Sharkey, Dina Green, Xiaohan Wu, Michael F. Walsh, Sita Dandiker, Zsofia K. Stadler
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank Dr Benjamin Roman for helpful initial conversations and Kaitlyn Tkachuk and Jeffery Levin for their support.

REFERENCES

1. Offit K: The future of clinical cancer genomics. Semin Oncol 43:615-622, 2016
2. Ignatiadis M, Sledge GW, Jeffrey SS: Liquid biopsy enters the clinic—Implementation issues and future challenges. Nat Rev Clin Oncol 18:297-312, 2021
3. The Pew Charitable Trusts: The Role of Lab-Developed Tests in the in Vitro Diagnostics Market. https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market
4. Ayala-Lopez N, Nichols JH: Benefits and risks of direct-to-consumer testing. Arch Pathol Lab Med 144:1193-1198, 2020
5. Feero WG, Wicklund CA: Consumer genomic testing in 2020. JAMA 323:1445-1446, 2020
6. Allyse MA, Robinson DH, Ferber MJ, Sharp RR: Direct-to-consumer testing 2.0: Emerging models of direct-to-consumer genetic testing. Mayo Clin Proc 93:113-120, 2018
7. Niemiec E, Kalokairinou L, Howard HC: Current ethical and legal issues in health-related direct-to-consumer genetic testing. Per Med 14:433-445, 2017
8. Parkins K: Is FDA LDT Surveillance Set to Improve as VALID Act Heads to Resolution? 2022. https://www.medicaldevice-network.com/analysis/fda-ldt-surveillance-set-to-improve-as-valid-act-heads-to-resolution/
9. National Center for Biotechnology Information: GTR: Genetic Testing Registry. https://www.ncbi.nlm.nih.gov/gtr/
10. DNA Testing Choice. 2022; DNAtestingchoice.com, 2021. https://dnatestingchoice.com/
11. Regaldo A: More Than 26 Million People Have Taken an At-Home Ancestry Test, 2019. https://www.technologyreview.com/s/612880/more-than-26-million-people-have-taken-an-at-home-ancestry-test/
12. Cairns E: Grail Launches Pan-Cancer Screen—For Those Who Can Pay Out of Pocket, 2021. https://www.evaluate.com/vantage/articles/news/snippets/grail-launches-pan-cancer-screen-those-who-can-pay-out-pocket
13. Hale C: Chosen Wisely: Grail, Quest Team up on Cancer Blood Test, 2021. https://www.fiercebiotech.com/medtech/chosen-wisely-grail-quest-team-up-cancer-blood-test
14. Wang C, Cahill TJ, Parlato A, et al: Consumer use and response to online third-party raw DNA interpretation services. Mol Genet Genomic Med 6:35-43, 2018
15. Tandy-Connor S, Guiltinan J, Krempely K, et al: False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 20:1515-1521, 2018
16. Parkins K: The Theranos Saga: A Wake-Up Call for the Lab-Developed Test Market, 2022. https://www.medicaldevice-network.com/analysis/theranos-ldt-regulation/
17. USFDA: Everlywell COVID-19 Test Home Collection Kit. https://www.fda.gov/media/138144/download
18. USFDA: Labcorp COVID-19 RT-PCR Test, 2020. https://www.fda.gov/media/136148/download
19. USFDA: Emergency Use Authorization (EUA) Summary for the Quest Diagnostics RC COVID19 +Flu RT-PCR Test Used With the Quest Diagnostics Self-Collection Kit for COVID-19 +Flu, 2020. https://www.fda.gov/media/144177/download
20. HHS Assistant Secretary for Public Affairs: Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests, 2020. https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html
21. Sarata AK: HHS Announcement on FDA Premarket Review of Laboratory-Developed Tests (LDTs), 2020. https://crsreports.congress.gov/product/pdf/IN/IN11548
22. HHS Assistant Secretary for Public Affairs: Statement by HHS Secretary Xavier Becerra on Withdrawal of HHS Policy on Laboratory-Developed Tests. https://www.hhs.gov/about/news/2021/11/15/statement-hhs-secretary-xavier-becerra-withdrawal-hhs-policy-laboratory-developed-tests.html
23. Hawana J, Zegarelli B: About Face: Laboratory-Developed Tests for Covid-19 Now Subject to EUA Requirements. https://www.mintz.com/insights-center/viewpoints/2146/2021-11-18-about-face-laboratory-developed-tests-covid-19-now
24. Arrington J: Reps Arrington, Sewell, Ruiz, and Hudson Introduce Bipartisan Bill to Remove Barriers to Innovate Multi-Cancer Screening Technology for Medicare Beneficiaries. https://arrington.house.gov/news/documentsingle.aspx?DocumentID=417
25. Burke W: Genetic tests: Clinical validity and clinical utility. Curr Protoc Hum Genet 81:9.15.1-8, 2014
26. FDA: Overview of IVD Regulation. US Food and Drug Administration, 2019. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation
27. FDA: Laboratory Developed Tests. US Food and Drug Administration, 2018. https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests
28. Stade NK: FDA Challenges Direct-to-Consumer Genetic Tests, 2016. https://www.law360.com/articles/772679/fda-challenges-direct-to-consumer-genetic-tests
29. Philippidis: Treading with Caution: PGX Test Developers Pursue Dialogue as FDA Maintains its Enforcement Stance, 2019. https://www.genengnews.com/insights/treading-with-caution/
30. FDA: Direct-to-Consumer Tests. https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list

31. Oh B: Direct-to-consumer genetic testing: Advantages and pitfalls. Genomics Inform 17:e33, 2019
32. Sharkey C: Direct-to-consumer genetic testing: The FDA's dual role as safety and health information regulator. DePaul Law Review 68, 2019
33. Baird S: Don't try this at home: The FDA's restrictive regulation of home testing device. Duke Law J 67:383-426, 2017
34. Gottlieb S: Remarks at the American Clinical Laboratory Association Annual Meeting. Washington, DC, US Food and Drug Administration, 2018
35. FDA: FDA Unveils a Streamlined Path for the Authorization of Tumor Profiling Tests Alongside its Latest Product Action, 2017. https://www.fda.gov/news-events/press-announcements/fda-unveils-streamlined-path-authorization-tumor-profiling-tests-alongside-its-latest-product-action
36. FDA: List of Devices for Third Party Review. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfThirdParty/current.cfm
37. Mandelker D, Zhang L, Kemel Y, et al: Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 318:825-835, 2017
38. Van Der Wouden CH, Carere DA, Maitland-Van Der Zee AH, et al: Consumer perceptions of interactions with primary care providers after direct-to-consumer personal genomic testing. Ann Intern Med 164:513-522, 2016
39. Roberts JS, Gornick MC, Carere DA, et al: Direct-to-consumer genetic testing: User motivations, decision making, and perceived utility of results. Public Health Genomics 20:36-45, 2017
40. Seward B: Direct-to-consumer genetic testing: Finding a clear path forward. Ther Innov Regul Sci 52:482-488, 2018
41. Kalokairinou L, Zettler PJ, Nagappan A, et al: The promise of direct-to-consumer COVID-19 testing: Ethical and regulatory issues. J Law Biosci 7:lsaa069, 2020
42. Wilson TE, Halverson C: Home testing for COVID-19: Lessons from direct to consumer genetics. J Community Genet 11:497-499, 2020
43. Moscarello T, Murray B, Reuter CM, Demo E: Direct-to-consumer raw genetic data and third-party interpretation services: More burden than bargain? Genet Med 21:539-541, 2019
44. Horton R, Crawford G, Freeman L, et al: Direct-to-consumer genetic testing. BMJ 367:l5688, 2019
45. Memorial Sloan Kettering Cancer Center Clinical Genetics Service Healthcare Professional Clinical Experience With Direct-to-Consumer Genetic Testing. REDCap Survey Link. https://redcap.mskcc.org/surveys/?s=LC4PPXEEAK
46. Gray SW, Gollust SE, Carere DA, et al: Personal genomic testing for cancer risk: Results from the impact of personal genomics study. J Clin Oncol 35:636-644, 2017
47. Brierley KL, Campfield D, Ducaine W, et al: Errors in delivery of cancer genetics services: Implications for practice. Conn Med 74:413-423, 2010
48. Farmer MB, Bonadies DC, Mahon SM, et al: Adverse events in genetic testing: The fourth case series. Cancer J 25:231-236, 2019
49. Dinulos MBP, Vallee SE: The impact of direct-to-consumer genetic testing on patient and provider. Clin Lab Med 40:61-67, 2020
50. Lennon AM, Buchanan AH, Kinde I, et al: Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science 369: eabb9601, 2020
51. Liu MC, Oxnard GR, Klein EA, et al: Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol 31: 745-759, 2020
52. Nadauld LD, McDonnell III CH, Beer TM, et al: The PATHFINDER study: Assessment of the implementation of an investigational multi-cancer early detection test into clinical practice. Cancers (Basel) 13:3501, 2021
53. Beer T, McDonnell CH, Nadauld L, et al: Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. J Clin Oncol 39, 2021 (suppl 15; abstr 3010)
54. Taylor WC: Comment on 'Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA' by M. C. Liu et al. Ann Oncol 31:1266-1267, 2020
55. Fiala C, Diamandis EP: A multi-cancer detection test: Focus on the positive predictive value. Ann Oncol 31:1267-1268, 2020
56. Liu MC, Oxnard GR, Klein EA, et al: Response to W.C. Taylor, and C. Fiala and E.P. Diamandis. Ann Oncol 31:1268-1270, 2020
57. Nelson R, Chustecka Z: Blood Test for Multiple Cancers—Too Many False Positives? https://www.medscape.com/viewarticle/952834
58. Stetson D, Ahmed A, Xu X, et al: Orthogonal comparison of four plasma NGS tests with tumor suggests technical factors are a major source of assay discordance. JCO Precis Oncol 3:1-9, 2019
59. Taylor N: Lawmakers Reintroduce Diagnostic Regulation Bill That Split the Industry, 2021. https://www.medtechdive.com/news/lawmakers-reintroduce-diagnostic-regulation-bill-that-split-the-industry/602425/
60. Sharkey C, Wu X, Walsh M, Offit K: Regulatory and medical aspects of DTC genetic testing, in Consumer Genetic Technologies: Ethical and Legal Considerations. Cambridge, UK, Cambridge University Press, 2021
61. FDA: Table of Pharmacogenetic Associations. https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations
62. Rand P. VITAL Act of 2021. In: Senate—Health Education, Labor, and Pensions, ed. S.16662021. https://www.congress.gov/bill/117th-congress/senate-bill/1666
63. Swetlitz I: Genetic Tests Ordered by Doctors Race to Market, While 'Direct-to-Consumer' Tests Hinge on FDA Approval, 2018. https://www.statnews.com/2018/03/16/genetic-tests-fda-regulation/
64. Richardson L: Diagnostic Test Regulation Should Rank High on Agenda of New Congress. https://www.pewtrusts.org/en/research-and-analysis/articles/2021/01/11/diagnostic-test-regulation-should-rank-high-on-agenda-of-new-congress
65. 21st Century Cures Act, pub. L. No. 114-255 (2016). https://www.govinfo.gov/content/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf
66. Guerrini CJ, Wagner JK, Nelson SC, et al: Who's on third? Regulation of third-party genetic interpretation services. Genet Med 22:4-11, 2020
67. Evans BJ: The limits of FDA's authority to regulate clinical research involving high-throughput DNA sequencing. Food Drug Law J 70:259-287, ii, 2015
68. Reid S, Cadiz S, Pal T: Disparities in genetic testing and care among black women with hereditary breast cancer. Curr Breast Cancer Rep 12:125-131, 2020
69. Oglesbee D, Cowan TM, Pasquali M, et al: CAP/ACMG proficiency resting for biochemical genetics laboratories: A summary of performance. Genet Med 20: 83-90, 2018
70. § 493.1236 Standard: Evaluation of Proficiency Testing Performance. https://www.govinfo.gov/content/pkg/CFR-2012-title42-vol5/pdf/CFR-2012-title42-vol5-sec493-1239.pdf
71. FDA: FDA Takes New Action to Advance the Development of Reliable and Beneficial Genetic Tests That Can Improve Patient Care, 2018. https://www.fda.gov/news-events/press-announcements/fda-takes-new-action-advance-development-reliable-and-beneficial-genetic-tests-can-improve-patient
72. FDA recognizes clingen assertions in clinvar—Frequently asked questions. Clinical Genome Resource. https://clinicalgenome.org/docs/fda-recognizes-clingen-assertions-in-clinvar-frequently-asked-questions/
73. Wagner JK: FTC Takes Action to Protect Consumers From False Genetic Advertising Claims. https://theprivacyreport.com/2014/07/03/ftc-takes-action-to-protect-consumers-from-false-genetic-advertising-claims/
74. Rehm HL, Berg JS, Brooks LD, et al: Clingen—The Clinical Genome Resource. N Engl J Med 372:2235-2242, 2015

75. Gradishar W, Johnson K, Brown K, et al: Clinical variant classification: A comparison of public databases and a commercial testing laboratory. Oncologist 22: 797-803, 2017
76. Ray T: FDA Recommends Precertification Program to Legislators as They Consider DX Regulatory Reform, 2018. https://www.genomeweb.com/molecular-diagnostics/fda-recommends-precertification-program-legislators-they-consider-dx#.XkxP78hKjcs
77. Laakman A: The new genomic semicommons. UC Irvine Law Rev 5:1001-1040, 2014
78. Cline MS, Liao RG, Parsons MT, et al: BRCA challenge: BRCA exchange as a global resource for variants in BRCA1 and BRCA2. PLoS Genet 14:e1007752, 2018
79. FDA: FDA's Views on the Diagnostic Accuracy and Innovation Act (DAIA), 2018. http://www.fdalawblog.net/wp-content/uploads/2018/08/FDA-LDT-Draft-Leg.pdf
80. Khan R, Mittelman D: Consumer genomics will change your Life, whether you get tested or not. Genome Biol 19:120, 2018
81. Akpan N: Genetic Genealogy Can Help Solve Cold Cases. It Can Also Accuse the Wrong Person, 2019. https://www.pbs.org/newshour/science/genetic-genealogy-can-help-solve-cold-cases-it-can-also-accuse-the-wrong-person
82. HHS: Guidance Regarding Methods for De-Identification of Protected Health Information in Accordance With the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, 2012. https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html
83. Wharton School at University of Pennsylvania: Your Data Is Shared and Sold…What's Being Done About it? https://knowledge.wharton.upenn.edu/article/data-shared-sold-whats-done/
84. National Comprehensive Cancer Network. 2022. https://www.nccn.org/
85. U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/contact-us-form
86. Clingen: Clinical Genome Resource. https://clinicalgenome.org/
87. The Verifying Accurate Leading-Edge IVCT Development (VALID) Act of 2021. 2021. https://www.burr.senate.gov/imo/media/doc/2021%20VALID%20Act%20Section-By-Section.pdf
88. Mellert H, Foreman T, Jackson L, et al: Development and clinical utility of a blood-based test service for the rapid Identification of actionable mutations in non-small cell lung Carcinoma. J Mol Diagn 19:404-416, 2017
89. Woodhouse R, Li M, Hughes J, et al: Clinical and analytical validation of FoundationOne Liquid CDx, a novel 324-Gene cfDNA-based comprehensive genomic profiling assay for cancers of solid tumor origin. PLoS One 15:e0237802, 2020
90. Leighl NB, Page RD, Raymond VM, et al: Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. Clin Cancer Res 25:4691-4700, 2019
91. Zheng Z, Liebers M, Zhelyazkova B, et al: Anchored multiplex PCR for targeted next-generation sequencing. Nat Med 20:1479-1484, 2014
92. Abbosh C, Frankell A, Garnett A, et al: Phylogenetic Tracking and Minimal Residual Disease Detection Using ctDNA in Early-Stage NSCLC: A Lung TRACERx Study. Presented at Cancer Research, 2020. https://cancerres.aacrjournals.org/content/80/16_Supplement/CT023
93. Parikh AR, Van Seventer EE, Siravegna G, et al: Minimal residual disease detection using a plasma-only circulating tumor DNA assay in patients with colorectal cancer. Clin Cancer Res 27:5586-5594, 2021
94. Davis AA, Iams WT, Chan D, et al: Early assessment of molecular progression and response by whole-genome circulating tumor DNA in advanced solid tumors. Mol Cancer Ther 19:1486-1496, 2020
95. Bergamaschi A, Ning Y, Ku C-J, et al: Pilot study demonstrating changes in DNA hydroxymethylation enable detection of multiple cancers in plasma cell-free DNA. medRxiv 2020.01.22.20018382, 2020
96. Cristiano S, Leal A, Phallen J, et al: Genome-wide cell-free DNA fragmentation in patients with cancer. Nature 570:385-389, 2019
97. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al: Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 370:1287-1297, 2014
98. Imperiale TF, Kisiel JB, Itzkowitz SH, et al: Specificity of the multi-target stool DNA test for colorectal cancer screening in average-risk 45-49 year-olds: A cross-sectional study. Cancer Prev Res (Phila) 14:489-496, 2021
99. Wan N, Weinberg D, Liu TY, et al: Machine learning enables detection of early-stage colorectal cancer by whole-genome sequencing of plasma cell-free DNA. BMC Cancer 19:832, 2019
100. Ulz P, Perakis S, Zhou Q, et al: Inference of transcription factor binding from cell-free DNA enables tumor subtype prediction and early detection. Nat Commun 10:4666, 2019
101. Klein EA, Richards D, Cohn A, et al: Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncol 32:1167-1177, 2021
102. Beer TM, McDonnell CH, Nadauld L, et al: A prespecified interim analysis of the PATHFINDER study: Performance of a multicancer early detection test in support of clinical implementation. J Clin Oncol 39, 2021 (suppl; abstr 3070)
103. Beer TM, McDonnell CH, Nadauld L, et al: Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. J Clin Oncol 39, 2021 (suppl; abstr 3010)
104. Liu MC, Oxnard GR, Klein EA, et al: Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol 31: 745-759, 2020
105. Lennon AM, Buchanan AH, Kinde I, et al: Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science 369: eabb9601, 2020
106. Offit K. Clinical Cancer Genetics: Risk Counseling and Management. Wiley-Liss, 1998, pp 419
107. Tandy-Connor S, Guiltinan J, Krempely K, et al: False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 20:1515-1521, 2018
108. Esplin ED, Haverfield E, Yang S, et al: Limitations of direct-to-consumer genetic screening for HBOC: False negatives, false positives and everything in between. Cancer Res 79, 2019 (suppl; abstr P4-03-06)
109. Hercher L. 23andMe Said He would Lose His Mind. Ancestry Said the Opposite. Which was right? The New York times, 2018 https://www.nytimes.com/2018/09/15/opinion/sunday/23andme-ancestry-alzheimers-genetic-testing.html
110. Kolata G. The Online Gene Test Finds a Dangerous Mutation. It May Well Be Wrong. 2018. https://www.nytimes.com/2018/07/02/health/gene-testing-disease-nyt.html
111. Horton R, Crawford G, Freeman L, et al: Direct-to-consumer genetic testing. BMJ 367:l5688, 2019
112. Stewart KFJ, Wesselius A, Schreurs MAC, et al. Behavioural changes, sharing behaviour and psychological responses after receiving direct-to-consumer genetic test results: A systematic review and meta-analysis. J Community Genet 9:1-18, 2018

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Regulation of Laboratory-Developed Tests in Preventive Oncology: Emerging Needs and Opportunities

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Kenneth Offit
Patents, Royalties, Other Intellectual Property: Patent pending on therapeutic applications of targeting ERCC3 mutations in cancer. Diagnosis and treatment of ercc3-mutant cancer US20210137850A1
Other Relationship: AnaNeo Therapeutics, Inc

Michele Caggana
Research Funding: Sarepta Therapeutics, PTC Therapeutics, Solid Biosciences, Wave Life Sciences, Pfizer, Inc, (Inst)

Zsofia K. Stadler
Consulting or Advisory Role: Adverum (I), Regenxbio (I), Gyroscope (I), Neurogene (I), Genentech/Roche (I), Regeneron (I), Outlook Therapeutics (I), Optos Plc (I)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Summary of VALID Act[87]

The VALID Act of 2021
Section 1. Short Title and Table of Contents
Section 2. Definitions
Section 3. Regulation of In vitro clinical tests: Amends the Federal Food, Drug, and Cosmetic Act (FDCA) to include the new subchapter for in vitro clinical tests, subchapter J Section 587. Definitions Section 587A. Applicability: Establishes the types of tests that the legislation applies to Section 587B. Premarket review: Establishes a process for the development of new and modification of existing IVCTs Section 587C. Breakthrough In vitro clinical tests: Establishes a program to expedite certain new, urgently needed IVCTs under a new "breakthrough" designation Section 587D. Technology certification: Describes a technology certification process under which IVCT developers can submit a single representative test to the FDA for review in order to establish a scope under which changes may be made without new FDA approval Section 587E. Mitigating measures: Permits the FDA to set mitigating measures for IVCTs Section 587F. Regulatory Pathway Redesignation: Allows the FDA to change test designations based on new information Section 587G. Advisory Committees: Controls the FDA's use of committees for the review and approval of IVCT applications Section 587H. Request for Informal Feedback: Encourages test developers to request informal feedback about the IVCT approval process Section 587I. Registration and listing: Establishes the process to register IVCTs with the FDA Section 587J. Test design and quality requirements: Limits the scope of FDA regulation to the design and manufacture of IVCTs for laboratories not regulated by the FDA and establishes new quality requirements for those that are Section 587K. Labeling requirements: Controls the labeling of IVCTs products Section 587L. Adverse Event reporting: A process for developers to report adverse events Section 587M: Corrections and Removals: Establishes a process allowing developers to voluntarily issue corrections and retract tests from the market Section 587N. Restricted In vitro clinical tests: Describes the circumstances allowing the FDA to add approval requirements to reduce patient risk and ensure test validity Section 587O. Appeals: Requires regulatory and scientific reasoning to be provided regarding significant IVCT review decisions and allows developers to request appeals of those decisions Section 587P. Accredited Persons: The FDA may accredit qualified entities to review applications and conduct inspections Section 587Q. Recognized Standards: Allows the FDA to set IVCT performance standards Section 587R. Investigational use: Controls the use of IVCTs for research purposes Section 587S. Collaborative Communities for In vitro clinical tests: Allows the FDA to gather ideas from diverse stakeholders for the improvement of the IVCT regulatory process Section 587T. Comprehensive Test information system: Establishes a website for the FDA to disseminate public information on IVCTs and securely interact with developers Section 587U. Pre-emption: This law cannot be pre-empted at lower levels of government Section 587V. Adulteration: Criteria under which an IVCT is deemed adulterated Section 587W. Misbranding: Criteria under which an IVCT is deemed misbranded Section 587X. Postmarket surveillance: FDA may require postmarket surveillance of IVCTs Section 587Y. Electronic Format for submissions: Submissions must be electronic. Section 587Z. Postmarket Remedies: Refunds, repairs, or replacements may be directed
Section 4. Enforcement and other provisions
Section 5. Transition: Describes the process of change from old to new rules
Section 6. Emergency use authorization: IVCTs are eligible for emergency use authorization
Section 7. Antimicrobial susceptibility tests: Amends law to address use of IVCTs
Section 8. Combination products: Amends law to address product combinations including IVCTs
Section 9. Resources: User fees will fund IVCT submission reviews

Abbreviations: FDA, US Food and Drug Administration; IVCT, in vitro clinical test; VALID, Verifying Accurate Leading-edge IVCT Development.

TABLE A2. Comparison of Selected Commercial Laboratories Offering Molecular Detection of Cancer From Liquid Biopsy Specimens

Test Indication[a]	Company (test)	FDA Approval	Disease Type	Test Methodology	Reported Test Performance					Study Population
					Stage	Sensitivity	Specificity	PPV	FPR	
Therapeutic decision	Biodesix (GeneStrat) Founded in 2003		NSCLC	Targeted tumor mutations	NA	78.6%-100%[b]	100%	NA	NA	Donor samples without cancer and variant-negative or variant-positive with cancer[88]
	Foundation medicine (Foundation one liquid CDx) Founded in 2010	August 2020	NSCLC, prostate, ovarian, and breast cancers	Tumor genomic profiling	NA	96.3%[c,d,e]	99.9%[c,d,e]	100% (*ALK*), 66.6% (*ATM, BRCA1*, and *BRCA2*), 77.1% (*MET*)[c,e]	0.013%[c,e]	Banked donor samples with various cancer types and cell line DNA[89]
	Guardant (Guardant 360) Founded in 2013	August 2020	Solid tumors including NSCLC	Tumor genomic profiling	IIIB/IV NSCLC	80%-98.2%[f]	100%	100%[f]	NA	Pretreatment blood sample *v* standard-of-care tissue genotyping in patients[90] with NSCLC
Minimal residual disease and recurrence	ArcherDx (Stratafide) Founded in 2013; acquired by Invitae 2020	BDD	Solid tumor	Sequencing	NSCLC stages I-III	89%-100%[c,d,g]	100%[c,d,g]	NA	NA	Tumor from donors with various cancers (FISH assays) and blood from donors with NSCLC[91,92]
	Guardant (Guardant Reveal)		CRC	Tumor genomic and methylation profiling	Stage I-IV CRC	55.6%-91%[h]	100%	100%	NA	Post-treatment blood samples from donors with confirmed CRC[93]
	Lexent Bio Founded in 2014		Solid tumors	Methylation assay	Stage III-IV nonhematologic tumor	54%	100%	NA	NA	Pre- and mid-treatment blood samples from donors with cancer[94]
	Natera (Signatera) Founded in 2004	BDD	Solid tumors	Sequencing	CRC stages I-III	79%	99%	NA	NA	Paired tumor and germline analyses from donors with CRC at various time points including pre- and postoperative[33]

(continued on following page)

TABLE A2. Comparison of Selected Commercial Laboratories Offering Molecular Detection of Cancer From Liquid Biopsy Specimens (continued)

Test Indication[a]	Company (test)	FDA Approval	Disease Type	Test Methodology	Reported Test Performance					Study Population
					Stage	Sensitivity	Specificity	PPV	FPR	
Presymptomatic screening	Bluestar genomics Founded 2016	BDD	Solid tumors	Methylation assay	Breast cancer (primarily stages I-II)	69%	95%	NA	NA	Blood samples from donors without and with various types of cancer (pre-treatment)[95]
					Lung cancer	49%				
					Prostate cancer	64%				
					Pancreatic cancer (primarily stages I-II)	83%				
	Delfi Founded in 2019		Solid tumors	Genome-wide DNA fragmentation assay	Overall from CRC, biliary, breast, gastric, lung, ovary, and pancreatic cancers	57%-100%[i,j]	98%	25%	NA	Blood samples from donors without and with various types of cancers (pretreatment)[96]
					I	68%-73%	95%-98%			
					II	72%-78%				
					III	79%-91%				
					IV	77%-82%				
	Exact Sciences (Cologuard) Founded in 1995		CRC, advanced precancerous lesions	Targeted methylation, targeted mutation, and hemoglobin immunochemical assays	Overall	92.3%	86.6%-95.2%[g]	30.2%	67.2%	Multitarget stool DNA testing compared with the fecal immunohistochemical test[97,98]
					I	90%[e]				
					II	100%[e]				
					III	90%[e]				
					IV	75%[e]				
					Advanced adenomas and sessile serrated lesions	32.7%-42.4%[g]				
					Polyps with high-grade dysplasia	69.2%				
	Freenome Founded in 2014		Colon cancer	Methylation assay	CRC stages I-IV	85%	85%	NA	NA	Blood samples from donors without cancer and with CRC, breast, and prostate cancers[99,100]
					I	71%	72%			
					II	74%	77%			

(continued on following page)

TABLE A2. Comparison of Selected Commercial Laboratories Offering Molecular Detection of Cancer From Liquid Biopsy Specimens (continued)

Test Indication[a]	Company (test)	FDA Approval	Disease Type	Test Methodology	Reported Test Performance					Study Population
					Stage	Sensitivity	Specificity	PPV	FPR	
	Grail Founded in 2015; acquired by Illumina in August 2021	BDD	Multicancer (50+)	Targeted methylation assay	Overall	51.5%[k]	99.3%-99.5%[g]	43.3%-45%[g]	0.5%-0.7%[c,g,k]	Blood samples from donors without and with various types of cancers (pretreatment)[101-104]
					I	16.8%-18%				
					II	40.4%-43%				
					III	77.0%-81%				
					IV	91.1%-93%				
	Thrive (CancerSEEK) Founded in 2016; acquired by Exact Sciences in 2021	BDD for pancreatic and ovarian cancers	Multicancer	Sequencing and protein biomarker analysis	NA	15.6%-27.1%[l]	98.9%-99.6%[l]	19.4%-28.3%[l]	0.6%	Blood samples from donors without cancer with imaging to confirm positive blood tests[105]

Abbreviations: BDD, breakthrough device designation; cfDNA, cell-free DNA; CRC, colorectal cancer; FDA, US Food and Drug Administration; FPR, false-positive rate; NA, not available; NSCLC, non–small-cell lung cancer; PET-CT, positron emission tomography and computed tomography; PPV, positive predictive value.

[a]Not including tests in the pipeline but without published data available.

[b]Values differ per variant tested (*EGFR, KRAS*, and *EML4-ALK*).

[c]Sensitivity and specificity were not derived as per conventional comparison with reference but instead with an orthogonal company–owned technology.

[d]Calculated on the basis of a subset of targeted variants.

[e]Reported on company website.

[f]Higher sensitivity and positive predictive values are for *EGFR, ALK, ROS1, BRAF*, and targets only.

[g]Range from different company-published studies.

[h]Higher sensitivity with serial longitudinal and surveillance (within 4 months of recurrence) sampling.

[i]Values differ per cancer type.

[j]Higher sensitivity when Delfi was combined with mutation detection in cfDNA.

[k]Sensitivity and false-positive rate as calculated by company.[54]

[l]Higher specificity and lower sensitivity with PET-CT imaging.

TABLE A3. Selected Literature and Case Reports Following Self-Directed Genetic Testing, Grouped by Challenges Traditionally Addressed by Genetic Counseling[106]

Challenge With Self-Directed Testing	Case Summaries
Analytic	Of 12 individuals with non-Ashkenazi Jewish founder *BRCA1* or *BRCA2* mutations identified through DTC testing, eight (67%) were found to be false positives[107]
	Analyses show that in a cohort of 119,328 patients referred for *BRCA1* and *BRCA2* testing, 19% and 94% of individuals of Ashkenazi Jewish and non-Ashkenazi Jewish ancestry, respectively, would receive a false-negative result through founder variant testing offered through DTC companies. Similarly, in a cohort of 270,806 patients referred for *MUTYH* testing, 40% of biallelic carriers and 22% of monoallelic carriers would receive a false-negative result with limited variant testing. The risk to miss a mutation in *BRCA1*, *BRCA2*, or *MUTYH* was higher among individuals of Asian, African American, and Hispanic ancestry or ethnicity as compared with White ancestry or ethnicity. The same study identified that in a cohort of 102 patients, 52 were found to have analytic false positives from their third-party raw genomic data analysis[108]
	A man was unable to clinically confirm an incidental finding of risk for Alzheimer's disease from DTC raw data[109]
	A physician was led to a self-diagnosis of Lynch syndrome after receiving third-party raw data interpretation. Clinical testing did not confirm the Lynch syndrome mutation[110]
	A young man was found to have both *BRCA2* and *MSH2* mutations from self-directed testing and online analysis of raw genomic data; clinical testing did not confirm any inherited cancer mutations[a]
	A young woman with a DTC-positive result for Peutz-Jeghers syndrome received nonconfirmatory results through our clinic, negating the need to undergo intensive cancer surveillance measures[a]
	A young woman pursued confirmation testing for a *BRCA* mutation identified in her raw data obtained from DTC testing. She stated that she would pursue prophylactic bilateral mastectomy if confirmed. Clinical confirmation testing did not confirm the *BRCA* mutation[a]
	A young woman without a personal history of cancer was found to have multiple *BRCA1* (one mutation), *BRCA2* (three mutations), *MLH1* (five mutations), *MSH2* (10 mutations), and *MSH6* (two mutations) mutations from self-directed testing and online analysis of raw genomic data. For one of the *MSH2* mutations, the report indicated a likely an artifact and miscall. Family history was inconsistent with a known hereditary predisposition to cancer. Clinical confirmation testing did not confirm these mutations[a]
Interpretative	Genetic variants were reported as being associated with increased risk by a DTC company or by a third-party interpretation service, but classified as benign by other clinical laboratories[111]
	A young woman engaged in DTC whole-genome sequencing. She was concerned for her health and was adopted with little knowledge of her biologic family. The results suggested an increased risk for breast cancer and other health conditions on the basis of inference from genome-wide association studies not adjusted for her ancestry, and single-nucleotide polymorphism allele frequencies compared with a company database combining phenotypes, that is, not an unaffected control population[a]
	A female in her 30s presented to clinic with a report showing two *CFTR* mutations identified in the raw data analysis from DTC testing. Both mutations were cited to be likely false positives on the report. She had recent bronchitis and digestive issues and self-diagnosed cystic fibrosis. She conveyed her concern for her healthy children (both below age 10 years) who were each found to carry both the same *CFTR* mutations in their raw genomic data provided by the same DTC laboratory. The patient also initiated dietary changes as a result of the nutrigenomics portion of her report. The patient was referred for a sweat test with her primary care provider[b]
	A female underwent genetic testing from a laboratory that provides CIT services. Her testing revealed a *PMS2* variant of uncertain significance and a likely pathogenic *CHEK2* mutation. The report inappropriately stated that the patient may be affected with or predisposed to Li-Fraumeni syndrome, resulting in adverse emotional sequalae. Clinical genetic testing on first-degree relatives and family members is pending[a]
Psychosocial or medical follow-up	After self-directed testing revealed a *BRCA1* mutation in a young woman, she did not seek medical consultation and thus received no intensified cancer surveillance (eg, breast MRI screening). A year later, she was diagnosed with a breast cancer metastatic to lymph nodes[a]
	A young couple tested their teenage daughter for recreational (nonmedical) purposes and received results indicating *BRCA2* mutation, resulting in severe adverse emotional sequelae[b]
	As a holiday gift, a father gave his teenage daughter a DTC genetic test kit to learn about her ancestry. A *BRCA1* mutation was reported for this minor, resulting in emotional upset and possibly questionable medical advice from a nongenetics professional. Confirmation testing is being considered, but there are insurance coverage concerns from the family because of her age[a]
	A young woman pursued DTC testing for recreational purposes. She did not recall explicit counseling or education about cancer risk testing and had adverse psychological sequelae after detection of an Ashkenazi Jewish *BRCA* founder mutation and subsequent discovery that she was conceived via sperm donation[a]
	A recent systematic review and meta-analysis of consumer responses to DTC testing found minimal subsequent health behavior changes (eg, 24% of consumers had a positive lifestyle change, 7% had subsequent preventive medical checks, and 33% shared result with a health care professional)[112]

NOTE. Mutation signifies a pathogenic variant.

Abbreviations: CIT, consumer-initiated-testing; DTC, direct-to-consumer testing; MRI, magnetic resonance imaging.

[a]Offit K, unpublished.

[b]Green D, unpublished.

The Role of Lab-Developed Tests in the In Vitro Diagnostics Market

As lab-developed tests grow increasingly complicated, federal oversight has lagged

REPORT

October 22, 2021

Read time: 37 min

Projects: Health Care Products

National Cancer Institute

Overview

In vitro diagnostic (IVD) tests—which use blood, saliva, and other human samples to detect the presence or risk of certain diseases—are a pillar of modern medicine. Doctors and patients rely on them to guide life-or-death medical decisions, from choosing a cancer

treatment[1] to managing a pregnancy.[2] They also have been critical tools in the fight against COVID-19.

Although the U.S. Food and Drug Administration approves or clears many IVDs before they reach patients, an unknown number of a type of IVD—lab-developed tests (LDTs)—enter the market without FDA review or any other independent regulatory review, simply because they are created and used in the same facility. The Centers for Medicare & Medicaid Services (CMS) regulates labs but has limited insight into the quality, reliability, or usefulness of LDTs, including whether patients have been harmed as a result of their use. (See Figure 1.)

To inform policymakers' efforts to strengthen diagnostics oversight, The Pew Charitable Trusts commissioned research to measure how many tests are run every year using LDTs, and how, when, and why laboratories use these kinds of tests. No database encompasses all available LDTs, so any attempt to characterize the market must rely on estimates built on certain assumptions and be refined with additional data. This study leveraged multiple data sources to provide a current snapshot of the diagnostics market. (See Methodology.) The research—based on insurance claims data, a nonprobability web survey of 195 lab managers, and 20 interviews with executives from clinical labs and diagnostic manufacturers—yielded several findings.

First, because LDTs are not centrally registered or tracked, no one knows precisely how many of them are on the market, when and why they are used, or how their performance compares with FDA-reviewed diagnostics.

- An estimated 3.3 billion in vitro diagnostic tests—both FDA-reviewed and LDTs—are run every year. Although it is clear that LDTs are commonly deployed in many labs, it is not clear exactly how often they are used or for what clinical purposes. Insurance claims and electronic health records do not distinguish between LDTs and FDA-reviewed diagnostics, and there are no comprehensive databases of all LDTs in use.
- When surveyed, even seasoned clinical lab managers demonstrated confusion over what constitutes an LDT. For example, some survey respondents did not realize that anytime a lab makes a change to an FDA reviewed test—such as altering how specimens are handled—it has effectively created an LDT.
- Lab managers generally expressed a preference for using diagnostics that have undergone FDA review because they are often simpler to use. However, labs often rely on LDTs in cases where an FDA-reviewed test is unavailable or needs modifications for use in a particular population. Interviewees said they may also run LDTs to reduce costs or improve the speed or efficiency of the testing process.

Second, LDTs have changed considerably since Congress established the current regulatory framework for diagnostics in 1976, and the regulatory gaps now present unnecessary risks to patients.

- Today, labs run far more complex and high-risk tests for a wider range of uses than in 1976. Lab managers reported using LDTs more commonly in certain areas such as oncology and rare and infectious diseases—fields that rely heavily on genetic testing and other sophisticated methods, or where scientific understanding is evolving quickly. In these fields, inaccurate results can cause significant harm because providers and patients often rely heavily on test results to determine treatment plans. For example, false positives for cancer-causing mutations can lead patients to have surgery they do not need, whereas a false negative test result for an infection can cause patients to forgo potentially lifesaving treatment or spread that infection to others.
- When FDA was originally granted oversight of medical devices, most LDTs served a limited number of patients—typically those living near the labs that developed them—but today they can reach millions of people. For example, there are many direct-to-consumer genetic tests that claim to determine an individual's risk of developing cancer and other diseases, and that can easily be shipped to consumers without a doctor's prescription. However, FDA has reviewed very few;[3] the rest are unapproved LDTs.

Third, increased transparency of the diagnostics market and a risk-based approach to LDT regulation would enable clinicians and patients to make more-informed decisions about diagnostics without disrupting their access to the tests.

- Many in the clinical laboratory industry and in academic medical centers have opposed recent efforts by lawmakers, FDA, public health advocates, and other stakeholders to strengthen FDA oversight, saying it would impede innovation, increase costs, and disrupt patient care. Although lab managers interviewed for this report echoed those concerns, they also generally agreed that appropriately structured FDA oversight could improve patient safety and increase the scientific rigor and quality of the tests on the market.

FDA, Congress, public health advocates, and other stakeholders have debated how best to modernize IVD regulation for more than a decade. The most recent and most comprehensive proposal to date is the bipartisan Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021, which would direct FDA to regulate all diagnostics, including LDTs, based on their risk to patients if tests give the wrong result, rather than on where they are created and used. However, there is still disagreement among these key stakeholders over whether the bill adequately balances patient safety protections with the need to bring

innovative tests to market quickly.

As federal policymakers consider approaches to strengthening oversight of in vitro diagnostics, this research and the following principles can help guide their thinking:

- To effectively regulate these products, FDA must have a clear picture of what tests are in use and be able to collect sufficient information on how they are performing. At a minimum, this should include a requirement that all tests be registered with the agency; developers report adverse events related to their diagnostics; and the agency be empowered to request information regarding the validity and performance of those products when it has concerns.
- Given the large yet unknown number of LDTs currently on the market, any reform will need to include a mechanism for bringing these tests into compliance with FDA regulations in a way that minimizes disruptions to patient care. Two options that policymakers could consider are phasing in FDA reviews of LDTs or exempting these tests from premarket review while ensuring that the agency has sufficient post-market authority to require data on their performance and take enforcement action when necessary to protect patients.[4] (See Appendix E.)
- In vitro diagnostics are regularly modified or adapted to address patient needs and to respond to advances in scientific understanding. Any new regulatory approach for diagnostics must be flexible enough to allow developers to modify tests or develop new ones in order to meet patient need without undue delay.

However, adequate safeguards must be in place to ensure that tests are valid, reliable, and of high quality. Again, as with any medical product, regulatory oversight should be proportional to the associated risks.

- The lack of a shared definition of what constitutes an LDT—even among laboratory experts—highlights the broader lack of familiarity of many labs with FDA regulations. Bringing LDT developers under FDA oversight will require a transition period that allows labs adequate time to come into compliance. It will also require extensive outreach and education after reform is passed to ensure a common understanding of FDA regulations and what compliance will entail.
- FDA, in turn, will also need adequate time and additional funding to develop new guidance documents and regulations and to implement them by conducting more reviews and inspections of labs.

Figure 1

Key Public Health Protections Missing From Federal Oversight of Lab-Developed Tests

Despite similarities, LDTs and FDA-reviewed tests are not held to the same standards

	FDA-reviewed in vitro diagnostics	Lab-developed tests
Moderate- and high-risk tests are reviewed externally before use on patients	Yes	No
Tests are registered in a public database	Yes	No
Public reporting of adverse events related to an incorrect test result is mandatory	Yes	No
Product labeling is reviewed and approved to ensure that it is comprehensive and accurate	Yes	No
Marketing claims must be supported by evidence and approved before use in a clinical setting	Yes	No
Oversight body is able to recall faulty tests	Yes	No

Regulatory background and history

FDA has regulated medical devices since the passage of the Medical Device Amendments of 1976, including products "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease."[5] As such, the agency has authority over in vitro diagnostic (IVD) tests and their components. In vitro diagnostic refers to any clinical test that analyzes samples taken from the human body. Under the current regulatory regime, IVDs developed for the commercial market are subject to regulatory requirements set by the agency to ensure safety and effectiveness.

FDA has historically exempted tests made and used in a single laboratory from nearly all regulatory requirements under the Food, Drug, and Cosmetic Act because the agency has generally viewed LDTs as posing a lower risk to patients than IVDs manufactured at commercial scale and sold to labs. When FDA was originally granted oversight over medical devices in 1976, most LDTs were relatively simple, or they provided customized tests for rare

conditions that could not be assessed with commercially available IVDs. Although some LDTs continue to be developed at a small scale and used locally, others, particularly those that are modified versions of commercial IVDs, may run at significant volumes—especially in a large commercial lab that processes thousands of samples a day. LDTs have also become more complex, are used for a wider range of conditions that affect many more people, and are sometimes marketed nationwide.

As LDTs have grown in use and complexity, FDA regulations have not kept pace. Instead, LDTs are principally regulated by CMS under separate regulations known as Clinical Laboratory Improvement Amendments (CLIA). CLIA oversight focuses on laboratory operations and staff training but does not assess the validity of individual tests in a lab. Because LDTs have not been required to meet FDA review standards, their number and the extent of their use is unknown. In 2014, FDA estimated that 650 U.S. laboratories developed and deployed LDTs,[6] while the American Clinical Laboratory Association maintained that the 11,633 labs that were certified at that time to develop such tests did so.[7]

CLIA standards differ from those applied during FDA premarket review. FDA regulates IVDs as medical devices and classifies these tests based on the level of risk that potentially inaccurate results pose to patients and public health. During the premarket review process, a developer must provide evidence demonstrating that a test is both analytically and clinically valid, which are key concepts in assessing a test's reliability and accuracy. (See box below.)

> **Analytical validity** refers to how well a test performs in detecting or measuring the presence of a given chemical compound, hormone, or genetic marker in a given sample. Analytically valid tests are precise (they provide a high degree of specificity), accurate (they measure or detect what they are intended to), and reliable (they regularly reproduce the same results).
>
> **Clinical validity** refers to how accurately a test predicts the presence of, or risk for, a given condition. A genetic test intending to detect the presence of a genetic mutation is clinically valid for a particular cancer if a meaningful association between that mutation and the incidence of the disease has been demonstrated.

For those laboratories administering tests that have not received FDA clearance or approval, CLIA regulations do not allow the release of any test results until the laboratory demonstrates its ability to analytically validate the tests it performs. However, unlike FDA's review of IVDs, a determination of analytical validity for a laboratory regulated under CLIA cannot be extrapolated to other sites or patient populations. In addition, a laboratory's analytical validation is reviewed as part of a survey that takes place every two years—meaning that an unreliable test might not be caught for two years.[8] FDA review of analytical

validation, in comparison, is performed before a test is marketed for use in patients, and is more comprehensive and focused on a test's safety and effectiveness.[9] CLIA is also not intended to assess the clinical validity of the tests performed in that lab—this type of validation is left to the labs themselves.[10]

Table 1

Federal Oversight of Diagnostic Tests Is Fragmented[11]

Tests are regulated according to where they are developed and used, not the risks posed to patients

	FDA	CMS
Primary statutory authority	Food, Drug, and Cosmetic Act, as amended by the Medical Device Amendments of 1976	Public Health Services Act, as amended by the Clinical Laboratory Improvement Amendments (CLIA) of 1988
Oversight	All IVDs (including LDTs and reagents) are categorized as medical devices, but FDA has historically not exercised its regulatory authority with respect to LDTs.	Labs conducting tests on human samples. Inspectors evaluate the qualifications of lab personnel and testing processes and review their analytical validation processes for all tests, whether LDT or IVD.
Validation requirements	Analytical validity Clinical validity	Analytical validity
How are tests validated?	Through premarket review, manufacturers of moderate- and high-risk IVDs must establish that a test detects or measures the intended analyte with appropriate precision and accuracy. Human studies are typically required to demonstrate the test's ability to predict a disease or condition as intended.	Labs performing tests that are not subject to FDA clearance or approval must establish performance characteristics of that test ("an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval").
When are tests reviewed?	At various points before the legal marketing of that test.	During inspections every two years (may be up to two years after an LDT is first performed).

Adverse event reporting	Mandatory reporting of adverse events by manufacturers, device user facilities (hospitals, nursing homes, etc.), and importers. Providers and patients may also voluntarily report serious adverse events.*	Not required. No mechanism exists to collect such information.
Recall authority?	Yes	No

** U.S. Food and Drug Administration, "Medical Device Reporting (MDR): How to Report Medical Device Problems," https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.*

Source: As governed by Public Law 94-295, Public Law 100-578, and associated implementing regulations; Centers for Medicare & Medicaid Services.

This fragmented oversight system, whereby tests are regulated according to where they are developed and used rather than their risk to patients, can pose dangers to public health. Given that CLIA's regulatory system does not require a laboratory to demonstrate an LDT's clinical validity, the chance that an inaccurate test will be introduced into the market increases. Inaccurate tests can expose patients to harm, including false-positive results, which could lead them to pursue unnecessary treatments or delay the timely diagnosis of underlying conditions. Similarly, false-negative results can delay or prevent patients from receiving proper treatment, potentially allowing the disease or condition to progress unchecked. For example, many direct-to-consumer genetic tests—such as genetic health risk tests, which predict a person's risk for developing diseases such as cancer or Alzheimer's—are developed and used as LDTs. The clinical validity of some of these tests is uncertain, as there is ongoing scientific disagreement about the role that genetic variants may play in contributing to many diseases. A positive result from a test that is not clinically valid, therefore, might cause unnecessary emotional distress to a patient.

Furthermore, unlike FDA standards, CLIA regulations do not require makers of LDTs to publicly report adverse events that may stem from the use of their tests, nor is there a system in place to track these events. Therefore, if an inaccurate LDT was used, the number of patients affected and how they were affected might never be known. For example, a test called OvaSure was marketed as an LDT by LabCorp to detect ovarian cancer in high-risk populations. It was later discovered that only 1 out of every 15 positive results was a true

positive, potentially leading patients to undergo unnecessary, dangerous, and invasive surgeries.[12] FDA sent LabCorp a warning letter, and the test was removed from the market within months, but because there is no mechanism for adverse event reporting for LDTs, the full scale of that test's impact remains unclear.

Over the years, as testing technologies have become more complex, clinicians' use of these tests has presented greater risks to patient and public health. (See "What Can Happen When Patients Are Exposed to Unreliable Tests?") However, although FDA maintains that LDTs are medical devices and fall under its jurisdiction, many LDT developers have thwarted attempts to bring them under the agency's oversight, arguing that these tests are procedures that fall under the practice of medicine. For years, policymakers on both sides of the aisle have debated how best to reform the current system of oversight. (See Appendix C for a timeline of key events in this long-standing discussion.) In 2010, FDA announced its intention to reconsider its policy of enforcement discretion over LDTs and held a two-day public meeting to solicit input from stakeholders. This led to the development of draft guidance that was published in 2014 bringing LDTs under the agency's existing regulatory framework.[13] However, this proposal met with significant pushback from many in the laboratory industry and within academic medical centers.[14] As a result, the agency announced that it would not issue final guidance,[15] and reform discussions then shifted to Congress, where negotiations eventually culminated in the Verifying Accurate Leading-edge IVCT Development (VALID) Act, which was introduced in March 2020.[16]

What Can Happen When Patients Are Exposed to Unreliable Tests?

Some categories of tests illustrate just how little oversight there is for even widely marketed LDTs and how risky inaccurate test results can be when patients are relying on their results to guide medical decisions around everything from pregnancy to cancer treatment.[17]

- **Noninvasive prenatal testing** is a method of determining the risk that a fetus will be born with certain genetic abnormalities, such as Down, Edwards, and Patau syndromes. These tests help parents make critical decisions about a pregnancy and, as such, need to be carefully designed, administered, and marketed. Of the more than 40 noninvasive prenatal tests, all are LDTs;[18] none have been cleared or approved by FDA. Some companies advertise these tests for use in populations where their accuracy is less established, or to diagnose a broader range of conditions despite the limited evidence for those uses.[19]
    - **Risk:** Expectant parents may be misled about the risk that a pregnancy has a chromosomal abnormality.

- **Direct-to-consumer (DTC) genetic tests** are, with relatively few exceptions, LDTs and not FDAapproved.[20] One study estimated that more than 26 million people had taken a DTC genetic health or ancestry test as of January 2019, with the number expected to reach 100 million by the end of 2021.[21] There is variable quality among manufacturers, however.[22] One

small study examined 49 patients who had taken a DTC genetic test and subsequently received follow-up testing. The authors found that 40% of the harmful variants reported back to those patients were false positives, indicating that the patients did not actually have those genetic variants.[23]

    - **Risk:** These incorrect results can lead to stress and unnecessary medical procedures.

- **Companion diagnostics** guide the safe and effective use of a particular therapy and are often a key factor in treatment decisions, increasing the risks to patients if the results are incorrect. In some cases, after FDA approves one companion diagnostic, labs create follow-on versions of those tests that they claim can identify the same mutation.[24] However, individual labs often have different approaches to analyzing samples. And some LDT developers claim to test for additional mutations that have not been adequately reviewed to predict drug response.[25]

    - **Risk:** The same patient may get different results depending on the LDT used,[26] receive ineffective therapies for a condition, or miss out on more beneficial ones. And many cancer treatments have serious side effects of their own, which can compound the harm for patients who receive an inappropriate therapy.[27]

The onset of the COVID-19 pandemic has only underscored the need for regulatory clarity. When a public health emergency was declared in January 2020,[28] FDA subsequently announced that it would require any test used as part of the pandemic response to apply for emergency use authorization (EUA), just as it had done for prior emergencies.[29] To further speed expansion of COVID-19 testing, FDA in March 2020 began allowing labs to bring a test to market immediately, provided that they apply for an EUA within 15 days.[30]

EUAs allow FDA to temporarily authorize urgently needed medical products while ensuring that the potential benefits to patients outweigh the risks. This quality check from the agency is crucial in ensuring that tests on the market meet baseline standards for accuracy and reliability before they are used on patients. The EUA process also allows the agency to track tests once on the market and to know how they are performing in the real world, issuing safety announcements[31] and even revoking authorizations where necessary.[32]

However, in August 2020, the Department of Health and Human Services (HHS) declared that FDA could not require premarket review for any LDT—whether developed for COVID-19 or any other condition—unless the agency first went through a time-consuming rule-making process.[33] This announcement did not state whether any of FDA's other emergency authorities, such as the ability to recall faulty tests, were still in effect. HHS subsequently declared that LDTs for use in a national public health emergency remain subject to appropriate FDA regulations under the Public Health Service Act in order "to prevent the introduction, transmission, or spread of communicable diseases." However, because most of the agency's authority over diagnostic tests stems from the Food, Drug, and Cosmetic Act,

FDA's power to regulate LDTs—whether during a public health emergency or not—remains unclear.[34]

Legislators are still considering how to reform IVD oversight in a way that ensures that all tests are held to riskbased standards of review while providing pathways for developers to bring innovative tests to market without undue delay. However, an incomplete understanding of the scale and complexity of the diagnostics market has impeded these discussions. Research assessing the size of the testing industry, its structure, and the role of LDTs within the market is essential to inform discussions about reform and to tailor new oversight mechanisms and resources to the risks of those tests.

Understanding the role of LDTs in the diagnostics market

Pew's study found that an estimated 3.3 billion IVD tests are performed in the U.S. every year. Interviews with lab professionals suggested that LDTs account for a significant portion of this total, but our analysis did not produce a reliable estimate of this part of the overall testing market. No single database tracks all LDTs currently in use, and claims data—which is typically used to estimate testing volume—does not distinguish between tests run as LDTs and those run as IVDs. Responses to our survey indicated that lab managers lack a widely shared definition for LDTs, further challenging efforts to characterize the market.

Who makes LDTs

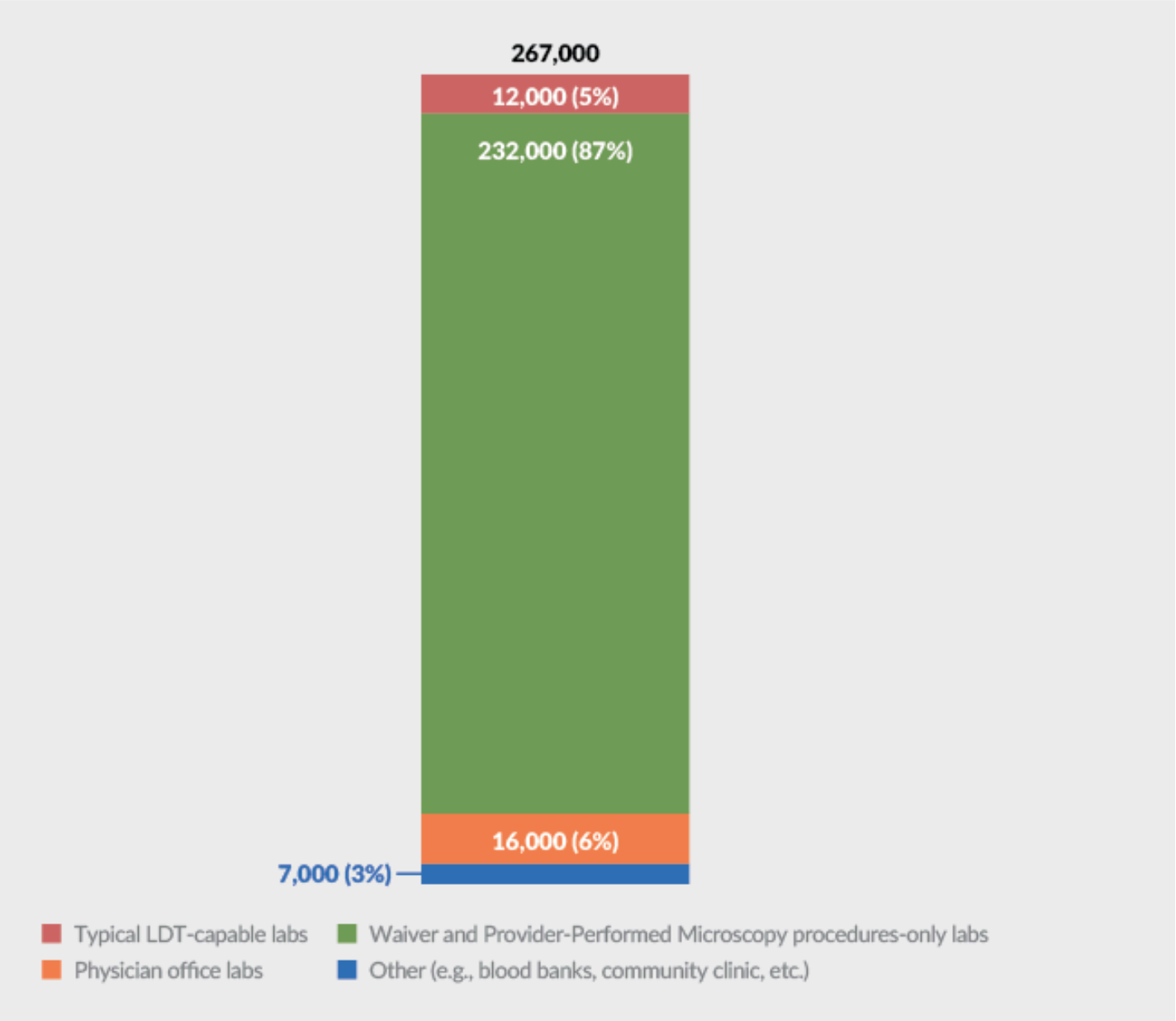
Not all clinical labs develop LDTs. Of the approximately 267,000 lab facilities in the U.S., the vast majority are simple operations set up to run conventional, easy-to-use blood tests and other low-risk tests without the need for specially trained laboratory personnel.[35] These tests—collectively referred to as "CLIA-waived" because they can be run outside a CLIA-certified setting—include those that can be performed anywhere, from the back of an ambulance to a school nurse's office, pharmacy, physician's office, or hospital.[36]

Developing a safe and effective test from scratch is a complex undertaking that involves significant training, reliable controls, and substantial investment in analytical equipment. For the most part, only labs certified by CLIA as high-complexity labs can develop and deploy LDTs, and an estimated 12,000 such laboratories were registered with CMS as of March 2020.[37] (See Figure 2.) Although this number is a small proportion of the approximately 267,000 labs in the U.S., it still makes up a considerable segment of the overall testing landscape, as many of these labs are large and process thousands of patient samples a day.

Figure 2

Only Certain Laboratories Develop LDTs

Of approximately 267,000 lab facilities in the U.S., an estimated 12,000 are likely to use LDTs



Source: BCG analysis of the Quality Improvement and Evaluation System (QIES) database

Qualified labs may create a new LDT in four basic ways (see Figure 3):

- Starting from scratch, assembling relevant testing reagents and other FDA-reviewed testing components.

- Combining elements of FDA-reviewed test kits with components made or separately acquired by the lab.
- Obtaining the protocol for a test developed as an LDT by another facility.
- Altering an FDA-cleared or -approved IVD by, for instance, enabling the product to analyze patient specimens that have been stored longer than the test's labeling allows.

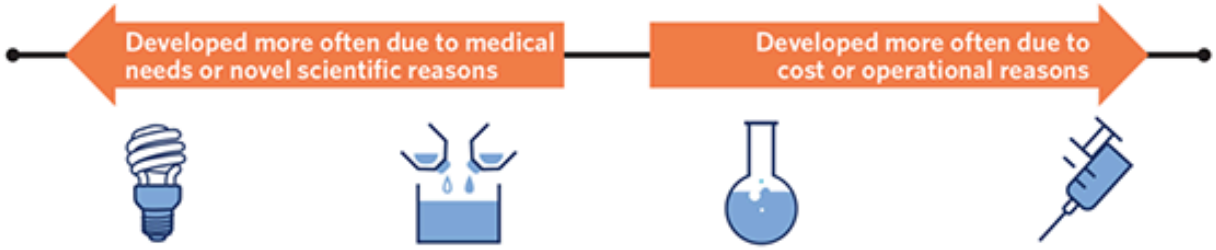
Considerations for reform

Although it is difficult to know precisely how many LDTs are on the market, or to accurately estimate the volume of tests that are run using LDTs, they are clearly common, and many labs rely on them in some capacity. This poses a challenge for policymakers considering reform, because a mechanism will be needed for bringing these tests under a new regulatory framework in a way that minimizes disruptions to patient care and critical laboratory services. There are two potential options that could be considered. Policymakers could adopt a risk-based, phased-in approach that would transition all existing tests under the new regulatory framework within some specified time frame, similar to what FDA proposed in its 2014 draft guidance on LDT regulation.[38] Alternatively, policymakers could issue a blanket regulatory exemption for tests that are on the market before a particular date, much as they have in past cases where FDA has been granted new authorities over an existing market.[39] However, this approach poses public health risks, because it would exempt from review many moderate- and high-risk tests that are currently driving the need for reform.

One solution to this issue would be to allow FDA broad authority to request data on these "pre-reform" tests and to require a full premarket review if it was deemed necessary to protect public health. Pre-reform tests should also be subject to the same registration and reporting requirements that apply to new tests entering the market, including adverse event reporting. To ensure that all pre-reform tests are accounted for and subject to FDA enforcement, developers should also be required to register them with the agency. A central registry would be a key tool for oversight and could also serve as an important public resource.

Figure 3

LDTs range from wholly lab-developed to slight modifications of IVDs



Type of LDT	Novel test	Test contains mix of existing FDA-approved/ nonapproved components	Vendor or centrally developed test	Modified IVD
Description	Test developed from scratch, assembling relevant components	Test developed by combining elements of FDA-reviewed test kits with components made or separately acquired by the lab	Test developed by obtaining the protocol for development from another facility that developed the LDT	Test developed by altering an FDA-reviewed IVD (e.g., running the test using saliva instead of nasal secretions)

Why labs develop LDTs

Lab managers interviewed for this study noted that they prefer to use FDA-reviewed commercial IVDs when those are available. They cited several reasons, including their relative ease of use and efficiency compared with LDTs. Some also noted that commercial IVDs are generally more reliable and are of high quality. Relying on commercial IVDs also reduces labs' potential liability if there is a problem with the test. However, they all noted that LDTs are sometimes necessary or preferable.

In many cases, labs may develop a test if FDA has not approved a suitable IVD. There are many scenarios in which this might be the case. There might be a limited commercial incentive to develop a test that will go through FDA review—for example, for certain rare diseases or conditions. Alternatively, an LDT might represent the prototype of a diagnostic test that will ultimately be submitted for FDA approval. In other cases, the test in question is evolving rapidly in response to emerging science, and developers might perceive FDA review as being too slow to keep pace. (See Figure 4.) Approximately half of our nonprobability survey respondents stated that they used LDTs when no IVD was commercially available.

Figure 4

Reasons an FDA-Reviewed IVD Might Not Be Available for a Particular Use

Lab managers cite lack of market incentives, the rapid pace of test innovation, and regulatory costs as key drivers of LDT development

Question: For tests where no FDA-approved IVD exists for the testing indication and an LDT is utilized, what are the most common reasons why no IVD exists? Percentage of respondents selecting in Top 3.

	Total
Test is too low-volume to warrant filing for IVD	46%
Novel test—will eventually become IVD	45%
Test is evolving quickly (e.g., new markers)	43%
Test is instrument- and interpretation-based (e.g., mass spec, flow cytometry, immunohistochemistry)	35%
Filing for IVD would be too expensive	28%
Test is specific to a single lab/lab company and no desire currently exists to market it outside of lab/lab company	23%
Other	1%

The survey also sought deeper insight into why lab managers would choose to employ an LDT. Open responses to offer the "top reasons" for using LDTs tended to fall into four broad categories: patient need, clinical workflow, rapid access, and cost.

- **Patient need**—When a disease such as COVID-19 emerges or spreads, the spike in demand for testing can outstrip the available supply of IVDs from device manufacturers. In such cases, clinical laboratories with the requisite equipment, supplies, and expertise can step in to provide additional testing, much as they have during the current pandemic. In other cases, a test may be altered in some way to make it less invasive or easier to perform—for example, changed to run on saliva instead of a sample taken from deep in a patient's nasal cavity. In oncology, tests that are validated in one type of

cancer may be adapted for use in another type of cancer. For example, no FDA-approved IVDs exist for the KRAS gene mutation in pancreatic cancer, but clinicians sometimes modify an available IVD test for KRAS in colorectal cancer, thereby creating an LDT.

- **Clinical workflow**—Any deviation from a manufacturer's instructions for administering an IVD creates an LDT. For instance, an IVD may be approved for use with samples taken within the past 48 hours. However, a reference lab performing thousands of these tests across a broad geographical area may require more time to receive and process the samples. In such cases, the lab can perform an analysis to determine whether the delay has any bearing on the validity of the test and document the results for inspectors.
- **Rapid access**—IVDs can take considerable time to gain FDA approval and reach the market. However, the speed of scientific research and technological development in the diagnostics market can outpace FDA review, particularly in rapidly evolving fields such as genetic testing. In those contexts, an LDT may be developed as an early prototype and then transformed into a standardized, FDA-approved IVD once it has been refined through experimentation and the developer has accumulated enough data to demonstrate that it meets FDA standards for safety and effectiveness. Alternatively, some tests, such as those that rely on next-generation sequencing technology, may be highly complex to run and require specific training to interpret, both of which are factors that can make a test more difficult to standardize and produce at a commercial scale for use in many labs.[40] In these cases, the developer may prefer to maintain the test as an LDT.
- **Cost**—All IVDs include components designed to make their systems resilient under a range of procedural and handling conditions. However, a sophisticated and well-equipped clinical lab might consider these safeguards both unnecessary and expensive, so it could modify the test to save money. For example, labs might substitute reagents or other components that can be purchased at a lower cost, then validate those modifications to ensure that the test still works as expected. In this way, some labs might reduce their operating expenses. Examples of this phenomenon are common, especially with large laboratory chains with multiple sites that often substitute LDTs for IVDs such as complete blood count testing kits.

Considerations for reform

Given the important role that IVDs—including LDTs—play in the health care system, any new regulatory framework will need to balance several competing public health priorities. For example, it must be flexible enough to allow laboratory professionals to address legitimate

clinical needs, such as developing tests for rare diseases, in response to disease outbreaks, or to address areas with limited commercial incentive. In addition, it should be flexible in allowing labs to develop their own tests to increase the speed of the tests, reduce costs, and improve the efficiency of lab processes. As with any medical product, however, all clinical tests should be subject to the same system of oversight, and regulatory scrutiny should be proportional to the risk that a test poses to patients or to public health if it is inaccurate.

How and where LDTs are used

Previous studies have found that LDTs are used most frequently in molecular diagnostics, which includes genetic testing as well as tests targeting a range of other molecules.[41] Common applications include oncology and inherited diseases, but widespread use is also observed across a range of other applications, including toxicology or blood coagulation.[42] The lab managers who responded to our survey and participated in interviews generally echoed these findings. The concentration in oncology speaks to the increased trend toward targeted therapy, in which individual tumors are tested for specific cancer mutations, such as the BRAF gene in melanoma, to identify patients who are more likely to benefit from a particular therapy. So-called companion diagnostics are developed and marketed as IVDs by device companies. However, once these tests are approved by FDA, LDT developers often create follow-on co-diagnostic tests that they claim will identify the same mutations.[43] In some cases, this may not pose risks to patients.[44] However, because individual labs may have different approaches to analyzing samples—particularly for newer, more complex tests—the same patient may get different results depending on the LDT used.[45] And because many labs do not operate under an FDA-regulated quality system, there is less assurance that the test will not change over time.

Genetic testing for inherited conditions—including many screening tests that are administered to all newborns— and prenatal tests to detect fetal abnormalities also have a high level of LDT use. In fact, none of the more than 40 noninvasive prenatal tests on the market are FDA-reviewed.[46] As genetic research expands and more therapies are developed, the need for companion diagnostics will probably continue to rise—potentially resulting in either greater LDT volumes across a broad range of conditions or a higher number of applications for FDA to review.[47]

Other types of testing, particularly those that rely on well-established technologies and have been on the market for years, tend to have lower LDT use. Interviewees cited general chemistry tests, hematology tests, and certain well-established microbiology tests in this group.

Interviewees also noted that different types of labs tend to have varying approaches to LDT development. Academic medical centers and specialty labs that focus on particular disease areas or technologies, for example, are more likely to develop novel tests from scratch, and tend to do so to meet specific medical needs or as part of their ongoing research. Large reference labs, by contrast, are more likely to develop LDTs to make work more efficient or to reduce operating costs. For example, testing for sexually transmitted and other infectious diseases generates large test volumes that are often sent through large commercial reference labs. Although the labs may process these samples using a commercially available IVD, internal processes designed to improve efficiency may deviate from FDA-approved guidelines. Under CLIA rules, if the lab can document that its procedures do not alter the validity of the diagnostic, it is free to amend the procedure. In doing so, however, the lab creates an LDT.

Interviewees noted that public health labs—which include the CDC's as well as state and local labs—also rely on LDTs for a range of uses, including responding to local outbreaks of particular pathogens, conducting surveillance testing, and, notably, responding to public health emergencies such as COVID-19. However, smaller public health labs typically do not have the resources to develop novel tests from scratch; rather, they may be more likely to modify a commercial IVD or to use a test protocol developed elsewhere that they then validate in their own lab.

LDT use is also more common in technologies that rely on manual interpretation or are highly adaptable and can be used in a broad range of clinical contexts. This includes mass spectrometry and next-generation sequencing, which are testing methods that rely on sophisticated instrumentation and expert interpretation. Both have high rates of LDT use, and relatively few IVDs that rely on these methods are commercially available.

Considerations for reform

As these findings illustrate, LDTs are used in a variety of settings and for a broad range of purposes. However, they are particularly common in fields where inaccurate results can lead to serious, even life-threatening consequences, such as oncology and other fields that rely heavily on genetic testing. They are also frequently used in certain contexts where the science is rapidly evolving, and where tests must be quickly adapted to reflect new learning. Although any new regulatory framework will need to allow for this sort of ongoing innovation, it must also provide a baseline assurance of both analytical and clinical validity. The stakes for clinical validity are especially high in cases where a clinical decision is based entirely or primarily on the result of an IVD, such as companion diagnostics that are used to screen cancer patients to receive certain drugs.

Common misconceptions about LDTs

Pew's survey results revealed that even highly experienced laboratory professionals may not realize when they are using an LDT. Many respondents, for instance, claimed that all or a significant proportion of their mass spectrometry and next-generation sequencing tests were FDA-reviewed IVDs. However, there are relatively few FDA-approved mass spectrometry or next-generation sequencing tests. This points to a broader lack of understanding of the boundary between an LDT and an IVD.

Subsequent interviews revealed that many respondents did not realize that every time they deviate from an FDAreviewed test's protocol, they effectively create an LDT. Alternatively, some appeared to think that using FDAreviewed test components as part of a more complex testing procedure means that the test is FDA-approved.

However, this is not the case. Components and tools may help lab technicians and researchers with their analysis, but the test itself—which may be a multistep procedure generating an output interpreted by a laboratory professional—is considered an LDT.

Previous estimates of LDT use have varied widely for these reasons. For example, FDA suggested that 11,000

LDTs developed in 650 labs were in use during consideration of the agency's proposed guidance framework in 2014.[48] In contrast, researchers studying the market for genetic tests estimated that 75,000 such IVDs were in use in 2018, with the vast majority being LDTs.[49]

Considerations for reform

These misconceptions highlight the general lack of familiarity that many laboratory professionals have with FDA and its regulations, which could pose a challenge for the agency as it attempts to exert its authority over the LDT market. Bringing these developers under FDA regulation will require a transition period that will allow the lab community adequate time to come into compliance. It will also require extensive outreach and education after reform is passed to ensure a common understanding of those regulations and what compliance will entail. Such a transition period will also be necessary for FDA, which will need to write new regulations and guidance documents on how it will implement these reforms, and to hire staff to handle the influx of new applications and conduct the necessary inspections. These activities will necessarily require additional funding from Congress, and potentially user fees paid by test developers.

Lessons from COVID-19

The COVID-19 pandemic took hold in the middle of our research and offered a unique window into the impact of LDTs on public health. In our interviews and survey, labs' ability to ramp up testing was an important topic that highlighted the role that LDTs play in driving innovation in the market. Eighty-one percent of lab managers surveyed said they either offered or planned to offer COVID testing, with 21% of respondents saying their lab deployed an LDT COVID-19 test (versus a commercially manufactured EUA test that FDA reviewed). Furthermore, 59% of respondents said that without an LDT option, their ability to ramp up testing would have been further delayed. While not perfect, many LDTs filled a critical role in the early management of the pandemic and continued to provide additional testing capacity throughout 2020.

However, FDA plays a critical role in ensuring the quality and reliability of COVID-19 testing. The value of FDA review was made clear early in the pandemic when the agency briefly allowed COVID-19 antibody tests to come to market without undergoing the EUA process. Antibody tests are used to screen for past infection and can be an important tool in tracking outbreaks and developing mitigation strategies. However, many of these tests proved unreliable in practice, leading the agency to reverse its policy within weeks.[50] FDA also conducted a review of the EUA submissions it received from labs that had developed diagnostic tests aimed at identifying active COVID-19 cases. Of the 125 EUA requests it reviewed, 82 had design or validation issues that required correction, and some were denied authorization altogether. In many cases, the agency was able to work with the labs to resolve problems so that tests could eventually be used.[51]

Considerations for reform

As these examples illustrate, FDA review serves as a critical check on tests entering the market. It also ensures that the agency has a clear picture of the tests on the market and can receive information on how those tests are performing in the real world, including the incidence of false positives or false negatives, as well as documentation of patient harm. This in turn allows it to update the public when it becomes aware of a problem and pull a test from the market when necessary.

Implications for regulatory reform

The current diagnostic testing regulatory system—in which tests are regulated according to where they are developed and used, rather than the risk they pose if they are inaccurate—creates double standards and potential loopholes that undermine public health objectives. Although labs that make LDTs are subject to CMS regulation, they are not required to demonstrate clinical validity or report cases of patient harm from their products—

requirements that FDA applies to manufacturers that develop and sell IVDs for use in multiple facilities. They are also not held to the same quality standards that device manufacturers must meet.

As the diagnostics market has evolved and the role of LDTs has changed, diagnostics manufacturers, public health groups, patient advocates, and FDA have raised concerns about the public health effects of excluding thousands of tests—many of which have significant implications for patient care—from FDA review.

Over the past decade, there has been significant, sustained debate on how best to harmonize the regulatory pathway for IVDs and LDTs. Achieving consensus will require substantial public dialogue, with input from these key stakeholders as well as the health care researchers and professionals who rely on their output. As legislators evaluate the best path forward, the following guidelines may help guide their thinking:

- To effectively regulate these products, FDA must have a clear picture of what tests are in use and be able to collect sufficient information on how they are performing. At a minimum, this should include a requirement that all tests be registered with the agency; developers report adverse events related to their diagnostics; and the agency be empowered to request information regarding the validity and performance of those products when it has concerns.
- Given the large yet unknown number of LDTs currently on the market, any reform will need to include a mechanism for bringing these tests into compliance with FDA regulations in a way that minimizes disruptions to patient care. Two options that policymakers could consider are phasing in FDA reviews of LDTs or exempting LDTs from premarket review while ensuring that the agency has sufficient postmarket authority to require data on their performance and take enforcement action when necessary to protect patients.[52] (See Appendix E.)
- IVDs are regularly modified or adapted to address patient need and to respond to advances in scientific understanding. Any new regulatory approach for diagnostics must be flexible enough to allow test developers to modify tests or develop new ones in order to meet patient need without undue delay. However, adequate guardrails must be in place to ensure that these tests are valid, reliable, and of high quality. Again, as with any medical product, regulatory oversight should be proportional to the associated risks.
- The lack of a shared definition of what constitutes an LDT—even among laboratory experts—highlights the broader lack of familiarity of many labs with FDA regulations. Bringing LDT developers under FDA regulation will require a transition period that

allows labs adequate time to come into compliance. It will also require extensive outreach and education after reform is passed to ensure a common understanding of FDA regulations and what compliance will entail.

- FDA, in turn, will need adequate time and additional funding to develop new guidance documents and regulations and to implement them by conducting more reviews and inspections of labs.

Conclusion

Clinical diagnostics play an essential role in the U.S. health care system. Our research demonstrates that roughly 3.3 billion diagnostic tests are performed in the country each year. Although most of these tests are run on FDAapproved IVD kits, an unknown but probably sizable number follow a different path to market as LDTs. Although both categories of tests are used for similar clinical purposes, CLIA oversight of LDTs provides only an indirect review of test validity. Although the LDT regulatory process offers labs significant flexibility and enables a more rapid response to public health needs when no FDA-cleared or -approved test exists, the relative lack of oversight for LDTs puts the health of patients at risk.

LDTs were once more limited in scope, but changes in technology and industry practices have led to far greater numbers of patients being routinely exposed to tests—even high-risk ones—that undergo no premarket review. IVDs are subject to FDA standards for analytical and clinical validity, postmarket surveillance requirements, and adverse event reporting designed to identify, rectify, or recall problem tests. But no equivalent requirements are imposed upon LDTs, even though they may be used similarly to IVDs on patients. This is particularly concerning in fields that rely heavily on genetic testing, such as oncology, where test results may be the deciding factor in whether a patient receives a particular treatment.

Although regulatory harmonization has been discussed for decades, the current dual system —and the public health vulnerabilities that it perpetuates—remains in force. The COVID-19 pandemic only underscores the need to establish a unified regulatory framework that ensures the safe and effective use of all tests. The findings outlined in this report can help guide policy discussion about how to establish a risk-based oversight system that enables innovation while ensuring patient safety.

Glossary

- **Analyte.** A substance whose chemical constituents are being identified or measured.

- **Analytical validity.** A measure of how well a test performs in detecting or measuring the presence of a particular analyte.
- **CDC.** Centers for Disease Control and Prevention.
- **CLIA.** Clinical Laboratory Improvement Amendments, a section of the CMS authorization pertaining to regulation of U.S. laboratory testing.
- **Clinical validity.** A measure of how accurately a test predicts the presence of, or risk for, a given condition.
- **CMS.** Centers for Medicare & Medicaid Services.
- **CPT.** Current Procedural Terminology, the medical code set used to report medical, surgical, and diagnostic procedures.
- **EUA.** Emergency use authorization, a premarket notification classification used to obtain FDA permission to market a medical product without undergoing normal approval procedures because of a health crisis such as the COVID-19 pandemic.
- **FDA.** Food and Drug Administration.
- **FFS.** Fee-for-service, a method of payment for health care services also known as "traditional Medicare" when used in the context of Medicare health insurance.
- **Flow cytometry.** A scientific method for measuring the number, size, and nucleic content of cells using an instrument in which cells flow in a narrow stream through a beam of light.
- **G-codes.** Temporary codes used to identify health care procedures and services that have not yet been assigned CPT codes.
- **HCPCS.** Healthcare Common Procedure Coding System, a standardized coding system used by medical providers to submit health care claims to Medicare and other providers.
- **IVD.** In vitro diagnostic; includes any test that analyzes a human sample for a clinical purpose.
- **LDT.** Laboratory-developed test; IVDs that are developed and used within the same laboratory.
- **Mass spectrometry.** An analytical technique that measures the ratio of an ion's mass to its charge to obtain a unique isotopic signature that helps to identify the chemical identity or structure of molecules and compounds.
- **NGS.** Next-generation sequencing, a DNA sequencing technology that uses massively parallel systems to query the entire genome to identify specific sequences that

correspond to known pathologies.

- **Sensitivity.** The term used to describe how often a test correctly identifies a positive result, or the “true positive” rate.
- **Specificity.** The term used to describe how often a test correctly identifies a negative result, or the “true negative” rate.

Methodology

All FDA-reviewed tests are listed in a publicly available database maintained by the agency, but no database— public or private—encompasses all available lab-developed tests. Nor does any central repository capture the billions of clinician orders for tests that are performed on millions of patients in tens of thousands of settings each year and paid for through many different funding streams. Therefore, any attempt to characterize the LDT market must rely on estimation built on certain assumptions, and these estimates must be refined with additional data. This study leveraged multiple data sources to provide a current snapshot of the diagnostics market.

- **Market size.** To estimate the number of IVDs run annually, Boston Consulting Group (BCG) used 2017 Current Procedural Terminology (CPT) data from the CMS fee-for-service claims database. CPT codes allow us to identify common diagnostic tests for various medical conditions and applications. BCG also reviewed information from a large data aggregator, which includes electronic health records (EHRs) without patient identifying information for approximately 6% of the total U.S. market. Using observed differences between the Medicare-eligible and overall U.S. population, BCG extrapolated the data to arrive at a clinical diagnostic market size for the entire country. Appendix A contains a more detailed review of the market sizing methodology, data sources, and key assumptions.
- **LDT usage.** To better understand the nature of LDT use and factors contributing to this usage, the BCG team began with qualitative research anchored by 20 market interviews with lab directors and diagnostic testing professionals and executives, followed by a nonprobability web survey and a round of five in-depth follow-up qualitative interviews with respondents to the nonprobability survey. To ensure the quality of the survey, the questions were pretested with five potential survey respondents. The survey questions and responses were discussed in depth with each pretest participant to verify that respondents had interpreted the questions in the manner intended. Appendix B includes a more detailed review of the online LDT market survey, as well as the respondents, survey design, and interview questions. The team then reviewed published

literature and market analyses by third parties to help interpret the survey and interview findings. These sources are cited throughout the document.

- **Limitations.** It is difficult to make inferences about the LDT market because it is poorly tracked and highly fragmented. As mentioned, we used a nonprobability sample, meaning that the labs we surveyed are not representative of the industry at large. We used this approach because it was cost-effective and timely, but more importantly because the incomplete picture of the market makes it impossible for researchers to ensure that a given sample reflects the real composition of the market. This also means that confidence intervals to measure the degree of certainty around the market's use of LDTs cannot be constructed. We have attempted to ensure that the different sectors of the laboratory industry were represented in the sample and have conducted a series of comparisons and checks (see Appendix B for details) to ensure confidence in and lend credibility to the analysis. However, the lack of transparency in this market precludes any guarantee of precision in how survey respondents estimate the operations and in views of the industry, and ultimately prevented us from making reliable quantitative estimates about LDT use.

Endnotes

1. L. Buchen, "Cancer: Missing the Mark," *Nature* 471 (2011): 428-32, https://www.nature.com/news/2011/110323/full/471428a.html; M.H. Greene, Z. Feng, and M.H. Gail, "The Importance of Test Positive Predictive Value in Ovarian Cancer Screening," *Clinical Cancer Research* 14, no. 22 (2008), https://clincancerres.aacrjournals.org/content/14/22/7574.2; M. Boesen, "I Got a Double Mastectomy After a Genetic Test. Then I Learned the Results Were Wrong," HuffPost, Feb. 1, 2021, https://www.huffpost.com/entry/brca-genetic-testing-mastectomy_n_5c6c39fbe4b012225acd80d3.

2. A. Schuessler, "Mother Speaks Up About Risks of Prenatal Testing," *The Daily Journal*, Feb. 25, 2019, https://www.smdailyjournal.com/news/local/mother-speaks-up-about-risks-of-prenatal-testing/article_5739d5ca-38ab-11e9-a7bf-675355c57802.html; B. Daley, "Oversold Prenatal Tests Spur Some to Choose Abortions," *The Boston Globe*, Dec. 14, 2014, https://www3.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.html?arc404=true.

3. U.S. Food and Drug Administration, "Lists of Direct-to-Consumer Tests With Marketing Authorization," last modified Dec. 20, 2019, https://www.fda.gov/medical-devices/in-

vitro-diagnostics/direct-consumer-tests#list.

4. S. Gottlieb, M.D., former commissioner, Food and Drug Administration, "Blueprint for Breakthroughs—Charting the Course for Precision Medicine" (presentation, Friends of Cancer Research 7th Annual Blueprint for Breakthrough Forum, Sept. 13, 2018), https://www.fda.gov/ news-events/speeches-fda-officials/blueprint-breakthroughs-charting-course-precision-medicine-09132018.
5. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321h, https://www.govinfo.gov/app/details/USCODE-2010-title21/USCODE-2010title21-chap9-subchapII-sec321; U.S. Food and Drug Administration, "Classification of Products as Drugs and Devices and Additional Product Classification Issues," 2017, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/classificationproducts-drugs-and-devices-and-additional-product-classification-issues.
6. Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability, 79 Fed. Reg. 59779-82 (Oct. 3, 2014), https://www.federalregister.gov/documents/2014/10/03/2014-23586/food-and-drug-administration-notification-and-medical-device-reporting-forlaboratory-developed.
7. American Clinical Laboratory Association, "ACLA Written Statement for 21st Century Cures Hearing on LDT Regulation," Sept. 9, 2014, https://www.acla.com/acla-written-statement-for-21st-century-cures-hearing-on-ldt-regulation/.
8. Centers for Medicare & Medicaid Services, "CLIA Overview" (2013), https://www.cms.gov/Regulations-and-Guidance/Legislation/ CLIA/Downloads/LDT-and-CLIA_FAQs.pdf.
9. Ibid.
10. Ibid.
11. As governed by Public Law 94-295, Public Law 100-578, and associated implementing regulations. United States Public Law 94-295: Medical Device Amendments of 1976 (1976), https://www.govinfo.gov/content/pkg/STATUTE-90/pdf/STATUTE-90-Pg539.pdf; United States Public Law 100-578: Clinical Laboratory Improvement Amendments of 1988 (1988), https://www.govinfo.gov/content/pkg/STATUTE-102/pdf/STATUTE-102-Pg2903.pdf#page=1; Centers for Medicare & Medicaid Services, "CLIA Overview."

12. Buchen, “Cancer: Missing the Mark”; Greene, Feng, and Gail, “The Importance of Test Positive Predictive Value.”

13. U.S. Food and Drug Administration, “Laboratory Developed Tests,” last modified Sept. 27, 2018, https://www.fda.gov/medical-devices/invitro-diagnostics/laboratory-developed-tests; U.S. Department of Health and Human Services et al., ““Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories” (2014), https://www.fda.gov/media/89841/download.

14. American Clinical Laboratory Association, “ACLA Joins Physicians, Hospitals and Provider Stakeholders in AMA Letter Requesting FDA Withdraw Proposed Draft Guidance to Regulate Laboratory Developed Tests (LDTs),” news release, Nov. 19, 2014, https:// www.acla.com/acla-joins-physicians-hospitals-and-provider-stakeholders-in-ama-letter-requesting-fda-withdraw-proposed-draftguidance-to-regulate-laboratory-developed-tests-ldts/; Association for Molecular Pathology, “AMP Submits Written Comments to FDA on Proposed Regulation of Laboratory Developed Tests,” news release, Feb. 2, 2015, https://www.amp.org/AMP/assets/File/pressreleases/2015/1-29-15_AMPSubmitsCommentstoFDAonLDTRegulation.pdf; Association of American Medical Colleges, “Policy Priorities to Improve Our Nation’s Health From America’s Medical Schools and Teaching Hospitals” (2016), https://www.aamc.org/system/files/c/2/472838-policy-priorities-improve-nations-health.pdf.

15. S. Kaplan, “FDA Puts Off Closing Lab-Test ‘Loophole,’ Leaving Decision to Congress and Trump,” STAT, https://www.statnews.com/2016/11/18/fda-lab-test-loophole/; U.S. Food and Drug Adminstration, “Discussion Paper on Laboratory Developed Tests (LDTs)” (2017), https://www.fda.gov/media/102367/download.

16. Verifying Accurate Leading-Edge IVCT Development Act of 2020, S. 3404, U.S. Senate—116th Congress 2nd Session (2020), https://www.congress.gov/bill/116th-congress/senate-bill/3404/text.

17. L. Richardson, “Clinical Lab Tests Need Stronger FDA Oversight to Improve Patient Safety,” The Pew Charitable Trusts, Jan. 11, 2021, https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/01/clinical-lab-tests-need-stronger-fda-oversight-to-improvepatient-safety.

18. M. Molteni, “How Much Prenatal Genetic Information Do You Actually Want?” *Wired*, March 27, 2019, https://www.wired.com/story/how-we-reproduce-testing/.

19. Society for Maternal Fetal Medicine, "SMFM Statement: Maternal Serum Cell-Free DNA Screening in Low Risk Women," accessed July 27, 2021, https://www.smfm.org/publications/157-smfm-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women; R. Farrell et al., "Online Direct-to-Consumer Messages About Non-Invasive Prenatal Genetic Testing," *Reproductive Biomedicine & Society Online* 10, no. 1 (2016): 88-97, https://doi.org/10.1016/j.rbms.2016.02.002.

20. U.S. Food and Drug Administration, "Lists of Direct-to-Consumer Tests With Marketing Authorization," last modified Dec. 20, 2019, https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list.

21. A. Regalado, "More Than 26 Million People Have Taken an at-Home Ancestry Test," *MIT Technology Review*, Feb. 11, 2019, https://www.technologyreview.com/s/612880/more-than-26-million-people-have-taken-an-at-home-ancestry-test/.

22. S. Tandy-Connor et al., "False-Positive Results Released by Direct-to-Consumer Genetic Tests Highlight the Importance of Clinical Confirmation Testing for Appropriate Patient Care," *Genetics in Medicine* 20 (2018): 1515-21, https://www.nature.com/articles/gim201838?mc_cid=b693215d3b&mc_eid=08a1c14744; A.D. Bowser, "Direct-to-Consumer Genetic Testing Fraught With Validity Concerns," MDedge, April 16, 2019, https://www.mdedge.com/internalmedicine/article/199003/business-medicine/direct-consumergenetic-testing-fraught-validity.

23. Tandy-Connor et al., "False-Positive Results Released."

24. A. Towse and L.P. Garrison Jr., "Economic Incentives for Evidence Generation: Promoting an Efficient Path to Personalized Medicine," *Value Health* 16, no. 6 (2013), https://doi.org/10.1016/j.jval.2013.06.003.

25. J. Shuren, "Jeffrey Shuren, M.D., J.D., Director of the FDA's Center for Devices and Radiological Health and Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research on Agency's Warning to Consumers About Genetic Tests That Claim to Predict Patients' Responses to Specific Medications," news release, Nov. 1, 2018, https://www.fda.gov/news-events/pressannouncements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md.

26. A. Stenzinger et al., "Tumor Mutational Burden Standardization Initiatives: Recommendations for Consistent Tumor Mutational Burden Assessment in Clinical Samples to Guide Immunotherapy Treatment Decisions," *Genes, Chromosomes & Cancer* 58, no. 8 (2019): 578-88, https://pubmed.ncbi.nlm.nih.gov/30664300/.

27. U.S. Food and Drug Administration, “In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff” (2014), https://www.fda.gov/media/81309/download.

28. U.S. Department of Health and Human Services, “Determination That a Public Health Emergency Exists,” last modified Jan. 31, 2020, https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx.

29. U.S. Food and Drug Administration, “Emergency Use Authorizations for Medical Devices,” last modified March 1, 2021, https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices; U.S. Food and Drug Administration, “Coronavirus Disease 2019 (COVID-19) Emergency Use Authorizations for Medical Devices,” last modified June 30, 2021, https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/coronavirus-disease-2019-covid-19emergency-use-authorizations-medical-devices.

30. U.S. Food and Drug Administration, “Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised): Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff” (2020), https://www.fda.gov/media/135659/download.

31. U.S. Food and Drug Administration, “Risk of False Results With the Curative SARS-CoV-2 Test for COVID-19: FDA Safety Communication,” Jan. 4, 2021, https://www.fda.gov/medical-devices/safety-communications/risk-false-results-curative-sars-cov-2-testcovid-19-fda-safety-communication.

32. U.S. Food and Drug Administration, “Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chembio Antibody Test,” news release, June 16, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokesemergency-use-authorization-chembio-antibody-test.

33. D. Lim and Z. Brennan, “Trump Administration Limits FDA Review of Some Coronavirus Tests,” Politico, Aug. 19, 2020, https://www.politico.com/news/2020/08/19/trump-fda-review-coronavirus-tests-398924; U.S. Department of Health and Human Services, “Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests,” last modified Jan. 21, 2021, https://web.archive.org/web/20210121202702/https:/www.hhs.gov/coronavirus/testing/recission-guidances-informalissuances-premarket-review-lab-tests/index.html. HHS subsequently removed the original policy announcement but has not retracted the policy.

34. R. Charrow, general counsel, letter to Stephen Hahn, commissioner of food and drugs, "Federal Authority to Regulate Laboratory Developed Tests," June 22, 2020, https://www.politico.com/f/?id=00000174-e9b2-d951-a77f-f9fe04fa0000; D. Diamond and D. Lim, "Memo Details HHS Push to Upend FDA's Testing Oversight," Politico, Oct. 2, 2020, https://www.politico.com/news/2020/10/02/hhsmemo-fda-testing-oversight-425139.

35. Centers for Medicare & Medicaid Services, "Laboratories by Type of Facility (Exempt and Non-Exempt)" (March 2020), https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/factype.pdf; Centers for Disease Control and Prevention, "Waived Tests," Jan. 25, 2021, https://www.cdc.gov/labquality/waived-tests.html.

36. Centers for Medicare & Medicaid Services, "Laboratories by Type of Facility (Exempt and Non-Exempt)."

37. BCG analysis of the Quality Improvement and Evaluation System (QIES) database.

38. U.S. Department of Health and Human Services et al., "Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories."

39. J.M. Adams and A.R. Talati, "NDI Guidance: The Waiting Game," Regulatory Affairs Professionals Society, Oct. 30, 2017, https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/10/ndi-guidance-the-waiting-game.

40. P.H. Gilligan and M.B. Miller, "Will Regulatory and Financial Considerations Dampen Innovation in the Clinical Microbiology Laboratory?," *American Society for Microbiology* (Feb. 2, 2016), https://mbio.asm.org/content/7/1/e02178-15.

41. B.W. Buchan and N.A. Ledeboer, "Emerging Technologies for the Clinical Microbiology Laboratory," *American Society for Microbiology Journals* (2014), https://cmr.asm.org/content/27/4/783; S.H. Katsanis and N. Katsanis, "Molecular Genetic Testing and the Future of Clinical Genomics," *Nature Reviews Genetics* 14, no. 6 (2013): 415-26, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4461364/; B.L. Wickes and N.P. Wiederhold, "Molecular Diagnostics in Medical Mycology," *Nature Communications* 9 (2018), https://doi.org/10.1038/s41467-018-07556-5.

42. Kalorama Information, "The Worldwide Market for In Vitro Diagnostic Tests, 12th Edition" (Aug. 2, 2019), https://kaloramainformation.com/product/the-world-market-for-in-vitro-diagnostic-tests-12th-edition/.

43. Towse and Garrison, "Economic Incentives."

44. A.S. Kim et al., "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing," *JAMA Oncology* 4, no. 6 (2018): 838-41, https://jamanetwork.com/journals/jamaoncology/fullarticle/2665746; M.M. Park et al., "ER and PR Immunohistochemistry and HER2 FISH Versus Oncotype Dx: Implications for Breast Cancer Treatment," *The Breast Journal* 1 (2014): 3745, https://doi.org/10.1111/tbj.12223.

45. Stenzinger et al., "Tumor Mutational Burden Standardization Initiatives."

46. National Down Syndrome Society, "Noninvasive Prenatal Tests (NIPTs)," accessed April 30, 2021, https://www.ndss.org/programs/ndsslegislative-agenda/healthcare-research/noninvasive-prenatal-tests-nipts/; Molteni, "How Much Prenatal Genetic Information Do You Actually Want?"

47. V.A. Miller, "FDA Regulation of Laboratory-Developed Tests," *Clinical Advances in Hematology & Oncology* 14, no. 5 (2016), https://www.hematologyandoncology.net/archives/may-2016/fda-regulation-of-laboratory-developed-tests/.

48. Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests.

49. K. Phillips et al., "Genetic Test Availability and Spending: Where Are We Now? Where Are We Going?" *Health Affairs (Millwood)* 37, no. 5 (2018): 710-16, https://pubmed.ncbi.nlm.nih.gov/29733704/.

50. Z. Brennan and D. Lim, "FDA Pushed Through Scores of Inaccurate Antibody Tests Without Agency Review," Politico, April 27, 2020, https://www.politico.com/news/2020/04/27/reliable-antibody-tests-coronavirus-207589; D. Lim, "FDA Reverses Policy That Let Over 100 Antibody Tests on Market Without Review," Politico, May 4, 2020, https://www.politico.com/news/2020/05/04/fda-enactsstricter-rules-for-antibody-tests-after-congressional-investigation-233867.

51. J. Shuren and T. Stenzel, "COVID-19 Molecular Diagnostic Testing—Lessons Learned," *The New England Journal of Medicine* 383, no. e97 (2020), https://www.nejm.org/doi/full/10.1056/NEJMp2023830.

52. Gottlieb, "Blueprint for Breakthroughs—Charting the Course for Precision Medicine."

RELATED

Topics	Health Care, U.S. Policy
Projects	Health Care Products
Places	United States

The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies

Office of Public Health Strategy and Analysis
Office of the Commissioner
Food and Drug Administration

November 16, 2015

Executive Summary

Laboratory developed tests (LDTs) serve an increasingly important role in health care today. They also have become significantly more complex and higher risk, with several notable examples of inaccurate tests placing patients at otherwise avoidable risk.

While laboratories that offer LDTs are subject to the Federal Food, Drug, and Cosmetic Act (FD&C Act), in addition to the Clinical Laboratory Improvement Amendments (CLIA), FDA has generally exercised enforcement discretion towards these tests (i.e., generally not enforced applicable provisions under the FD&C Act and FDA regulations).

Therefore, most laboratories that offer LDTs follow only the regulatory requirements of CLIA, which are intended to regulate the operations of laboratories, but are not specifically intended to regulate in vitro diagnostic devices. Despite the contention from some that "CLIA is enough," all of the tests described as problematic in this report were offered from laboratories following the minimum requirements of CLIA.

We examined events involving 20 LDTs that illustrate, in the absence of compliance with FDA requirements, that these products may have caused or have caused actual harm to patients. In some cases, due to false-positive tests, patients were told they have conditions they do not really have, causing unnecessary distress and resulting in unneeded treatment. In other cases, the LDTs were prone to false-negative results, in which patients' life-threatening diseases went undetected. As a result, patients failed to receive effective treatments.

Other LDTs provided information with no proven relevance to the disease or condition for which they are intended for use, while still others are linked to treatments based on disproven scientific concepts. In addition to patient harm, inaccurate or unreliable tests can be costly to society. We estimated these costs, if sufficient data were available.

I. Introduction

A. Background

In 1976, as part of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act), Congress gave FDA the authority to regulate in vitro diagnostics (IVDs) as medical devices.[1] Laboratory developed tests (LDTs) are the subset of IVDs intended for clinical use that are designed, manufactured, and used in a single laboratory, as opposed to other IVDs made by a conventional manufacturer and used by many laboratories.

An IVD meets the device definition irrespective of where and by whom it is manufactured; LDTs are therefore subject to the requirements of the FD&C Act and fall under FDA jurisdiction. Historically, however, FDA has generally used its enforcement discretion to not enforce the device provisions of the FD&C Act for LDTs.

In the 1970s, LDTs were limited in number and used fairly simple technologies, typically to diagnose rare diseases and conditions in small numbers of patients.

As technology and science have advanced, LDTs have increased in complexity and availability and are now used to diagnose common, serious medical conditions, including cancer and heart disease. Others guide therapy for these and other conditions, while still others predict one's personal risk of developing a particular disease. Some individual laboratories that initially developed LDTs have now morphed into separate businesses that market complex tests nationwide. These activities take place in much larger populations than the local or limited patient populations who may have used these products four decades ago.

As the field of medicine evolves, the need for accurate, reliable, and clinically meaningful tests is essential. For instance, the advancement of Precision Medicine,[*] depends upon accurate diagnosis in order to better target therapies. But inaccurate or unreliable LDTs and unsupported or disproven claims can undermine progress in Precision Medicine and other fields.

While certain LDTs have undoubtedly brought benefits to many patients, the increase in complexity and patient volume brings a concomitant risk that patients will be harmed – and, in fact, have been harmed – and highlights the need for appropriate oversight. It is not the intention of this report to undermine the value of LDTs, but rather to highlight that the current oversight framework is inadequate and, hence, why FDA has proposed to increase its oversight for these tests.[2]

FDA oversight for LDTs is needed to address several serious concerns:

- Lack of evidence supporting the clinical validity of tests.

[*] Precision Medicine encompasses prevention and treatment strategies that take individual variability into account.

Most fundamentally, patients expect that any test administered or ordered by their health care provider will generate a result upon which they can base decisions that can affect their life and health. Inaccurate tests can result in the failure to detect life-threatening diseases, might cause patients to elect unproven therapies over proven ones, or can cause patients unnecessarily to undergo uncomfortable and even dangerous procedures. The examples presented in this report illustrate each of these circumstances. FDA oversight would help ensure that regulated tests are supported by rigorous evidence, thus assuring patients and health care providers that they can have confidence in the test result.

- Deficient adverse event reporting.

Device adverse event reporting requirements provide a mechanism by which adverse events (serious injuries, deaths, malfunctions likely to cause/contribute to serious injuries/deaths) associated with use of a medical device can be reported by a manufacturer to the FDA and tracked. This is an important tool both for manufacturers (to identify problems with their test systems that may develop over time) as well as FDA (to identify potential public health issues and to take regulatory action, as appropriate). Currently, information on adverse events associated with LDTs is not systematically collected or reported.

- No premarket review of performance data.

The time to evaluate the safety and effectiveness of a product is before it is marketed, not after it has been used by thousands of patients. Premarket review, particularly for high-risk LDTs, is all the more important in the absence of satisfactory adverse event reporting.

- Unsupported manufacturer claims.

A critical part of premarket review is the assurance that manufacturer claims are supported by the available data. In the absence of appropriate oversight, unsupported claims have the potential to seriously mislead patients and health care providers. The cases reviewed provide several examples of such claims.

- Inadequate product labeling.

Without FDA review and oversight of LDT labeling, the labeling may not provide adequate information for patients and providers, including adequate information on interpreting a test result and determining whether and when follow-up testing is necessary.

- Lack of transparency.

In the absence of appropriate oversight, patients and health care providers may be unaware of any scientific basis for manufacturer claims or any support that the LDT performs as claimed. Indeed, patients and providers may not even be aware that an uncleared/unapproved LDT has been used or that an FDA-cleared/approved test could have been used instead.

- Uneven playing field.

Laboratories and other IVD manufacturers that go through the process of conducting the research necessary to validate their devices and seek premarket review are placed at an unfair disadvantage when their LDT competitors do not follow the same standards to support their claims and the safety and efficacy of their device. Under the status quo, manufacturers have every incentive not to seek FDA clearance/approval, and the public is thus denied the advantages and improvements in scientific rigor the research and review process ensures.

- Threats to the scientific integrity of clinical trials.

Clinical investigators studying other products often rely on LDTs to select patients for participation in a clinical trial and, if the patient is enrolled, whether to provide the patient with a particular treatment. If the tests are inaccurate, the scientific conclusions derived from these trials may also be inaccurate.

- No comprehensive listing of all LDTs currently being used.

This prevents an overall assessment of the LDTs on the market, including the extent of inaccurate or unreliable LDTs.

It is often claimed that FDA regulation of LDTs is unnecessary because the tests are sufficiently regulated under the Clinical Laboratory Improvement Amendments (CLIA). While CLIA created requirements that are essential for ensuring that laboratories and their personnel maintain standards of high quality (i.e., it is primarily concerned with the process of testing), compliance with CLIA regulation alone does not ensure that the diagnostic devices themselves are safe and effective.[2] As noted by the Centers for Medicare and Medicaid Services (CMS), which oversees the CLIA program:

> The CMS' analytical validity review is intended to determine if a specific test finds what it is supposed to find (i.e. the analyte it is intended to detect) when laboratories perform testing on patient specimens. Therefore, the analytical validation must be performed by the laboratory intending to use the test on patient specimens. Furthermore, the laboratory's analytical validation of an LDT is reviewed during its routine biennial survey – after the laboratory has already started testing. Moreover, the routine CLIA survey does not include a review of the clinical validation of a LDT – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient.
>
> In contrast, the FDA's review of analytical validity is done prior to the marketing of the test system, and, therefore, prior to the use of the test system on patient specimens in the clinical diagnosis/treatment context. Further, the FDA's analytical validity review is more in-depth and more comprehensive than that of the CLIA program, and it is focused on the test system's safety and effectiveness. As a result, FDA review may uncover errors in test design or other problems with a test system. Also, while CMS' CLIA program does not address the clinical validity of any test, FDA's premarket review of a test system includes an assessment of clinical validity.[3]

FDA's experience with non-LDT IVDs gives a sense of the issues that may arise with LDTs. In 2014 alone, FDA issued 31 warning letters to IVD manufacturers for various reasons, including adulteration due to violations of quality system regulations. That year, inspections of IVD manufacturers identified problems such as inadequate design validation and inadequate investigation of devices failures. In addition, FDA classified and reviewed 313 product recalls that were performed by the IVD industry. The same sorts of problems would be expected with LDTs, but could go undetected because there is generally no premarket review and limited adverse event reporting for LDTs. In fact, these problems may be more common because laboratories that produce LDTs may not follow key aspects of the quality system regulations, such as design controls and supplier controls.

B. Public Health Statistics: understanding public health problems

To better understand the issues surrounding the evaluation of LDTs and the cases presented in this report, a basic public health vocabulary related to diagnostic test performance is provided below.

I. True positive: A person who has a positive test result and actually has the disease/condition.
II. False positive: A person who has a positive test result but does not actually have the disease/condition.
III. True negative: A person who has a negative test result and actually does not have the disease/condition.
IV. False negative: A person who has a negative test result but actually has the disease/condition.
V. Sensitivity is the ability to of a test to detect the disease when it is present; it is defined as # true positives/# with the disease/condition.
VI. Specificity is the ability of a test to exclude the disease when it is absent; it is defined as # true negatives/# without the disease/condition.
VII. Positive Predictive Value (PPV) is the likelihood that a positive test truly represents the presence of the disease/condition; it is defined as # true positives/# all positives. A test has a high PPV if a large percentage of people who get a positive test result actually have the disease/condition.
VIII. Negative Predictive Value (NPV) is the likelihood that a negative test truly represents the absence of the disease/condition; it is defined as # true negatives/# all negatives. A test has a high NPV if a large percentage of people who get a negative test result really don't have the disease/condition.
IX. "Analytic Validity" refers to acceptably demonstrated performance in the measurement or detection characteristics of a test: how well the test measures or identifies something in a person, such as a protein or a gene mutation.
X. "Clinical Validity" is the acceptably demonstrated association of a test result with the presence or absence of the target disease/condition.

C. Glossary

ASD	Autism Spectrum Disorder
CDC	U.S. Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health, FDA
cfDNA	Cell-Free DNA
CHD	Coronary Heart Disease
CML	Chronic Myelogenous Leukemia
DNA	Deoxyribonucleic Acid
EUA	Emergency Use Authorization
FDA	U.S. Food and Drug Administration
HER2	Human Epidermal Growth Factor Receptor 2
HPV	Human Papillomavirus
IDE	Investigational Device Exemption
IOM	Institute of Medicine
LDT	Laboratory Developed Test
PCR	Polymerase Chain Reaction
PSA	Prostate Specific Antigen
RNA	Ribonucleic Acid

RT-PCR Reverse Transcription-Polymerase Chain Reaction
SNP Single Nucleotide Polymorphism

II. Case Studies of Problematic LDTs

To assess the public health impact of problematic LDTs, we identified 20 well-documented cases from publicly available information in medical journals, media reports and FDA Warning Letters. FDA is limited in its ability to identify such cases as adverse events on LDTs have generally not been reported to the Agency. FDA is aware of additional cases, but these are not included in this report because either the data demonstrating that the test is faulty are more limited or because these include confidential commercial information, which the Agency is prohibited by law from releasing to the public.

These cases are grouped according to their primary problem; many cases have more than one problematic aspect. For five of these cases, economic assessments of impact were conducted by FDA's Economics Staff.

A. Tests that Yield Many Positive Results when the Disease or Condition is not Actually Present (False-Positives)

i. Lyme Disease Diagnostic Tests

Category	LDT Characteristics
LDT Name	Lyme disease antigen and culture tests
Description	Test to detect portions of the bacterium that causes Lyme disease or antibodies to the bacterium
Purpose	Diagnose Lyme disease
Target Population	Patients with symptoms suggestive of Lyme disease
Alternatives	Over 80 FDA-cleared diagnostic tests
LDT Problem 1	In clinical use, large numbers of patients with positive tests do not have Lyme disease
Clinical Consequence	Patients with false-positive tests may be treated with unnecessary medications; delayed diagnosis of true underlying condition
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards
Cost Impact of Inaccuracy	$1,226 per case

Lyme disease is caused by infection with the bacterium *Borrelia burgdorferi*, transmitted to humans by the bite of an infected tick. The diagnosis is based on a history of exposure to ticks along with typical symptoms, including fever, fatigue, muscle, and joint aches, and a characteristic rash.[4] CDC recommends a two--test process to detect antibodies against *B. burgdorferi*.[5] If an initial enzyme-linked immunosorbent assay test is positive or indeterminate, it is followed by a confirmatory Western Blot test.

A patient is only diagnosed with Lyme disease if the confirmatory Western Blot is positive. As of May 2015, over 80 initial and confirmatory diagnostic blood tests for Lyme disease had been cleared by FDA.[6] Patients diagnosed with Lyme disease are treated with oral or intravenous antibiotics for 2-4 weeks. This relieves symptoms in 80%-90% of patients, but can lead to harmful side effects, including nausea, allergic reactions,[7] and intravenous site infection.[8] A falsely positive diagnosis of Lyme disease can lead to patients experiencing harmful side effects without clinical benefit, an increase in the risk of creating infectious organisms resistant to the antibiotics used to treat Lyme disease, and delay in the diagnosis of a patient's true underlying condition.

Between 2000 and 2005, a "Dot Blot" test for urine antigens against Lyme disease was offered, claiming a 97% "true positive rate," although this term does not have a clear meaning in public health terms.[9] An independent evaluation conducted in 2001 ran the test five times for the same 10 healthy subjects (i.e., 50 tests) and found that the test was consistently falsely positive in all tests run for two subjects (10 false-positive tests) and gave contradictory results on at least two pairs of tests for 8 subjects (i.e., at least 16 false-positive tests), leading to the conclusion that at least half of all test results were incorrect or uninterpretable, and that this test should not be used for Lyme disease detection.[9]

Further research also indicated that, because of lack of a clear correlation with clinical disease, urine tests in general are not appropriate for the diagnosis of Lyme disease,[10] but sales continued with between 50,000 and 70,000 tests sold in 2005.[11] Early that year, however, the LDT was implicated in 8 reports of false-positive diagnoses.[11]

Diagnostic tests for Lyme antigens in the blood also have been marketed. One marketed between 2003 and 2005 was prone to false-positives. On the basis of false-positive results, two couples underwent months of unnecessary treatment with antibiotics and other alternative medications.[12] After litigation, a judge awarded them a total of $30 million in damages.[12]

In April 2014, CDC issued a warning related to a Lyme disease culture test.[13] The Agency had conducted a review[14] that "raised serious concerns about false-positive results caused by laboratory contamination and the potential for misdiagnosis." Consequently, CDC recommended that only FDA-cleared/approved diagnostics for Lyme disease be used.

FDA estimated the cost of a false-positive diagnosis as the direct medical treatment costs for a patient with early-stage Lyme disease. The most relevant and comprehensive estimate (in Year 2000 dollars) comes from a study of Lyme disease patients with varying severities of disease and includes the costs of health care provider visits, consultation, serologic testing, therapy, hospitalization, and out-of-pocket costs of prescription and non-prescription drugs.[15] Updating the mean per-patient costs to current dollars using the medical care component of the Consumer Price Index yields an estimate of $1,226[16] for the cost to society for each case.[17]

ii. OvaCheck Ovarian Cancer Screening and Detection Test

Category	LDT Characteristics
LDT Name	OvaCheck
Description	Blood test and companion algorithm to create a genetic profile of markers displayed by cancer cells
Purpose	Screen and detect ovarian cancer
Target Population	Women at risk for ovarian cancer
Alternatives	Other biomarkers or physical symptoms
LDT Problem 1	No validation that test predicts or detects ovarian cancer
LDT Problem 2	Inflated accuracy claims by the manufacturer
Clinical Consequence	Women with false-positive tests may undergo unnecessary surgery to remove healthy ovaries
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims; assurance of consistent manufacturing practices and standardized instrument calibration
Cost Impact of Inaccuracy	Not estimated; not brought to market

Ovarian cancer is one of the more common and deadly cancers, with 14,000 deaths per year in the United States.[18] There is currently no reliable screening test for ovarian cancer, so most women are diagnosed only after the disease has spread widely, resulting in the poor prognosis.[19] Depending on the

extent of disease spread, treatment can include surgery to remove the ovaries, the uterus, and any visible cancer, followed by chemotherapy and sometimes radiation.[20] Effective early detection would reduce the mortality from ovarian cancer, but a screening test that over-diagnoses the disease will lead to extensive medical workups and potential unnecessary treatment. Importantly, a test that was prone to false-positives would be readily discerned in this clinical situation – the surgical specimen would have no cancer cells. But false-positives related to other tests might not be as easily detected.

In the late 1990s, a group of federal scientists believed, based on their research, that they had developed a new protein signature that could detect early ovarian cancer. OvaCheck, a commercial test, was developed using a technique called mass spectrometry that could distinguish between blood samples from ovarian cancer patients and those from healthy women based on that protein signature.[21] Subsequently, researchers derived a positive predictive value (PPV) of 94%,[22,23] suggesting that only 1 out of every 17 positive OvaCheck tests would be a false-positive.

However, the reported PPV was based on an incorrect ovarian cancer prevalence of almost 50% (derived using the ratio of 50 cancer cases to 66 controls in their study, a ratio the researchers determined by who they decided to enroll), rather than the true prevalence of 1 case for every 2,500 women in the screening population, greatly inflating the PPV from the true 0.8% to the reported 94%. Thus, in clinical practice, fewer than 1 per 100 women who test positive would actually have ovarian cancer.[24,25] Some of these false-positives would likely be detected by subsequent workup, but a subset would likely proceed to surgery.

In February 2004, FDA's Center for Devices and Radiological Health issued a letter to the company indicating the need for premarket review of the device.[26] Responding to public pressure, the investigators made their data public, but independent analyses found that the results were not reproducible and that calibration of the mass spectrometry instrument was faulty.[27] Other researchers claimed that the algorithm to interpret test results was not valid, and that the analytic methodology was flawed.[28]

The device was not brought to market in the U.S. and so an accounting of costs associated with a false-positive diagnosis is not possible. However, the cost could have been similar to that for OvaSure and PreOvar (see below). But for the intervention of FDA and others, women could have been exposed to this test and many would have been incorrectly diagnosed and possibly treated for ovarian cancer that they did not have.

iii. OvaSure™ Ovarian Cancer Screening Test

Category	LDT Characteristics
LDT Name	OvaSure Screening Test
Description	Blood test on fourbiomarkers based on initial research in the published literature reporting an association with ovarian cancer
Purpose	Screen for and detect ovarian cancer
Target Population	Women at risk for ovarian cancer
Alternatives	Other biomarkers or physical symptoms
LDT Problem 1	No validation that test predicts or detects ovarian cancer

LDT Problem 2	Inflated PPV claims by the manufacturer, so many patients with a positive test won't have the disease
Clinical Consequence	Women with false-positive tests may undergo unnecessary surgery to remove healthy ovaries
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	$12,578 per ovary removal after false-positive

In an effort to develop better cancer detection methods, researchers at Yale published a study on a test that they claimed had a PPV of 99.3%[29] (i.e., almost all positive test results appeared to represent actual ovarian cancer patients). The test, OvaSure, and a companion interpretation algorithm were marketed to screen for early stage ovarian cancer in high-risk women, beginning in June 2008.[29]

However, the PPV was derived using the ratio of cancer cases to controls in a single study (46%, a ratio the researchers determined by who they decided to enroll), rather than from the prevalence of the disease in the screening population. This meant that the PPV of 99.3% was inflated beyond what would be experienced in clinical practice. For example, the true PPV dropped to 6.5% if the actual population prevalence of 0.04% was used,[30] meaning that only 1 in 15 patients who tested positive actually had the disease and the remaining 14 women with a positive result could undergo unnecessary surgery to remove healthy ovaries, if subsequent workup did not rule out the disease.

In July 2008, the Society of Gynecologic Oncologists issued a formal statement that additional clinical validation of the test's effectiveness was needed before it should be offered outside a research study.[31] In light of these concerns, FDA notified the manufacturer in August 2008 that it considered OvaSure to be a "high-risk test that has not received adequate clinical validation, and may harm the public health."[32] The manufacturer did not provide further validation, prompting FDA to issue another letter, this time a warning letter.[33] In October 2008, OvaSure was pulled from the market.[30]

Using data from the Healthcare Cost and Utilization Project (HCUP), a nationally representative sample of hospital discharges, the average cost of surgery to remove the ovaries would be $9,200 per patient. We assumed an average hospital stay of 3 days, a post-surgical recovery of 10 work days, and estimated the value of an hour's work at $31.52.[34] Assuming a woman would miss 13 days of work, the total value of lost productivity per patient would be $3,378 ($31.52 x 8 x 13). Adding the direct medical cost yields a total cost to society of $12,578 per patient receiving a false-positive result. This estimate does not account for the costs, economic and psychosocial, of infertility and hormone replacement therapy for women who needlessly had their ovaries removed.

iv. PreOvar KRAS-Variant Ovarian Cancer Screening Test

Category	LDT Characteristics
LDT Name	PreOvar KRAS-Variant Test
Description	Blood or saliva test for KRAS-variant genetic mutation
Purpose	Identify women with elevated risk of ovarian cancer; guide treatment for ovarian cancer patients
Target Population	Women at risk for and with a diagnosis of ovarian cancer

Alternatives	Other biomarkers or medical history to assess personal risk and likelihood of response to therapy
LDT Problem 1	Lack of validation that KRAS-variant correlates with cancer risk and therapeutic response
LDT Problem 2	Faulty data analysis
Clinical Consequence	Women with false-positive tests may undergo unnecessary surgery to remove healthy ovaries; women with ovarian cancer may receive other inappropriate treatments
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims; evaluation of company data analyses
Cost Impact of Inaccuracy	$12,578 per ovary removal after false-positive

A certain variant in the KRAS gene has been reported in one publication to impart an elevated risk of ovarian cancer, particularly in women with a positive family history.[35] PreOvar, an LDT to detect the KRAS-variant mutation to aid in the prediction of ovarian cancer risk (for at-risk women undergoing screening) and to predict response to treatment (for those with a cancer diagnosis), was offered beginning in 2010.[36]

In September 2010, the Society of Gynecologic Oncology (SGO) released a statement that the test was developed and marketed to the public with insufficient clinical validation.[37] Concerned that the initial study was too small to generate a definitive assessment of ovarian cancer risk, researchers from the Ovarian Cancer Association Consortium performed an independent evaluation of over 21,000 subjects, finding no evidence of an association between the KRAS-variant and ovarian cancer.[38]

Amid growing controversy, the Consortium conducted a new analysis using its database of controls, cancer cases and patients with gene variants, and concluded that a group of variants, including KRAS, were not predictive of ovarian cancer. The authors suggested that earlier associations may have been due to small sample size or associations between the KRAS variant and other factors.[39,40] Despite these actions from the scientific community, this test remains on the market,[41] and the company's website states that the test "results are >99.9% accurate,"[41] placing women at risk of being incorrectly told that they have a high risk of ovarian cancer or a better chance of responding to therapies.

This might, in turn, place women being screened at risk for undergoing unnecessary diagnostic and surgical procedures, and expose women with ovarian cancer to potentially inappropriate treatment. The cost of ovarian removal following a false-positive diagnosis would be identical to that for OvaSure (see above) and thus is not duplicated here.

v. Whooping Cough (Pertussis) Diagnostic PCR Test

Category	LDT Characteristics
LDT Name	Whooping Cough (Pertussis) PCR Test
Description	Single or multiple target PCR tests
Purpose	More rapid and improved diagnosis of whooping cough
Target Population	People who have been exposed to whooping cough; those suspected to have whooping cough

Alternatives	Bacterial culture; FDA-cleared PCR tests; blood antibody test
LDT Problem 1	In clinical use, patients with positive test may not have whooping cough
Clinical Consequence	Patients with false-positive tests were incorrectly diagnosed and incorrectly treated
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Pertussis, or whooping cough, is a bacterial illness spread through coughing and sneezing by an infected person. The CDC reports that between 300,000 and 626,000 adults get whooping cough each year in the U.S.[42] Historically, the disease was diagnosed by its hallmark symptoms, which are cold-like complaints along with prolonged bouts of coughing that can lead to vomiting. Because of its ability to compromise the airway, whooping cough can be deadly to infants, but is also dangerous for elderly or frail patients.

It is generally treated with a course of antibiotics; these drugs can also prevent the disease in people who have been exposed but are not ill, a standard practice known as "post-exposure prophylaxis." The antibiotics used are common, but can have side effects ranging from nausea, vomiting and headache to rare, but potentially fatal, irregularities in the heart's rhythm. A vaccine (Tdap) is estimated by CDC to be 85-90% effective initially in preventing new whooping cough cases, but vaccine efficacy wanes over several years, putting people who are exposed to pertussis at risk of infection.

Doctors can diagnose whooping cough with a variety of tests, some of which are FDA-cleared, including bacterial culture, a blood antibody test, and tests on samples from the nose and throat to detect bacterial DNA. Culture is considered the most accurate diagnostic test. Rapid detection tests identify pertussis by matching a clinical sample to one or two "target" gene sequences using a technique called polymerase chain reaction (PCR). If one target is used, additional testing often is necessary. They also allow public health officials to act quickly to prevent an outbreak. However, standardization and central oversight of the quality of those PCR tests not cleared by FDA is lacking.

In March 2006, a health worker at the Dartmouth University hospital in New Hampshire presented to a clinic with a 3-week history of classic symptoms and was diagnosed with whooping cough on a single-target LDT PCR, started on antibiotics, and furloughed for 5 days.[43] The subsequent investigation identified 15 workplace contacts of the initial case who had respiratory illness and a positive or equivocal result on the LDT PCR. The hospital suspected a whooping cough outbreak. The expanding investigation led to the identification of additional symptomatic patients, and all laboratory workers at the hospital were provided with post-exposure antibiotic prophylaxis and vaccination.

The hospital then began testing all symptomatic people with the LDT PCR. By June, 134 cases of suspected whooping cough had been identified. The PCR test was positive or equivocal in 98 of these cases (73%), and an additional 36 cases were identified using symptoms alone. Twenty-seven of these 134 cases were submitted for culture. None were positive. Substantial resources were invested to investigate and control this suspected outbreak.

Overall, 978 workers with symptoms were treated, and, out of an abundance of caution, furloughed from their posts as they waited to see if their PCR test would be negative; 1,311 close contacts of

suspected cases were given post-exposure prophylaxis antibiotics, and 4,524 workers were vaccinated. As a result, many people who did not have whooping cough lost productive days of work, and were exposed to treatments that can have harmful side effects. The risk of developing antibiotic-resistant organisms was increased.

B. Tests that Yield Many Negative Results when the Disease or Condition is Actually Present (False-Negatives)

i. Oncotype DX HER2 Breast Cancer RT-PCR Test

Category	LDT Characteristics
LDT Name	Oncotype DX HER2 RT-PCR
Description	Rapid PCR test for tumor HER2 receptors
Purpose	Use HER2 receptor level to guide treatment
Target Population	Newly diagnosed Stage I and II breast cancer patients
Alternatives	FDA-approved HER2 receptor tests
LDT Problem 1	Test has poor sensitivity – many tests reported as normal HER2 levels will actually have high HER2 levels
Clinical Consequence	Patients with false-negative tests won't receive appropriate treatment, and cancer may progress
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards
Cost Impact of Inaccuracy	$775,278 estimated cost per false-negative case

The majority of breast cancers test positive for particular hormone receptors, proteins that bind their corresponding hormone and stimulate the cancer to grow. About 1/4th[44] to 1/5th[45] of breast cancer patients have on their tumors more than the normal amount of a certain type of receptor, known as human epidermal growth factor receptor 2 (HER2). These women have higher rates of breast cancer recurrence and mortality (i.e., a worse prognosis) than those who are HER2-negative. Cancer doctors, therefore, recommend that every patient with invasive breast cancer undergo HER2 testing.

Women who over-express HER2 receptors are treated with one or more drugs such as trastuzumab (Herceptin®) in addition to chemotherapy. Trastuzumab targets HER2 receptors and improves tumor response rates, time to progression, and survival.[46] However, it also can cause serious though rare heart disease,[47] and is costly, estimated by the Journal of Oncology at approximately $100,000 for a year of therapy in 2006 dollars.[45] The majority of tests used to detect HER2 protein or gene amplification are LDTs, but, at least in the past, approximately 20% of tests may have been inaccurate,[45] creating concern that some invasive breast cancer patients may be exposed to treatments that are less than optimal when the test fails to detect high HER2 levels.

Starting in 2008, Genomic Health began adding results from the HER2 test, which is part of the 21-gene signature that makes up the Oncotype DX Breast Cancer test, to their test report. The Oncotype Dx test provides individualized breast cancer treatment options and recurrence risk estimates based on the genes expressed in a tumor.[48,49] The RNA-based form of HER2 test is not included in the guidelines issued by the American Society of Clinical Oncology (ASCO) as a test to be used to decide whether

trastuzumab is indicated. Instead, ASCO focuses on FDA-approved tests known as fluorescence in situ hybridization (FISH) tests and immunohistochemistry (IHC) tests for detecting HER2 gene amplification and protein overexpression, respectively.[50]

The underlying issue is that there is no demonstrated direct correlation between number of RNA copies of the gene, the basis for Oncotype Dx HER2 RT-PCR, and the number of protein copies on the cell surface. As a consequence, it is not possible to infer that high or low amounts of RNA correspond to high or low amounts of HER2 protein.

In 2011, a group of prominent pathologists from three independent laboratories found discrepancies between this HER2 RT-PCR and the FDA-approved tests. The LDT reported large numbers of tumors that tested positive on FISH-HER2 as equivocal (33% of FISH-positive cases) or negative (39% of FISH-positive cases).[51] In 2014, the LDT missed all three HER2-positive patients included in a study, diagnosing two as negative and one as equivocal. As a result, the two patients who tested HER2-negative failed to receive trastuzumab, placing them at higher risk for cancer progression.[52]

We estimated the social cost when patients fail to receive appropriate trastuzumab therapy by multiplying the number of years a patient could gain from appropriate cancer treatment by the value of a statistical life-year (VSLY). Standard estimates for the VSLY are $129,213, $258,426, and $387,639.[53,54,55] Research has shown that the projected life expectancy is 3 years longer for HER2-positive patients who receive trastuzumab in addition to chemotherapy, compared to those receiving chemotherapy alone.[56] Multiplying the 3 life-years gained from therapy by the middle VSLY value of $258,426 allows us to estimate the cost to society for each patient who fails to receive trastuzumab as $775,278.

ii. Human Papillomavirus Test using SurePath Collection Medium

Category	LDT Characteristics
LDT Name	SurePath Collection Medium for cervical samples collected for Human Papillomavirus (HPV) Test
Description	Collection medium to permit DNA or RNA test to detect HPV strains conferring high risk for cervical cancer
Purpose	To determine or assist in the management of pre-cancerous lesions of the cervix
Target Population	Women with an equivocal Pap Test; women over 25 tested for HPV alone; women over 30 if tested with Pap Test and HPV test simultaneously for cervical cancer screening
Alternatives	FDA-approved combinations of cervical sample collection media and HPV assay
LDT Problem 1	Use of test with unknown sensitivity
Clinical Consequence	Patients with false-negative test results may receive improper patient management; pre-cancerous cells may progress to cancer and patients may require more extreme medical interventions.
Potential Impact of FDA Oversight	Assurance there is premarket review of test performance

Cost Impact of Inaccuracy	Not estimated

The majority of cervical cancer is caused by an infection with one or more "high risk" strains of the human papillomavirus (HPV). Current guidelines[57] state that women should be screened regularly[58] for cervical cancer, as periodic screening has been shown to reduce mortality from cervical cancer.[57] To date, FDA has approved 6 HPV tests; these tests are approved with specific collection media that permit transport to the testing location. For women with equivocal Pap test results, all these approved assays have negative predictive values (NPVs) above 99%, so a negative test can avert colposcopy, an examination of the cervix that is the next step in the workup of suspected cervical cancer.

In addition to the currently available FDA-approved HPV tests, some laboratories are using cervical samples collected in the SurePath collection medium, even though this medium has only been approved for Pap testing, but not for HPV testing. The manufacturer of the SurePath collection medium has not publicly reported the NPV or the PPV for any HPV tests used with cervical samples in the SurePath medium.[59]

In June 2012, it issued a technical bulletin to laboratories stating that the use of cervical samples in the SurePath collection medium for HPV testing "may, under certain conditions, provide false-negative results."[60] In 2013, an investigative journalist reported that labs were using HPV test results derived from cervical samples that had been collected in the SurePath medium, despite the warning.[59]

Under existing guidelines, a false-negative test result could lead to the absence of patient follow-up and, ultimately, to preventable cancer progression. For this reason, the professional societies that set U.S. cervical cancer screening guidelines specifically recommend against the use of LDTs for cervical cancer screening.[57]

C. Tests with the Potential to Yield both Many False-Positive and False-Negative Results

i. Noninvasive Prenatal Testing (A.K.A. cell-free DNA testing)

Category	LDT Characteristics
LDT Name	Noninvasive prenatal cell-free DNA testing (NIPT, or cfDNA)
Description	Blood test to identify traces of fetal chromosomes in maternal blood
Purpose	To detect a range of fetal chromosomal abnormalities
Target Population	Pregnant women concerned about a fetal chromosomal abnormality
Alternatives	Invasive testing, including amniocentesis and chorionic villi sampling; "quad testing" of multiple substances combined with ultrasound imaging
LDT Problem 1	Lack of clinical validation that tests detect and predict fetal abnormalities at an appropriate rate
LDT Problem 2	Many false-positive results when used in the general population

Clinical Consequence	Women with false-positive results may abort a normal pregnancy; women with false-negative results may deliver a child with an unanticipated genetic syndrome
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Human cells normally have 23 pairs of chromosomes. A fetus with an extra chromosome ("trisomy"), a condition with unknown cause, is usually incompatible with life, leading to miscarriage. However, infants can survive if they are born with a trisomy of one of three chromosomes: 21 (Down syndrome), 18 (the rare Edwards syndrome) and 13 (the very rare Patau syndrome). While children with Down syndrome may lead relatively independent lives, the vast majorities of infants with Edwards and Patau syndromes have significant birth defects and die within a year of birth.[61]

Mothers who are over 35 or have a previous genetically abnormal pregnancy are at elevated risk for a trisomy pregnancy. Two standard non-invasive screening tests are offered to every pregnant woman: a first trimester ultrasound measuring the thickness of the fetal neck fold and a second trimester quadruple marker screening blood test.[62] A woman who is at high risk or has a positive screening test typically undergoes one of two invasive diagnostic tests to examine fetal chromosomes: chorionic villus sampling, which examines tissue from the early placenta, and amniocentesis, which samples the amniotic fluid through a needle inserted into the uterus.[63] Both involve a risk of miscarriage and fetal malformation, so it is important not to undertake them without adequate justification.

Noninvasive prenatal testing (NIPT) offers women who test positive on an initial non-invasive test or are otherwise at high risk the promise of avoiding the dangers of an invasive diagnostic procedure. There is typically some exchange of blood between mother and fetus due to microscopic bleeding within the placenta, and NIPT can detect traces of fetal chromosomes in maternal blood and determine whether a trisomy is present.[64]

At least four companies in the U.S. have recently begun offering these tests, using a technique called cell-free DNA testing (cfDNA). Marketing materials cite very high accuracy rates. One company claims that its test has a "very low false-positive rate,"[65] while another company claims a specificity of 99.9% for trisomy 18 (1 out of every 1000 results expected to be a false-positive) and 99.95% for trisomy 13 (5 out of every 10,000 results expected to be a false-positive).[66]

However, trisomy 18 and 13 are so rare (1 in 5,000 for trisomy 18 and 1 in 10,000 for trisomy 13) that even these high specificities should yield more false-positive than true-positive results, requiring follow-up testing for confirmation.[64] A clinical case series describes 8 women who received false-positive NIPT results for trisomy 18 and 13, including one patient who terminated her pregnancy after screening positive for trisomy 13, but was found to have a normal pregnancy on post-abortion testing.[67] Further testing showed the fetus had normal chromosomes.

A 2014 investigative report described three families who considered abortions based on what further testing showed to be false-positive results.[68,69] A study of one test calculated a PPV of 83% for 4 tested genetic conditions, and found that 22 (6%) of women who received positive results obtained abortions without a follow-up invasive diagnostic test.[70] Citing concern that these tests could be used in the

general, low-risk population with resulting low PPVs, the American College of Obstetricians and Gynecologists issued a statement in December 2012 that NIPT should not be offered to such women.[63]

Although the main concern is over the test's PPV for the rarer trisomies, in 2012, a patient reported a false-negative result to FDA after she received normal NIPT results and unexpectedly delivered an infant with trisomy 21.[71] Additional cases were documented in an investigative report in the Boston Globe in 2014.[72]

D. The Factor Detected has no Clear Relevance to the Disease

i. Fibromyalgia FM/a Diagnostic Test

Category	LDT Characteristics
LDT Name	FM/a Test
Description	Blood test to identify immune cytokine markers
Purpose	Claimed to diagnose and quantify fibromyalgia
Target Population	Patients with suspected fibromyalgia, based on a physician's history and physical exam
Alternatives	Clinician history and physical examination
LDT Problem 1	Biomarker not adequately shown to be associated with fibromyalgia
LDT Problem 2	Improper clinical trial design to validate test
Clinical Consequence	Patients with false-positives may take inappropriate medications; may delay diagnosis and treatment for underlying conditions
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Fibromyalgia is a syndrome consisting of fatigue and a body-wide reduced pain threshold, and commonly occurs in association with psychiatric symptoms including anxiety and depression.[73] Most patients with the diagnosis are women, and, although there is no cure, symptoms can be treated with FDA-approved medications (e.g., pregabalin (Lyrica), duloxetine (Cymbalta), and milnacipran (Savella)) along with exercise and behavioral therapy.[74] The condition does not have a known cause and is typically diagnosed based on a physician's history and physical examination.

A small 2012 study (110 fibromyalgia patients, 91 controls) reported a lower-than-normal cytokine immune response among patients with fibromyalgia compared to controls.[75] The FM/a Test appeared on the market within months of this publication, offered as an LDT claiming to diagnose the disease by documenting altered immunity as an explanation of symptoms experienced by fibromyalgia patients.[76] The manufacturer suggests that the test diagnoses the disease, and markets the test for people undergoing a diagnostic workup of fibromyalgia.[76]

A number of critiques of the study methodology appeared subsequently.[77] These included concerns that the control group was inadequate[78] and that the authors had not adjusted for other conditions known

to change cytokine levels that may have been present at different rates in the fibromyalgia and control groups.[79] The company failed to conduct clinical trials to verify that the immune system deficiency reported in the study was clinically relevant to fibromyalgia. Approximately 1,000 tests were sold for $744 apiece during the first month the test was offered.[78]

Making an inaccurate diagnosis of fibromyalgia can be especially harmful when the patient may be suffering from a different, treatable condition with similar symptoms. Such conditions include Lyme disease and rheumatoid arthritis, for which effective therapies exist. Moreover, patients wrongly diagnosed with fibromyalgia may take unnecessary medications for that condition and be exposed to associated adverse effects.

ii. KIF6 Genotyping Test to Predict Heart Disease Risk and Statin Therapy Response

Category	LDT Characteristics
LDT Name	KIF6 "Statincheck" Genotyping Assay
Description	Genotype test for KIF6 variant
Purpose	Predict risk of heart disease and response to statin therapy
Target Population	Patients at risk for coronary heart disease (CHD)
Alternatives	Standard history, standard laboratory work-up and behavioral risk factor assessment
LDT Problem 1	Biomarker not adequately shown to be predictive of CHD or of statin response
LDT Problem 2	Test incorrectly validated
LDT Problem 3	Unproven product claims
Clinical Consequence	Over- or under-treatment with statins
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Therapy with a class of drugs known as statins reduces the risk of heart attack and death from heart disease by about 1/3 in patients with coronary heart disease (CHD).[80] However, side effects of these drugs range from muscle pain and cramping to more serious reactions such as nerve damage, mood, sleep and cognitive impairment, and, rarely, muscle breakdown leading to kidney failure.

In 2007 and 2008, two population-based observational cohort studies suggested that a certain genetic variant, the KIF6 genotype, imparted a moderately elevated risk of cardiovascular events.[81,82] The findings from three medium-sized, randomized controlled trials by the same group of authors supported this relationship,[83,84] although the size of effect was modest, and one trial found that only KIF6 carriers (those with only one copy of the gene) had an increased risk in a sub-group, but those who were homozygous for the KIF6 variant (i.e., had two copies of the gene) were not, a paradoxical finding.[85] However, a large meta-analysis of 19 case-control studies found no association between KIF6 status and risk of CHD events.[86]

In a related line of research, results from two medium-sized, randomized, controlled trials suggested that KIF6 carriers experienced a greater reduction in CHD when placed on statin therapy (compared with placebo) than experienced by non-carriers.[87] A third randomized, controlled trial found a greater relative reduction in risk only in one sub-group of patients,[85] and a fourth trial's results supported the reduction in risk for a similar sub-group,[88] but only measured KIF6 status in approximately half of the patients on statins.[80] A fifth trial reported that KIF6 status had no impact upon response to statin therapy.[89] Finally, the large definitive WPS trial of 18,348 patients found no relationship between KIF6 status and statin response.[80] By 2010, more than 150,000 tests had been performed.[90]

In April 2011, FDA informed the manufacturer that its submission for premarket device approval was not approvable, stating that the evidence submitted was insufficient to support the test's safety and effectiveness in determining risk of heart disease or in predicting statin response.[91]

Inaccurate assessment of patient risk or likelihood of responding to statin therapy could lead to overtreatment, with an associated risk of adverse events, as well as undertreatment, with the risk of failing to prevent cardiovascular events and deaths.[80] The company withdrew its marketing application. However, the KIF6 test remains on the market as an LDT, and the manufacturer's website continues to make a claim, unsupported by the evidence, that KIF6 carriers may have elevated CHD risk and demonstrate favorable response to statins.[92]

iii. Target Now Cancer Biomarker Test

Category	LDT Characteristics
LDT Name	Target Now
Description	Molecular test to detect 20 cancer biomarkers for a range of tumor types
Purpose	Profile a cancer and suggest chemotherapy
Target Population	Patients with refractory or recurrent cancer
Alternatives	Follow standard chemotherapy regimens
LDT Problem 1	List of suggested treatments generated by the test have not necessarily been shown to have an impact for a patient's particular cancer
LDT Problem 2	List of suggested treatments generated by test have not been studied in combination
LDT Problem 3	Improper clinical trial design to validate test
Clinical Consequence	Patients may forego standard cancer therapy for unproven alternative therapy, with related risk of serious adverse events
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Scientists increasingly recognize that cancers have unique molecular profiles that can be used to personalize therapies. The Target Now test, first offered in 2008, uses multiple technologies to provide molecular profiles for a variety of cancers. It then generates a list of suggested drugs, shown in the scientific literature to target those biomarkers, but not necessarily demonstrated to have clinical effect

in the particular cancers affecting each patient.[93] If two targets are identified that are associated with what the manufacturers consider a well-tolerated drug combination, that combination is suggested.[94]

By the end of December 2010, more than 12,550 tests had been sold.[95] That year, in a single uncontrolled study of 86 patients with recurrence of various metastatic cancers, 66 patients had tumors that generated biomarker targets detected by the test and received treatment according to the list of suggested drugs generated by the test.[94] At four months, 14 patients had not experienced progression, and 18 experienced a longer time to progression than they had on the regimens in use when they enrolled in the study.[94] This study was small and had no control arm, and so provides little evidence of clinical validity.[95,96]

Patients undergoing this test may forego standard treatment and opt for the list of alternatives put forth on the test report, even though the test has not been clinically validated and these treatments have not necessarily been clinically proven, in combination or in the context of the patient's particular cancer. The study reported no treatment-related deaths, but did report nine treatment-related serious adverse events, such as anemia, dehydration, pancreatitis, and nausea and vomiting.[94]

iv. Prolaris Prostate Cancer Biomarker Test

Category	LDT Characteristics
LDT Name	Prolaris
Description	Prognostic genetic panel of 46 genes from tumor biopsy
Purpose	Predict risk of recurrence and death, and to guide treatment
Target Population	Men with localized prostate cancer
Alternatives	Prostate specific antigen (PSA) test, Gleason score
LDT Problem 1	Test not evaluated for its ability to meaningfully improve clinical outcomes
LDT Problem 2	Insufficient evidence for manufacturer marketing claims
Clinical Consequence	Patients potentially receive inappropriate cancer treatment
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Prostate cancer is diagnosed in 233,000 men in the U.S. a year and is associated with 29,480 deaths annually.[97] For a man diagnosed with prostate cancer, the so-called Gleason score, based on biopsy cancer cell characteristics, along with the prostate specific antigen (PSA) level provide a standard measure of cancer severity and guide treatment decisions. Treatment options depend on expected severity and range from "watchful waiting" (withholding treatment but monitoring the patient carefully) for men with low-risk tumors, to hormone therapy, surgery, radiation or chemotherapy for men with symptomatic or metastatic cancer. Side effects of these interventions include urinary incontinence, sexual impotence, and infertility. About 10% of all prostate cancer patients elect watchful waiting, but experts hypothesize that up to 40% of patients may actually qualify for that approach.[98]

In an effort to further differentiate low- from high-risk patients, the Prolaris test was introduced as an LDT in March 2010. The genetic panel measures expression of 46 genes correlated with prostate cancer cell proliferation,[99] generating a score that, when combined with the Gleason score and the PSA level, is

claimed to predict the 10-year risk of prostate cancer progression and the risk of death.[100] We would expect those with poorer predicted outcome scores are more likely to elect active treatment.

The test is being used to make patient management decisions. In a 2014 study, 65% of more than 300 physicians (mostly urologists) caring for men diagnosed with prostate cancer reported that the test score influenced their initial treatment plan.[101] After receiving the test score, 37% of physicians who initially planned to recommend active interventions recommended watchful waiting instead, while 30% recommended active intervention instead of watchful waiting.[101] However, no study has prospectively examined whether these treatment decisions represent clinically appropriate management of prostate cancer.[102] As a result, patients could be either over-or undertreated for prostate cancer.

v. Chronic Fatigue Syndrome XMRV Test

Category	LDT Characteristics
LDT Name	XMRV-Chronic Fatigue Syndrome (CFS) Test
Description	PCR tests to detect mouse virus with reported link to CFS
Purpose	Detect "cause" of CFS
Target Population	Patients with CFS or suggestive symptoms
Alternatives	Clinical diagnosis based on symptoms
LDT Problem 1	Evidence that mouse virus is linked to CFS was based on contaminated study samples, and has since been disproved
LDT Problem 2	No verification that patients with positive test have CFS
Clinical Consequence	Patients with positive tests may take non-indicated antiviral drugs
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Chronic Fatigue Syndrome (CFS) is a disorder with unknown cause. In October 2009, a study published in the journal *Science* suggested a possible association between the newly-discovered *xenotropic Moloney murine leukemia virus-related virus* (XMRV) and CFS.[103] Three laboratories began offering a rapid PCR blood test as an LDT to detect XMRV.[104,105,106] When a September 2010 study[107] reported similar findings linking XMRV to CFS, the public became concerned that CFS could be transmitted through blood.[108] By December 2010, the American Red Cross,[109] Canada, Australia, New Zealand, and several European countries had banned blood donations from CFS patients.[110]

However, one manufacturer publicly discontinued its test in April 2010[111] when internal validation studies failed to replicate an association between XMRV and CFS. Several studies in Europe and China and two case-control studies from CDC in 2010[112] and from the University of Utah in 2011[113] found no association between XMRV and CFS. A study that attempted to repeat the testing on 15 XMRV-positive samples in 9 labs across the country failed to confirm XMRV in patients with CFS.[114] Two of the initial authors re-examined the samples and ascribed some of the findings to contamination.[115] The initial study was retracted by the editor of *Science* in December 2011.[116]

A number of CFS patients who tested positive for XMRV on these LDTs started off-label use of antiretroviral drugs,[117] which can be associated with potentially serious side effects, from nausea and vomiting to disorders of the blood and nervous systems.[118] Patients were subjected to stigma as many of the world's blood banks banned blood from CFS patients. The ban has since been reversed.

E. Tests Linked to Treatments Based on Disproven Scientific Concepts

i. CARE Clinics Autism Biomarkers Test

Category	LDT Characteristics
LDT Name	CARE Clinics BioMarkers
Description	Genetic biomarker and heavy metal intoxication test
Purpose	To determine the cause for Autism Spectrum Disorder (ASD) and to recommend treatment
Target Population	Children with ASD
Alternatives	American Psychiatric Association-approved behavioral and developmental diagnostic criteria for ASD
LDT Problem 1	No evidence that "causes" identified by the test correlate with ASD
LDT Problem 2	No evidence that recommended treatments improve ASD outcomes
Clinical Consequence	Children undergo inappropriate and harmful treatment based on test results
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims; protection of children from unproven therapies
Cost Impact of Inaccuracy	$66.1 million

Autism spectrum disorder (ASD) is a developmental disability that manifests along a broad clinical range, from a child with low measured intelligence, frequent repetitive behaviors, and limited communication to one with gifted intellectual and communicative faculties, average social interactions, and mild repetitive behaviors.[119] It is assumed to have multiple causes, although most have not yet been identified, and it does not have a recognized diagnostic test. Instead, doctors evaluate a child's behavior and development to make a diagnosis using criteria developed by the American Psychiatric Association.

In 2001, the Center for Autistic Spectrum Disorders was founded, opening affiliated CARE Clinic laboratories in Texas and in Florida. The CARE Clinics began marketing a number of tests for children with ASD, including a panel of biomarkers along with a heavy metal toxicity test that purported to identify the causes of a child's autism. These causes were in turn linked to a CARE Clinics Health Blueprint™ treatment plan, which included chelation, hyperbaric oxygen, and intravenous vitamin therapy. (Chelators bind to heavy metals such as lead and mercury and remove them from the body through the urine.)

These interventions for ASD have been discredited by the medical community, indicating no evidence for a role for heavy metal chelation in either preventing or treating ASD, and including a warning of the dangers and lack of scientific basis of chelation therapy for children with ASD from the American Academy of Pediatrics.[120] Of these interventions, chelation products are particularly popular and may have notable toxicities,[121] including allergic reactions, dehydration, and kidney failure.[122]

According to tax returns described on the Autism Watch website, the Center for Autistic Spectrum Disorders and the CARE Clinics received $9.8 million for these tests for 2,027 children reportedly tested between 2004 and 2007.[121] Compared with a child with a comparable behavioral condition, a family with a child with ASD will pay an additional annual average of $1,759 for health care,[123] $5,659 for lost family income,[124] and $7,562 for special education costs,[123,125] for a total of $14,980. We assumed that the children were only misdiagnosed until the end of 2007, the last year we have numbers for the Center.

Given this assumption, 427 children were misdiagnosed for four years, 150 were misdiagnosed for three years, 150 were misdiagnosed for two years, and 1,300 were misdiagnosed for one year, for a total of 3,758 misdiagnosed years. Assuming that all these children tested had other psychiatric conditions but were instead being treated as if they had autism, these incorrect diagnoses would have resulted in a cost of $56.3 million ($14,980 x 3,758). Together, the costs of the unnecessary tests and the improper diagnosis and treatment of these children accounted for an estimated total cost of $66.1 million ($56.3 million + $9.8 million).

ii. Heavy Metal Chelation Challenge Test

Category	LDT Characteristics
LDT Name	Various heavy metal challenge tests
Description	Urine chelation challenge test to measure levels of heavy metals
Purpose	To detect chronic heavy metal poisoning
Target Population	The general public
Alternatives	Routine blood screening without challenge test, for high-risk children
LDT Problem 1	In clinical use, patients with positive urine chelation challenge tests may not have heavy metal toxicity
LDT Problem 2	Manufacturer claims unsupported by evidence
Clinical Consequence	False-positive results may lead to the administration of inappropriate, unproven or dangerous therapies
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Heavy metals such as lead and mercury are ubiquitous in the environment, and thus trace amounts are common in urine, hair, or blood samples, although blood levels are the most reliable and must be assessed prior to treatment.[126] While heavy metal exposures to high doses over a short time period can cause acute poisoning and death, long-term exposure to low levels also may cause chronic poisoning and health problems.[127]

Lead and mercury are two of the most common heavy metals involved in poisoning, and they can cause vague abdominal complaints, organ damage, and developmental and neurological problems.[126,128,129,130] Elevated blood levels of heavy metals can be treated with chelation therapy.[131]

A "provoked chelation challenge test" uses the same chelating agents and measures heavy metals in the urine;[132] these are always higher than those measured without provocation. There are no accepted standards for interpreting provoked results,[133] although they have been used to justify chelation therapy to treat conditions claimed by some, often without satisfactory evidence, to be associated with heavy metal toxicity, including heart disease, Alzheimer's disease, and Autism Spectrum Disorders.[122] The American Academy of Pediatrics discourages the use of chelation as a treatment for children with Autism Spectrum Disorders, stating that the practice is particularly dangerous and lacks any scientific evidence of benefit.[120]

For example, one laboratory manufactures a provoked chelation challenge test but gives results using a normal, non-provoked reference scale, and the outcome may then result in recommendations for intravenous chelation therapy. This inappropriate use of chelation therapy can be costly, unnecessary, and harmful, as chelators also bind important minerals such as calcium and iron and remove them from the body. Chelation products also can cause allergic reactions, dehydration, and kidney failure.[122] Oregon's public health department has reported three deaths associated with chelation therapy,[132] and CDC reported the deaths of three individuals with heart attacks due to low blood calcium following chelation therapy between 2003 and 2005.[134] One of these was a 5-year-old who was being treated for autism. It is unknown whether these patients were exposed to any of the LDTs in question.

F. Tests that Undermined Drug Approval or Drug Treatment Selection

i. Omapro Companion Diagnostic to New Leukemia Medication

Category	LDT Characteristics
LDT Name	Omapro Companion Diagnostic
Description	Genetic test to detect T315I gene mutation in cancerous cells of chronic myelogenous leukemia (CML)
Purpose	To enroll research participants in a clinical trial and determine sub-population most likely to benefit from a new drug
Target Population	Adults with treatment-resistant CML and the T315I mutation
Alternatives	None
LDT Problem 1	Lack of standardized LDTs leads to unreliable selection of patients for clinical trial enrollment
LDT Problem 2	Drug sponsor used two different, non-comparable LDTs to enroll patients in a clinical trial
LDT Problem 3	Researchers did not obtain the proper investigational device exemption needed to carry out a research study
Clinical Consequence	Delay in approval of a drug with some benefit for treatment-resistant CML patients
Potential Impact of FDA	Assurance the test is appropriately validated for use in the

Oversight	clinical trial
Cost Impact of Inaccuracy	Not estimated

Chronic myelogenous leukemia (CML) is a cancer of the blood and immune system for which first-line treatment is a tyrosine kinase inhibitor (e.g., imatinib). Although treatment prolongs life, 30%-40% of patients become treatment-resistant within seven years.[135] Up to 20% of treatment-resistant patients, or 250 to 300 patients a year, have a T351I mutation in their cancerous cells.[135]

One manufacturer initiated a clinical trial that planned to test a new drug (Omapro; omacetaxine mepesuccinate) that targets cancer cells in a different way than the typical treatment and was designed specifically to target the CML sub-population with the T351I mutation. The study used two different LDTs to screen CML patients and enrolled only those with the mutation in the trial.[136]

The drug showed some benefit,[137] but the LDTs used different techniques, with different measurement ranges, and their ability to detect the mutation had not been validated, so it was not possible to compare enrollment strategies based on the two different tests. This prevented valid assessment of the drug's efficacy in the group with the mutation. In 2010, FDA's Oncologic Drug Advisory Committee voted against Omapro approval for this subgroup,[136] and the drug was not brought to market at that time.

In October 2012, after further consideration of the drug's potential as a treatment option for CML patients,[138] FDA granted approval of the same drug, under the name Synribo, for CML patients who had failed all other treatment, regardless of their T351I mutation status.[139] It remains unclear whether the drug's efficacy is confined to the subgroup with the mutation. Regardless, approval of the drug was delayed for two years as a result of issues with the LDTs.

ii. Duke University Chemotherapy Assessment Test

Category	LDT Characteristics
LDT Name	Duke University Chemotherapy Assessment
Description	Genetic assay of tumor cells
Purpose	Assign clinical trial patients to chemotherapy treatment according to test results
Target Population	Patients with ovarian, lung and breast cancer
Alternatives	Existing clinical guidelines for treatment of ovarian, lung and breast cancers
LDT Problem 1	Errors in data management and analysis
LDT Problem 2	Lack of clinical validation that test predicts response
Clinical Consequence	Patients enrolled in trials took unproven, potentially inadequate treatments
Potential Impact of FDA Oversight	Assurance the test is appropriately validated for use in the clinical trial
Cost Impact of Inaccuracy	Not estimated

In October 2006, cancer researchers at Duke University Medical Center published data from multi-gene expression studies on cells from patients with ovarian, lung and breast cancer.[140] The data suggested

that results from gene expression panels, implemented as LDTs, could predict individuals' responses to specific chemotherapy regimens.[140] Without further validation of predictive validity for the laboratory's LDTs, three clinical trials were conducted, using LDT results to allocate patients to chemotherapy treatments.[141]

As patients were being enrolled, members of the scientific community interested in using the tests in their own practices attempted to validate the initial study findings and discovered data management errors. Scientific rigor dictates that a test should be developed with one set of data, and validated on an entirely separate set of data in order to avoid over-estimation of performance. The Duke investigators, however, allowed overlap of the data sets,[142] which produced overestimates of test accuracy. In addition, outside researchers uncovered basic spreadsheet errors in the data used to select the genes for inclusion in the test,[143] as a consequence of which the test results were non-reproducible.[143,144] These errors also led to the inappropriate inclusion of at least 14 of the 50 genes in the LDT.[142]

The trials continued until a separate issue regarding false academic claims made by one of the principal investigators in the trials drew media attention to the earlier criticisms of the test. In response, the Institute of Medicine (IOM) conducted a special investigation of this and several similar situations, issued a statement[145] that internal oversight mechanisms within the university had failed, and that the most basic conclusions of the test were invalid.

In the IOM's assessment, greater FDA oversight and involvement may have uncovered errors and validation issues before the test was used in clinical trials. At a minimum, said the IOM, researchers should discuss LDTs with FDA prior to initiating validation studies, particularly when the test is intended for future clinical use.[146] In the ensuing months, the three trials were discontinued and 27 papers describing the test's performance were partially or completely retracted. This illustrates that publication in a peer-reviewed medical journal, even a prestigious one as in this case, is not equivalent to validation, because reviewers typically do not have access to the underlying data and often are not sufficiently expert in complex algorithms to identify errors. On November 9, 2015, the Office of Research Integrity in the Department of Health and Human Services concluded that one of the principal investigators had "engaged in research misconduct."[147]

As a consequence of the use of this insufficiently validated LDT, cancer patients were exposed to potentially inappropriate chemotherapy.

G. Other Unvalidated Tests

i. Vitamin D Deficiency Test

Category	LDT Characteristics
LDT Name	Vitamin D Test
Description	Liquid chromatography tandem mass spectrometry
Purpose	To determine a patient's vitamin D blood level
Target Population	The general population in early marketing claims; people at risk for Vitamin D toxicity or deficiency in current materials
Alternatives	FDA-cleared vitamin D tests from other manufacturers
LDT Problem 1	Faulty calibration of device

LDT Problem 2	Inadequate validation that test results correlate with clinical vitamin D excess or deficiency
LDT Problem 3	Lack of standardization of LDT between testing sites
Clinical Consequence	Over- or under-treatment of Vitamin D excess or deficiency
Potential Impact of FDA Oversight	Assurance of consistent manufacturing practices and standardized instrument calibration; assurance the test meets minimum performance standards
Cost Impact of Inaccuracy	Not estimated

Vitamin D is the product of sun exposure, but it can also be obtained through the diet and in dietary supplements. It maintains bone strength and supports the immune and nervous systems, as well as maintains proper levels of certain minerals (calcium, phosphorous) that the body needs to carry out its normal functions. Low levels have been associated with cancer, heart disease, and disorders of the immune system, although whether these relationships are causal is less clear.[148,149]

Between 2006 and 2007, a testing company changed its vitamin D test from an FDA-cleared test to an LDT that relied on a specialized mass spectrometry instrument, with the expectation that the LDT would be more accurate. However, company officials later reported faulty calibration of the instruments and failure to follow standard test procedures at four of the seven laboratories offering vitamin D testing.[150] Most of the inaccurate tests reported an inflated vitamin D level, leading some patients not to take potentially beneficial supplements. However, some tests reported a falsely low vitamin D level, which could lead patients to take unnecessary supplements – and risk vitamin D toxicity, which includes elevated calcium blood levels, nausea, vomiting, and kidney damage.[151] The company marketed the test heavily, including in a 2009 video produced with UCLA doctors that promoted the importance of testing for vitamin D.[152] In January 2009, the company notified thousands of physicians that the vitamin D test results of at least one of each of their patients from the prior two years was inaccurate and recommended retesting.[150,153] The editor of a pathology newsletter quoted in *The New York Times* coverage described these events as "the largest patient test recall I'm aware of in my 20 years in the business."[150]

ii. OncoVue Genetic Breast Cancer Risk Test

Category	LDT Characteristics
LDT Name	OncoVue
Description	Genetic test combining individual mutation profile with personal history
Purpose	Predict inherited breast cancer risk
Target Population	Women without breast cancer
Alternatives	Gail Model for predicting risk of breast cancer
LDT Problem 1	Specificity not assessed
LDT Problem 2	Lack of validation of test performance in clinical use
Clinical Consequence	Patients with elevated scores may undergo unnecessary mastectomy or tamoxifen prophylaxis; patients with low scores may have a false sense of security and forego recommended screenings

Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Factors such as age, environment, and personal medical history make up the Gail model, which is relatively well-validated for use to predict a woman's future risk of breast cancer. Ninety to ninety-five percent of breast cancer is caused by behavioral and environmental factors such as cigarette smoke, high levels of hormone exposure, obesity, and lack of exercise.[154] The remaining 5% is inherited.[154] Researchers have discovered single genes that carry an increased risk of breast cancer, such as the relatively rare BRCA genes; much of the remaining genetic risk may be explained by interaction between inherited genetic DNA variations called single nucleotide polymorphisms (SNPs).[155,156]

In 2006 a new LDT, OncoVue, was introduced to detect a group of 22 SNPs. The test was intended to combine multiple SNPs with the Gail model to predict a woman's future risk of breast cancer.[157]

Data from two abstracts (not otherwise reported in a peer-reviewed medical journal) showed that the LDT identified 56 of 169 breast cancer cases (33% sensitivity), compared to the 37 (22% sensitivity) that were predicted to be high risk in a retrospective application of the Gail model.[158,159] Because all patients in this study had cancer, its specificity in detecting patients without cancer has not been studied and is unknown. Without further testing, the test was marketed to the public.

Some observers believe that the use of such SNP panels to screen the population for breast cancer risk is premature.[160,161] For example, a woman with a low-risk score may be given a false sense of security and forego recommended screenings and a woman given a high-risk score might, in error, choose to undergo more intensive screening with ultrasound or MRI, take tamoxifen or raloxifene to prevent breast cancer, or even consider having her breasts removed to prevent cancer.[162]

iii. BrafV600E Genetic Mutation Test to Guide Melanoma Treatment

Category	LDT Characteristics
LDT Name	BrafV600E Mutation Tests
Description	PCR test to detect V600E BRAF gene mutation in melanomas
Purpose	Select patients for treatment with vemurafenib
Target Population	Patients with metastatic melanoma
Alternatives	FDA-approved diagnostic to detect V600E BRAF mutation
LDT Problem 1	Lack of evidence to support manufacturer claims that LDT performs better than alternatives
Clinical Consequence	Patients may inappropriately be administered vemurafenib
Potential Impact of FDA Oversight	Assurance the test meets minimum performance standards; evaluation of manufacturer claims
Cost Impact of Inaccuracy	Not estimated

Melanoma is a cancer of the skin that has a median survival of eight months if it spreads.[163] Tumors can have a genetic mutation called BRAF V600E, which is present in approximately 50% of metastatic melanoma cases.[164] A class of drugs including vemurafenib, shown to increase overall and progression-free survival in these patients compared to traditional chemotherapy, is approved by FDA for the

treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation, as long as the mutation was detected by an FDA-approved test.[165]

In August 2011, FDA approved the in vitro diagnostic Roche Cobas® 4800 test as a commercially distributed companion diagnostic to detect the BRAF V600 mutation,[166] whereupon at least nine laboratories[167,168] announced that they were offering their own LDT version of the BRAF test for the same intended use. Some of these detected several additional mutations that had not been shown to predict response to vemurafenib.

Some of the other manufacturers claimed improved performance over the FDA-approved test. For example, one manufacturer claimed that its LDT "surpasses other commercially-available tests."[167] In addition, some claimed that their test was more sensitive (i.e., it could detect the V600 mutation when a lower fraction of tumor cells had the mutation), but we have no knowledge whether mutation frequencies as low as those detected by the LDTs predict clinical response to vemurafenib. Thus patients could be recommended for vemurafenib therapy with perhaps no benefit. None of these LDTs have been approved by FDA, and FDA is not aware of evidence to support claims of superior performance or even to support the use of these LDTs to identify patients who may benefit from vemurafenib. Insurance companies may not cover vemurafenib if it is started after using an LDT, so patients may have to pay out-of-pocket.[169]

III. Conclusion

In this report, we have reviewed events related to 20 LDTs in which patients have been demonstrably harmed or may have been harmed by tests that did not meet FDA requirements. Tests that are inaccurate, unreliable, or have unproven or disproven claims expose patients to a range of harms. These include patients told incorrectly that they have life-threatening diseases and others whose life-threatening diseases have gone undetected.

Despite arguments from some that "CLIA is enough," all of the tests described as problematic in this report were offered from laboratories following the minimum requirements of CLIA. Specifically, CLIA does not:

- Ensure the safety and effectiveness of LDTs prior to marketing.
- Assess the quality of the design and manufacture of devices.
- Ensure test labeling provides adequate directions for use.
- Require truth in marketing materials and other labeling.
- Require adverse event reporting.
- Permit removal of unsafe devices from the market.
- Require informed consent for patients participating in clinical studies of LDTs.
- Establish procedures for the conduct of such studies.

These cases, therefore, highlight the need for greater FDA oversight of LDTs that is appropriately tailored so that it is complementary and does not duplicate the oversight currently provided under CLIA. Greater FDA oversight is needed to promote access to LDTs that provide benefits to patients and the health care system, while helping to ensure patients are not unduly exposed to harm.

[1] 21 U.S.C. 321(h). http://www.gpo.gov/fdsys/pkg/USCODE-2013-title21/html/USCODE-2013-title21-chap9-subchapII-sec321.htm. Accessed April 16, 2015.
[2] 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 3, 2014. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf. Accessed December 1, 2014.
[3] Centers for Medicare and Medicaid Services. Laboratory developed tests (LDTs): Frequently asked questions. October 22, 2013. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf. Accessed June 8, 2015.
[4] Centers for Disease Control and Prevention. Signs and symptoms of Lyme disease. April 12, 2011. http://www.cdc.gov/lyme/signs_symptoms/index.html. Accessed November 16, 2014.
[5] Centers for Disease Control and Prevention. Two-step laboratory testing process. April 12, 2011. http://www.cdc.gov/lyme/diagnosistesting/LabTest/TwoStep/. Accessed November 16, 2014.
[6] U.S. Food and Drug Administration. Devices at FDA. December 8, 2014. http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm. Accessed December 1, 2014.
[7] Wormser GP, Dattwyler RJ, Shapiro ED. The clinical assessment, treatment, and prevention of Lyme disease, Human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2006;43(9):1089-134.
[8] Centers for Disease Control and Prevention. Lyme disease Treatment. April 12, 2011. http://www.cdc.gov/lyme/treatment/index.html. Accessed November 14, 2014.
[9] Klempner MS, Schmid CH, Hu L, et al. Intralaboratory reliability of serologic and urine testing for Lyme disease. *Am J Medicine*. 2001;110(3):217-9.
[10] Rauter C, Mueller M, Diterich I, et al. Critical evaluation of urine-based PCR assay for diagnosis of Lyme borreliosis. *Clin Diagn Lab Immunol*. 2005;12(8):910–7.
[11] Hurley D, Santora M. Unproved Lyme disease tests prompt warnings. *New York Times*. August 23, 2005. http://www.nytimes.com/2005/08/23/health/policy/23lyme.html?pagewanted=all&_r=0. Accessed November 14, 2014.
[12] Margolies D. Who's left to pay this big verdict? *Kansas City Star*, May 25, 2009. http://www.aldf.com/Bowen_Laboratory_Settlement.pdf. Accessed November 20, 2014.
[13] Nelson C, Hojvat S, Johnson B, et al. Concerns regarding a new culture method for *Borrelia burgdorferi* not approved for the diagnosis of Lyme disease. *Morbidity and Mortality Weekly Report* 2014; 63:333.
[14] Johnson BJ, Pilgard MA, Russell TM. Assessment of new culture method for detection of *Borrelia* species from serum of Lyme disease patients. *Journal of Clinical Microbiology* 2014;52:721–4.
[15] Zhang X, Martin IM, Peña AC, Hopkins AB, Wroth L, Fix AD. Economic impact of Lyme disease. *Emerging Infect Dis*. 2006;12(4):653-660. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294685/. Accessed April 16, 2015.
[16] $1,226 = ($464 x 1.59 + $307 x 1.59).
[17] U.S. Department of Labor, Bureau of Labor Statistics (BLS). CPI Databases. 2013. http://www.bls.gov/cpi/tables.htm. Accessed March 26, 2013.
[18] Surveillance, Epidemiology, and End Results Program (SEER). SEER Stat Fact Sheets: Ovary Cancer. 2014. http://seer.cancer.gov/statfacts/html/ovary.html. Accessed November 5, 2014.
[19] Sfakianos GP, Havrilesky LJ. A review of cost-effectiveness studies in ovarian cancer. *Cancer Control*. 2011;18(1):59-64.
[20] Society of Gynecologic Oncologists. Ovarian Cancer: Treatment Options. 2014. https://www.sgo.org/patients-caregivers-survivors/patients/ovarian-cancer-what-are-the-treatment-options/. Accessed December 1, 2014.
[21] Institute of Medicine. Evolution of Translational Omics: Lessons Learned and the Path Forward. Appendix A, Case Studies. The National Academies Press (US). 2012. http://www.nap.edu/catalog/13297/evolution-of-translational-omics-lessons-learned-and-the-path-forward. Accessed May 28, 2015.

[22] Petricoin E, Ardekani A, Hitt B, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet*. 2002;359:572-7.
[23] Liotta L, Petricoin E, Ardekani A et al. General keynote: proteomic patterns in sera serve as biomarkers of ovarian cancer. *Gynecol Oncol.* 2003;88(1 Pt 2):S25-8; discussion S37-42.
[24] Pearl DC. Proteomic patterns in serum and identification of ovarian cancer. *Lancet*. 2002;360(9327):169-70.
[25] Elwood M. Proteomic patterns in serum and identification of ovarian cancer. *Lancet.* 2002;360(9327):170.
[26] Gutman SI. Letter to Levine PJ, President and CEO, Correlogic Systems, Inc. Food and Drug Administration, Center for Devices and Radiological Health. February 18, 2004. https://web.archive.org/web/20040711090448/http:/www.fda.gov/cdrh/oivd/letters/021804-correlogic.html. Accessed July 14, 2015.
[27] Baggerly K, Morris J, Coombs K. Reproducibility of SELDI-TOF protein patterns in serum: comparing data sets from different experiments. *Bioinformatics.* 2004;20(5):777-85.
[28] Diamandis E. Analysis of serum proteomic patterns for early cancer diagnosis: drawing attention to potential problems. *J Natl Cancer Inst. 2004;*96(5):353-5.
[29] Visintin I, Feng Z, Longton G, et al. Diagnostic markers for early detection of ovarian cancer. *Clinical Cancer Research*. 2008;14:1065-72.
[30] Buchen L. Missing the mark: Why is it so hard to find a test to predict cancer? *Nature*. 2011;471:428-32.
[31] Society of Gynecologic Oncologists Statement Regarding OvaSure(TM). July 2, 2008. https://www.sgo.org/wp-content/uploads/2012/09/Statement-on-OvaSure.pdf. Accessed December 1, 2014.
[32] Food and Drug Administration Center for Devices and Radiological Health. OvaSure (TM) Manufacturer Letter. August 2008. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm125130.htm. Accessed December 1, 2014.
[33] Food and Drug Administration Center for Devices and Radiological Health. Warning Letter. Inspections, Compliance, Enforcement, and Criminal Investigations. September 8, 2008. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048114.htm. Accessed December 1, 2014.
[34] U.S. Department of Labor, Bureau of Labor Statistics (BLS). National Industry-Specific Occupational Employment and Wage Estimates for Healthcare Practitioners and Technical Occupations (290000). May 2011. http://www.bls.gov/oes/. Accessed March 26, 2013.
[35] Ratner E, Lu L, Boeke M, et al. A KRAS-variant in ovarian cancer acts as a genetic marker of cancer risk. *Cancer Res*. 2010;70(16):6509-15.
[36]MiraDX. (No date). The KRAS-Variant & Cancer Risk. http://miradx.com/preovar-kras-variant-test-populations/. Accessed December 1, 2014.
[37] Society of Gynecologic Oncology. "PreOvar" Ovarian Cancer Risk Assessment Test. September 2010. https://www.sgo.org/newsroom/position-statements-2/preovar-ovarian-cancer-risk-assessment-test/. Accessed December 1, 2014.
[38] Pharaoh PD, Palmeiri RT, Ramus SJ, et al. Ovarian Cancer Association Consortium. The role of KRAS rs61764370 in invasive epithelial ovarian cancer: implications for clinical testing. *Clin Cancer Res*. 2011;17(11):3742-50.
[39] Risch HA, Berchuck A, Pharaoh PDP, et al. Ovarian Cancer Association Consortium. KRAS rs61764370 in Epithelial Ovarian Cancer - Response. *Clin Cancer Res*. 2011;17:6601.
[40] Permuth-Wey J, Chen Z, Tsai YY, et al. MicroRNA processing and binding site polymorphisms are not replicated in the Ovarian Cancer Association Consortium. *Cancer Epidemiol Biomarkers*. 2011;20:1793.
[41] MiraDX. (No date). FAQ. https://miradx.com/faq/. Accessed November 20, 2014.
[42] Centers for Disease Control and Prevention (CDC). Preventing Tetanus, Diptheria, and Pertussis among adults: Use of Tetanus toxoid, reduced Diptheria toxoid and acellular Pertussis vaccine. Morbidity and Mortality Weekly Report, Recommendations and Reports. 2006;55(RR17):1-33. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5517a1.htm.

[43] Centers for Disease Control and Prevention. Outbreaks of respiratory illness mistakenly attributed to Pertussis-*New Hampshire, Massachusetts, and Tennessee*, 2004-2006. *MMWR Morb Mortal Wkly Rep*. August 24, 2007;56(33):837-42. http://www.cdc.gov/MMWR/preview/mmwrhtml/mm5633a1.htm. Accessed May 28, 2015.
[44] Cancer Connect. Oncotype DX accurately determines HER2 status in breast cancer. http://news.cancerconnect.com/oncotype-dx-accurately-determines-her2-status-in-breast-cancer/. Accessed November 6, 2014.
[45] Wolff AC, Hammond MEH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Journal of Clinical Oncol*. 2006;25(1):118-45. http://jco.ascopubs.org/content/25/1/118.full.pdf+html. Accessed May 28, 2015.
[46] National Cancer Institute. FDA Approval for Trastuzumab. July 2013. http://www.cancer.gov/cancertopics/druginfo/fda-trastuzumab. Accessed December 8, 2014.
[47] The American Society of Clinical Oncology (ASCO). HER2 testing for breast cancer. CancerNet. http://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/her2-testing-breast-cancer. Accessed November 6, 2014.
[48] Butkus, B. Oncotype DX study raises questions about RT-PCR testing for HER2 expression. GenomeWeb. December 2011. https://www.genomeweb.com/pcrsample-prep/oncotype-dx-study-raises-questions-about-rt-pcr-testing-her2-expression. Accessed December 5, 2014
[49] Genomic Health. Oncotype DX. 2014. http://www.genomichealth.com/en-US/OncotypeDX.aspx#.VIXKRskwA3Q. Accessed December 8, 2014.
[50] Guideline Summary: American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for human epidermal growth factor receptor HER2 Testing in breast cancer. *Journal of Oncology Practice*. 2007;3(1):48-50. http://jop.ascopubs.org/content/3/1/48.full. Accessed May 28, 2015.
[51] Dabbs DJ, Klein ME, Mohsin SK, et al. High false-negative rate of HER2 quantitative reverse transcription polymerase chain reaction of the Oncotype DX test: An independent quality assurance study. *J Clin Oncol.* 2011;29:4279-85.
[52] Park MM, Ebel JJ, Zhao W, Zynger DL. ER and PR immunohistochemistry and HER2 FISH versus oncotype DX: implications for breast cancer treatment. *Breast J*. 2014;20(1):37-45.
[53] Cutler D. Are we finally winning the war on cancer? *J Economic Perspectives*. 2008;22:3-26.
[54] Murphy KM, Topel RH. The value of health and longevity. *J of Political Economy*. 2006;114(5):871-904.
[55] 74 Federal Register 33030. July 9, 2009.
[56] Garrison LP, Lubeck D, Lalla D, et al. Cost-effectiveness analysis of trastuzumab in the adjuvant setting for treatment of HER2-positive breast cancer. *Cancer*. 2007;110(3):489-98.
[57] Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Path.* 2012;137(4):516-42.
[58] CDC, USPSTF, and ACOG guidelines state that, starting at age 21, a woman at average risk of cervical cancer should be screened with a Pap test alone every three years; starting at the 30th birthday, cytology and HPV testing should be performed concurrently every five years. A woman 30 years of age or older can continue to be screened with the Pap Test alone every three years, but the professional societies prefer co-testing.
[59] Ortega, B. False-negative results found in HPV testing. The Arizona Republic. January 18, 2013. http://www.azcentral.com/news/articles/20130112hpv-testing-false-negative.html. Accessed December 1, 2014.
[60] BD Diagnostics. Letter to Laboratory Directors, June 8, 2012. http://archive.azcentral.com/ic/pdf/0113-bd-bulletin.pdf. Accessed February 27, 2015.
[61] National Institutes of Health. Genetics Home Reference. November 2013. http://ghr.nlm.nih.gov/condition/trisomy-13. Accessed December 1, 2014.
[62] Society of Maternal Fetal Medicine. Incorporating first-trimester Down syndrome studies into prenatal screening: executive summary of the National Institute of Child Health and Human Development workshop. 2004. https://www.smfm.org/publications/128-incorporating-first-trimester-down-syndrome-studies-into-prenatal-

screening-executive-summary-of-the-national-institute-of-child-health-and-human-development-workshop. Accessed December 1, 2014.

[63] The American College of Obstetricians and Gynecologists. Committee opinion: Noninvasive prenatal testing for fetal aneuploidy. December 2012. http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Noninvasive-Prenatal-Testing-for-Fetal-Aneuploidy. Accessed December 1, 2014.

[64] Nicolaides KH, Syngelaki A, Ashoor G, et al. Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol*. 2012:374.e1-374.e6.

[65] Sequenom. MaterniT21 Plus. 2014. http://laboratories.sequenom.com/maternit21plus/prenatal-test-information-for-providers. Accessed December 1, 2014.

[66] Illumina. Verifi™ prenatal test. 2014. http://www.verifitest.com/healthcare-professionals/. Accessed December 1, 2014.

[67] Mennuti MT, Cherry AM, Morrissette JJD, Dugoff L. Is it time to sound the alarm about false-positive cell-free DNA testing for fetal aneuploidy? *Am J Obstet Gynecol*. 2013;209(5):415-9.

[68] Daley B. Oversold and misunderstood: Prenatal screening tests prompt abortions. New England Center for Investigative Reporting. http://features.necir.org/prenatal-testing. Accessed December 22, 2014.

[69] Donaldson-James S. Prenatal tests have high failure rate, triggering abortions. NBC News. December 14, 2014. http://www.nbcnews.com/health/womens-health/prenatal-tests-have-high-failure-rate-triggering-abortions-n267301. Accessed December 22, 2014.

[70] Dar P, Curnow KJ, Gross SJ, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *American J Obstet Gynecol*. 2014;211(5):527.e-527.e17.

[71] U.S. Food and Drug Administration. MAUDE Adverse Event Report: SEQUENOM MATERNIT21. March 2012. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=2903746. Accessed December 1, 2014.

[72] Daley B. Oversold prenatal tests spur some to choose abortions. *Boston Globe*, December 14, 2014. http://www.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.html. Accessed April 11, 2015.

[73] Medscape. Fibromyalgia: New criteria improve diagnosis. February 2014. http://www.medscape.com/viewarticle/820613. Accessed December 1, 2014.

[74] WebMD. What is fibromyalgia? (No date) http://www.webmd.com/fibromyalgia/guide/what-is-fibromyalgia. Accessed December 1, 2014

[75] Behm FG, Gavin IM, Karpenko O, et al. Unique immunologic patterns in fibromyalgia. *BMC Clinical Pathology*. 2012;12:25.

[76] EpicGenetics. FM/A(R): A simple and definitive test for FM. 2014. http://thefibromyalgiatest.com/?p=7006. Accessed May 28, 2015.

[77] Wolfe F. Junk science – Junk ethics. (Blog post). February 2013. http://www.fmperplex.com/2013/02/25/junk-science-junk-ethics/. Accessed November 25, 2014.

[78] Bonislawski A. Despite researcher criticism, EpicGenetics' fibromyalgia test does $750K in sales in first month. April 2013. GenomeWeb. https://www.genomeweb.com/proteomics/despite-researcher-criticism-epicgenetics-fibromyalgia-test-does-750k-sales-firs. Accessed November 25, 2014.

[79] Tarkan L. Questions arise over new diagnostic test for fibromyalgia. Fox News. February 2013. http://www.foxnews.com/health/2013/02/26/questions-arise-over-new-diagnostic-test-for-fibromyalgia/. Accessed November 25, 2014.

[80] Hopewell JC, Parish S, Clarke R, et al. for the MRC/BHF Heart Protection Study Collaborative Group. No impact of KIF6 genotype on vascular risk and statin response among 18,348 randomized patients in the Heart Protection Study. *J Am Coll Cardiol*. 2011;57:2000-7. http://www.sciencedirect.com/science/article/pii/S0735109711007261. Accessed May 28, 2015.

[81] Shiffman D, Chasman DI, Zee RY, et al. A kinesin family member 6 variant is associated with coronary heart disease in the Women's Health Study. *J Am Coll Cardiol*. 2008;51:444-8.

[82] Morrison AC, Bare LA, Chambless LE, et al. Prediction of coronary heart disease risk using a genetic risk score: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2007;166:28-35.
[83] Shifman D, Sabatine MS, Louie JZ, et al. Effect of pravastatin therapy on coronary events in carriers of the KIF6 719Arg allele from the cholesterol and recurrent events trial. *Am J Cardiol*. 2010;105:1300-5.
[84] Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333(20):1301-7.
[85] Iakoubova OA, Robertson M, Tong CH, et al. KIF6 Trp719Arg polymorphism and the effect of statin therapy in elderly patients: Results from the PROSPER study. *Eur J Cardiovasc Prev Rehabil*. 2010;17:455-61.
[86] Assimes TL, Holm H, Kathiresan S, et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and coronary artery disease in 19 case-control studies. *J Am Coll Cardiol*. 2010;56:1552-63. http://content.onlinejacc.org/cgi/content/abstract/j.jacc.2010.06.022v1. Accessed May 28, 2015.
[87] Iakoubova OA, Tong CH, Rowland CM, et al. Association of the TRP719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary heart disease in 2 prospective trials: the CARE and WOSCOPS trials. *J Am Coll Cardiol.* 2008;51:435-43.
[88] Iakoubova OA, Sabatine MS. Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE-IT-TIMI 22 study. *J Am Coll Cardiol*. 2008;51:449-55.
[89] Ridker PM, MacFadyen JG, Fonseca FA, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER). *Circ Cardiovasc Outcomes*. 2009;2(6):616-23.
[90] Topol EJ, Damani SB. The KIF6 collapse. Journal of the American College of Cardiology 2010;56:1564-6.
[91] GenomeWeb Daily News. FDA tells Celera KIF6 unapprovable without changes. April 21, 2011. https://www.genomeweb.com/dxpgx/fda-tells-celera-kif6-test-unapprovable-without-changes. Accessed December 1, 2014.
[92] Quest Diagnostics. KIF6 Genotype Test. (No month) 2014. http://www.bhlinc.com/clinicians/test-descriptions/KIF6. Accessed December 1, 2014.
[93] Caris Life Sciences International. Caris Molecular Intelligence. October 2014. http://www.carislifesciences.com/oncology-molecular-intelligence. Accessed December 1, 2014.
[94] Von Hoff D, Stephenson JJ, Rosen P, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *Journal Clin Oncol*. 2010;28(33):4877-83.
[95] Garber K. Ready or not: personal tumor profiling tests take off. *J Natl Cancer Inst*. 2011;103(2): 84-6.
[96] Doroshow JH. Selecting systemic cancer therapy one patient at a time: Is there a role for molecular profiling of individual patients with advanced solid tumors? *J Clin Oncol.* 2010;28(33):4869-71.
[97] National Cancer Institute. Surveillance, Epidemiology and End Results Program (SEER). SEER Stat Fact Sheets: Prostate Cancer. 2014. http://seer.cancer.gov/statfacts/html/prost.html. Accessed December 16, 2014.
[98] Rettner R. Prostate cancer: can new test reduce unnecessary treatment? May 31, 2013. http://www.livescience.com/37027-prostate-cancer-genetic-tests.html. Accessed December 1, 2014.
[99] Prolaris. 2014. http://www.prolaris.com/. Accessed December 1, 2014.
[100] Global NewsWire. Prolaris test predicts mortality risk in prostate cancer biopsy study. May 20, 2014. http://investor.myriad.com/releasedetail.cfm?releaseid=848939. Accessed December 1, 2014.
[101] Crawford ED, Scholz MC, Kar AJ, et al. Cell cycle progression score and treatment decisions in prostate cancer: results from an ongoing registry. *Current Medical Research & Opinion*. 2014;30(6):1025-31.
[102] Azad A, Tran B, Sengupta S, Lawrentschuk N. Gene expression profiling of localized prostate cancer: Getting answers to the questions that really matter. *Journal of Clinical Oncology*. 2013;31(26):3295-6.
[103] Lombardi VC, Ruscetti FW, Gupta JD, et al. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science*. 2009;326(5952):585-9.
[104] VIPDx, a laboratory associated with the authors of the initial study, offered its LDT for $400 per test. http://phoenixrising.me/research-2/the-pathogens-in-chronic-fatigue-syndrome-mecfs/xmrv/xmrv-testing. Accessed November 12, 2014.

[105] Cooperative Diagnostics offered its LDT for $400 per test. http://www.fibromyalgia-symptoms.org/xmrv-virus.html. Accessed November 12, 2014.
[106] Clongen offered its LDT for $375. http://forums.phoenixrising.me/index.php?threads/clongen-lab-xmrv-test.1813/ Accessed November 12, 2014.
[107] Lo SC, Pripuzova N, Li B, et al. Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors. *Proc Natl Acad Sci*. 2010;107(36):15874-9.
[108]Cooperative Diagnostics. Flaws in Mouse Virus Link to Chronic Fatigue Syndrome Known Before Blood Ban, States Cooperative Diagnostics. http://www.marketwired.com/press-release/flaws-mouse-virus-link-chronic-fatigue-syndrome-known-before-blood-ban-states-cooperative-1521452.htm. Accessed November 12, 2014.
[109] Stein R. Red Cross bars chronic fatigue patients from donating blood. *The Washington Post*. December 3, 2010. http://voices.washingtonpost.com/checkup/2010/12/red_cross_bars_chronic_fatique.html. Accessed November 12, 2014.
[110] (No Author). Living with chronic fatigue syndrome. December 4, 2010. http://livingwithchronicfatiguesyndrome.wordpress.com/2010/12/04/the-us-announces-cfs-patient-blood-donation-ban/. Accessed November 12, 2014.
[111] Lakham K. Cooperative Diagnostics pulls XMRV molecular test from clinical market. April 5, 2010. http://sacfs.asn.au/news//2010/04/04_10_cooperative_diagnostics_pulls_xmrv_molecular_test.htm. Accessed June 8, 2015.
[112] Switzer W, Jia H, Hohn O. Absence of evidence of xenotropic murine leukemia virus-related virus infection in persons with chronic fatigue syndrome and healthy controls in the United States. *Retrovirology*. 2010;7:57.
[113] Shin CH, Bateman L, Schlaberg R, et al. Absence of XMRV and other MLV-related viruses in patients with Chronic Fatigue Syndrome. *Journal of Virology*. 2011;85(14):7195-202.
[114] Simmons G, Glynn SA, Komaroff AL, et al. for the Blood XMRV Scientific research working group. Failure to confirm XMRV/MLVs in the blood of patients with chronic fatigue syndrome: a multi-laboratory study. *Science*. 2011;332:814-7.
[115] Wren K. Science: More doubts on the XMRV-Chronic Fatigue connection. AAAS News. September 22, 2011. http://www.aaas.org/news/science-more-doubts-xmrv-chronic-fatigue-connection. Accessed December 1, 2014.
[116] Alberts B. Retraction of Lombardi et al. *Science*. 2011;334(6063):1636.
[117] ScienceDaily. Chronic fatigue syndrome not related to XMRV retrovirus, comprehensive study finds. May 4, 2011. www.sciencedaily.com/releases/2011/05/110504151337.htm. Accessed November 21, 2014.
[118] Reust CE. Common adverse effects of antiretroviral therapy for HIV disease. *Am Fam Physician*. 2011;83(12):1443-51.
[119] Centers for Disease Control and Prevention. Autism Spectrum Disorder. March 2014. http://www.cdc.gov/ncbddd/autism/signs.html. Accessed December 1, 2014.
[120] Myers SM, Johnson CP, the Council on Children with Disabilities. From the American Academy of Pediatrics: Management of children with autism spectrum disorders. *Pediatrics*.2007;120(5):1162-82. http://pediatrics.aappublications.org/content/120/5/1162.full. Accessed May 28, 2015.
[121] Barrett S. The rise and fall of CARE Clinics and the Center for Autistic Spectrum Disorders (CASD). Autism Watch. January 3, 2013. http://www.autism-watch.org/reports/casd/overview.shtml. Accessed December 1, 2014.
[122] U.S. Food and Drug Administration. FDA issues warnings to marketers of unapproved "chelation" products. October 14, 2010. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229320.htm. Accessed December 1, 2014.
[123] Croen LA, Najjar DV, Ray T, Lotspeich L, Bernal P. A comparison of health care utilization and costs of children with and without autism spectrum disorders in a large group-model health plan. *Pediatrics*. 2006;118:e1203-e1211.
[124] Montes G, Halterman JS. Association of childhood autism spectrum disorders and loss of family income. Pediatrics. 2008;821-6.
[125] Michigan CR. Financing Special Education: Analyses and Challenges. March 2012. Livonia, MI. http://maase.org/Files/CRC_Financing_SE_March_2012_rpt378.pdf. Accessed May 26, 2015.

[126] Warniment C, Tsang K, Galazka SS. Lead poisoning in children. *American Family Physician*. 2010;81(6):751-7. http://www.aafp.org/afp/2010/0315/p751.html. Accessed May 28, 2015.
[127] World Health Organization. Elemental Mercury and Inorganic Mercury Compounds: Human Health Aspects. Geneva, 2003. http://www.who.int/ipcs/publications/cicad/en/cicad50.pdf. Accessed December 1, 2014.
[128] Kathuria P, Rowden AK, O'Malley RN. Lead Toxicity. *Medscape*. January 28, 2014. http://emedicine.medscape.com/article/1174752-overview. Accessed December 1, 2014.
[129] Centers for Disease Control and Prevention. Case definition: mercury (organic). May 2013. http://emergency.cdc.gov/agent/mercury/mercorgcasedef.asp. Accessed December 1, 2014.
[130] Centers for Disease Control and Prevention. Case definition: mercury (inorganic). May 2013. http://emergency.cdc.gov/agent/mercury/mercinorgcasedef.asp. Accessed December 1, 2014.
[131] Centers for Disease Control and Prevention. Managing elevated blood lead levels among young children: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. March 2002. http://www.cdc.gov/nceh/lead/CaseManagement/caseManage_main.htm. Accessed December 17, 2014.
[132] Oregon Public Health Division Office of Environmental Public Health. Heavy metals and your health: frequently asked questions about testing, treatment and prevention. https://public.health.oregon.gov/HealthyEnvironments/HealthyNeighborhoods/LeadPoisoning/MedicalProvidersLaboratories/Documents/HeavyMetals.pdf. Accessed December 1, 2014.
[133] Ruha AM. Recommendations for provoked challenge urine testing. *J Med Toxicol*. 2013;9(4):318-25. http://www.ncbi.nlm.nih.gov/pubmed/24113861. Accessed May 28, 2015.
[134] Brown MJ, Willis T, Omalu B, Leiker R. Deaths resulting from hypocalcemia after administration of edetate disodium: 2003-2005. *Pediatrics*. 2006;188(2)e534-6.
[135] ChemGenex Pharmaceuticals, Inc. FDA Briefing Book: Oncology Drugs Advisory Committee Meeting, NDA 22-374 Omapro™. February 10, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM204345.pdf. Accessed November 12, 2014.
[136] U.S. Food and Drug Administration. Summary Minutes of the Oncologic Drugs Advisory Committee. March 22, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM207638.pdf. Accessed December 9, 2014.
[137] Teva Pharmaceutical Industries Ltd. Press Release: Teva receives approval for SYNRIBOTM (Omapro Mepesuccinate) for injection. Reuters. October 26, 2012. http://www.reuters.com/article/2012/10/26/idUS161284+26-Oct-2012+BW20121026. Accessed July 3, 2015.
[138] Teva Pharmaceutical Industries Ltd. Synribo is intended to be used in patients whose cancer has progressed, despite treatment with at least two tyrosine kinase inhibitors. http://www.tevapharm.com/Media/News/Pages/2012/1750668.aspx. Accessed November 24, 2014.
[139] U.S. Food and Drug Administration. Press Release. Omacetaxine Mepesuccinate October 2012. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm325990.htm. Accessed November 20, 2014.
[140] Potti A, Dressman HK, Bild A, et al. Genomic signatures to guide the use of chemotherapeutics. *Nature Medicine*. 2006;12:1294-1300. (Retracted January 2011)
[141] Kolata G. How bright promise in cancer testing fell apart. *The New York* Times. July 7, 2011. http://www.nytimes.com/2011/07/08/health/research/08genes.html. Accessed December 1, 2014.
[142] Coombes KR, Wang J, Baggerly KA. Supplementary Reports 0-9. *Nature Med*. 2007;13:1276-77. http://www.nature.com/nm/journal/v13/n11/suppinfo/nm1107-1276b_S1.html. Accessed December 1, 2014.
[143] Coombes KR, Wang J, Baggerly KA. Microarrays: retracing steps. *Nat Med*. 2007;13:1276-77. http://www.nature.com/nm/journal/v13/n11/full/nm1107-1276b.html. Accessed December 1, 2014.
[144] Baggerly K, Coombes K. Deriving chemosensitivity from cell lines: Forensic bioinformatics and reproducible research in high-throughput biology. *Annals of Applied Statistics*. 2009;3(4):1309-34.
[145] Institute of Medicine. Evolution of Translational Omics: Lessons Learned and the Path Forward. The National Academies Press (US). 2012. http://www.nap.edu/catalog/13297/evolution-of-translational-omics-lessons-learned-and-the-path-forward. Accessed December 1, 2014.

[146] Institute of Medicine. Evolution of Translational Omics: Lessons Learned and the Path Forward. Section 3, page 67-8. The National Academies Press (US). 2012. http://www.nap.edu/catalog/13297/evolution-of-translational-omics-lessons-learned-and-the-path-forward. Accessed December 1, 2014.
[147] 80 Federal Register 69230. November 9, 2015.
[148] Shanmugalingam T, Crawley D, Bosco C, et al. Obesity and cancer: The role of vitamin D. *BMC Cancer*. 2014;14:712.
[149] Welles CC, Whooley MA, Karumanchi SA, et al. Vitamin D deficiency and cardiovascular events in patients with coronary heart disease: data from the Heart and Soul Study. *Am J Epidemiol*. 2014;179(11):1279-87.
[150] Pollack A. Quest acknowledges errors in Vitamin D tests. *The New York Times*. January 7, 2009. http://www.nytimes.com/2009/01/08/business/08labtest.html?_r=0. Accessed December 1, 2014.
[151] Mayo Clinic. What is vitamin D toxicity, and should I worry about it since I take supplements? http://www.mayoclinic.org/healthy-living/nutrition-and-healthy-eating/expert-answers/vitamin-d-toxicity/faq-20058108. Accessed December 1, 2014.
[152] Quest Diagnostics Insight Newsletter. New video and web site highlight the importance of vitamin D testing. July 2009. http://www.examone.com/news-media/insight-newsletter/insight-newsletter-july-1-2009. Accessed December 1, 2014.
[153] GL Group. Quest notifies clients of inaccurate vitamin D tests. January 20, 2009. http://www.investorvillage.com/mbthread.asp?mb=10853&tid=6510198&showall=1. Accessed December 1, 2014.
[154] SEER Cancer Statistics Factsheets: Breast Cancer. National Cancer Institute. Bethesda, MD. November 25, 2014. http://www.cancer.gov/cancertopics/pdq/treatment/breast/Patient#_136. Accessed December 18, 2014.
[155] Aston CE, Ralph DA, Lalo DP, et al. Oligogenic combinations associated with breast cancer risk in women under 53 years of age. *Hum Genet.* 2005; 116(3):208-21.
[156] Pharoah PD, Antoniou AC, Easton DF, et al. Polygenes, risk prediction, and targeted prevention of breast cancer. *N Engl J Med*. 2008;358(26):2796-803.
[157]Progressive Medical Enterprises LLC. OncoVue (R) for Women. 2012. http://progressivemedical.org/oncovue%C2%AE-for-women. Accessed December 1, 2014.
[158] Dalessandri KM, Miike R, Wrensch MR. Validation of OncoVue, a new individualized breast cancer risk estimator in the Marin County, California adolescent risk study. 2008 San Antonio Breast Cancer Symposium; Texas, U.S.A. Abstract 502.
[159] Dalessandri KM, Miike R, Wrensch MR. Breast cancer risk assessment in the high risk Marin County population using OncoVue compared to SNPs from genome wide association studies. 2009 San Antonio Breast Cancer Symposium; Texas, U.S.A. Abstract 3057.
[160] Premera. Medical policy: Use of common genetic variants (single nucleotide polymorphisms) to predict risk of non-familial breast cancer. June 9, 2014. https://www.premera.com/medicalpolicies/cmi_126901.htm. Accessed December 1, 2014.
[161] Reeves GK, Travis RC, Green J, et al. Incidence of breast cancer and its subtypes in relation to individual and multiple low-penetrance genetic susceptibility loci. *JAMA*. 2010;304(4):426-34.
[162] Peres J. Experts question new DNA test for breast cancer risk. *Chicago Tribune*. October 22, 2006. http://articles.chicagotribune.com/2006-10-22/news/0610220424_1_oncovue-breast-cancer-tamoxifen. Accessed December 1, 2014.
[163] Genentech. BRAF in metastatic melanoma. 2014. http://www.biooncology.com/research-education/braf/metastatic-melanoma. Accessed December 1, 2014.
[164] Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. *J Translat Med*. 2012;10:85.
[165] Genentech. Vemurafenib (Zelboraf) drug label. October 25, 2013. https://www.pharmgkb.org/download.do?objCls=Attachment&objId=Vemurafenib_10_17_13.pdf. Accessed December 1, 2014.
[166] U.S. Food and Drug Administration. Medical Devices: Cobas 4800 BRAF V600 Mutation Test. August 17, 2011. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm268836.htm. Accessed December 1, 2014.

[167] NeoGenomics Laboratories. BRAF V600E, K, & D Mutations: Identify 10-15% more patients who may respond to vemurafenib. 2014. http://www.neogenomics.com/braf-v600e-melanoma.htm. Accessed December 1, 2014.
[168] Molecular Response. BRAF V600E Mutation Test. 2014. http://molecularresponse.com/braf/. Accessed December 1, 2014.
[169] Ray T. Quest study finds Sanger-based BRAFT mutation test more sensitive than Roche's Cobas test. GenomeWeb. June 13, 2012. https://www.genomeweb.com/mdx/quest-study-finds-sanger-based-braf-mutation-test-more-sensitive-roches-cobas-te. Accessed December 18, 2014.