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December 2, 2023

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

Subject: Docket No. FDA–2023–N–2177 for “Medical Devices; Laboratory Developed Tests

Submitted electronically via www.regulations.gov

Dear Commissioner Califf:

The Association for Molecular Pathology (AMP) appreciates the opportunity to provide comments on the Food and Drug Administration’s (FDA) proposed rule on “Medical Devices; Laboratory Developed Tests” (Docket No. FDA–2023–N–2177), which we believe would drastically alter the regulation of laboratory testing services and harm the professional services provided by our members and thus, clinical care. AMP is an international medical and professional association representing approximately 2,900 physicians, doctoral scientists, and medical laboratory scientists (technologists) who perform and/or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from the government, academic medicine, private, community, and hospital-based clinical laboratories, and the *in vitro* diagnostics industry.

To reflect that “LDTs” are medical professional services, AMP refers to them as laboratory developed testing procedures or LDPs. However, for the purposes of these comments, we will refer to these vitally important laboratory services as “LDTs” to reflect the terminology used in the proposed rule. AMP maintains that all LDTs should be accurate, precise, and used in a clinically appropriate manner. However, AMP strongly opposes FDA’s proposal to regulate these testing services as medical devices. As detailed in our comments below, FDA’s proposed changes to the definition of an *in vitro* diagnostic product, and its plan to end what the Agency refers to as “enforcement discretion”, would result in laboratory professionals being treated as manufacturers. The treatment of laboratory professionals as product manufacturers, instead of board-certified healthcare providers who develop and rigorously ensure the analytic validity of their LDTs, and who interpret their results within the context of available patient clinical information and other relevant test results, is not only inappropriate and unjustified, but will unequivocally hinder and harm patient care. We offer these comments to refute the basis by which FDA has issued the proposed rule and draw attention to the proposed rule’s unaccounted and/or unappreciated harms that would ensue if FDA were to regulate LDTs as medical devices.¹

¹ In filing comments on this proposed rule, AMP does not waive any legal claim that the FDA lacks the statutory authority to regulate laboratory developed testing procedures. Nothing in these comments is

AMP strongly urges FDA to rescind the proposed rule and instead defer to Congress to establish a streamlined, flexible, and cost-effective pathway forward for updating laboratory testing requirements in a way that continues to protect patients and supports innovation.

Section I: Laboratory Developed Testing Procedures are Not Medical Devices

LDTs are medical services legally provided by board-certified specialist physicians, geneticists, and other doctoral-level laboratory professionals who apply their professional, scientific, and medical knowledge to optimize patient care. With regards to our membership, molecular pathology professionals are qualified to offer these services because they have completed extensive post-graduate education and clinical training, taken board-certification examinations administered by the American Board of Pathology or the American Board of Medical Genetics and Genomics under the umbrella of the Accreditation Council for Graduate Medical Education, or other recognized professional boards under the Clinical Laboratory Improvement Amendments (CLIA, e.g., American Board of Medical Microbiology). They continuously update their scientific knowledge and maintain their certification as required and they insure their professional practice activities with medical malpractice insurance. FDA has failed to account for the role of the appropriately qualified professional in every aspect of the design, performance, and expert interpretation of an LDT and inappropriately categorizes their work as expert healthcare providers as “manufacturing” a device. While these professionals carry out their work in clinical laboratory facilities, it is the professionals themselves who perform the LDT. In fact, the role of an appropriately qualified individual is required by law. LDTs are categorized as high-complexity tests under the implementing regulations of the Clinical Laboratory Improvement Amendments (CLIA) and thus, any CLIA-certified laboratory offering LDTs must have a laboratory director who meets the qualification requirements under 42 CFR § 493.1443. These licensed professionals are ultimately responsible for all processes and procedures of the laboratory, including LDTs.

It is the role of the professional providing the service in a single clinical laboratory that is a defining difference from *in vitro* diagnostic (IVD) test kits which are commercially manufactured, packaged, and sold for use by others in any institution across the country. LDTs are not physical products but rather an all-encompassing approach using tools and knowledge to provide clinical information to physicians and their patients. AMP maintains that LDTs are within the practice of medicine and not within FDA’s jurisdiction to regulate as medical devices. Indeed, legal experts Clement and Tribe (2015) have argued that LDTs are medical services and not subject to medical device regulations as well.²

Moreover, legal uncertainty regarding FDA’s authority to regulate LDTs has been described by the former General Counsel to the Department of Health and Human Services who said that “policymakers may wish to consider whether [the Centers for Medicare and Medicaid Services

intended to impact adversely in any way AMP’s right, alone or in combination with other stakeholders, to pursue separate comments, litigation, or other remedies with respect to the proposed rule or related issues.

² Clement P.D. & Tribe, L.H. 2015. Laboratory Testing Services, As the Practice of Medicine, Cannot be Regulated as Medical Devices. Counsel to the Am. Clinical Laboratory Ass’n. <http://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf>

(CMS)]... is better suited legally and logistically to regulate LDTs”.³ AMP believes that CMS is best positioned to holistically oversee laboratories, personnel, and LDTs, which are inextricably linked. Further, we believe updating CLIA to be the most streamlined, flexible, and cost-effective pathway forward for modernizing laboratory testing requirements in a way that protects patients and supports innovation. Any attempt by the FDA to regulate LDTs otherwise would be inconsistent with CLIA and the implementing regulations and exceeds FDA’s statutory authority.

Section II: The Proposed Rule Will Harm Laboratory Medicine and Lead to Barriers for Patient Access

The diversity of laboratories in the United States is an enormous strength, and each type of laboratory uniquely contributes to our healthcare system, its ability to provide care for patients meeting a diverse set of needs. Community and hospital clinical laboratories are optimally positioned to meet the testing capacity needs in their local area due to their physical proximity to patients. For example, hospital-based molecular professionals provide direct input to tumor boards and other complex patient discussions involving molecular testing results that guide patient care. Additionally, community and hospital clinical laboratories are often more likely to provide the faster turnaround times necessary to manage the critical requirements of patients who need immediate care. Commercial reference laboratories can streamline laboratory processes and are often able to perform higher volumes of tests; however, their services are not always provided with the personalization and medical-system integration afforded by local care. Public health laboratories are essential to the surveillance of pathogens and focus on diseases and the health status of population groups.

The strength of this vibrant laboratory community was undeniable during the COVID-19 pandemic, as it worked to ensure that the country had sufficient testing capacity and that laboratories could adapt to vast supply chain interruptions impacting the availability of testing platforms, testing kits, reagents, swabs, viral transport medium, laboratory consumables, and personal protective equipment. Even outside of a global health emergency, laboratories have unique expertise in testing for specific types of diseases or technologies. A number of laboratories provide care in rural areas or certain regions with high numbers of patients in underserved populations. Others are improving and streamlining to reduce the cost of laboratory testing to broaden access. Moreover, as we recover from the last two public health emergencies, some laboratories are committed to monitoring for future biothreats.

However, if the proposed rule is finalized, the significant increase in regulatory costs required to provide clinical laboratory services would decimate the laboratory community, leading to closures, reduced testing menus, etc. all to the detriment of patient care. For instance, data in FDA’s accompanying impact analysis⁴ makes it abundantly clear that laboratories without high revenues would be unable to shoulder the costs associated with compliance with the medical device regulations. The summarized information in the impact analysis appears to mask the impact of the costs of compliance by stretching those costs over a 20-year period. In contrast, most of the costs incurred on laboratories would be during the four years associated with FDA’s phaseout policy, and upon further analysis, the FDA’s data reveals that the one-time cost for

³ Charrow, R. 2020. Memorandum to the Commissioner of Food and Drugs on Federal Authority to Regulate Laboratory Developed Tests. <https://www.thefdalawblog.com/wp-content/uploads/2021/11/HHS-Legal-Memo-on-LDTs-by-Charrow-00864663.pdf>

⁴ <https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/laboratory-developed-tests-regulatory-impact-analysis-proposed-rule>

this four-year period per laboratory is estimated to be \$29.6 million.⁵ This does not include the cost of user fees. The laboratory community will struggle to absorb these exorbitant costs, even more so considering that AMP believes the FDA likely dramatically miscalculated the scope and scale of these costs, as explained in detail below in Section IV of our comments.

Specifically, the FDA states that 90% of the assumed 1,200 laboratories impacted by the proposed rule are small businesses⁶, and over the four-year phaseout period, those entities' revenue is only approximately \$19.5 million each, on average.⁷ Thus, the cost of compliance is far beyond the financial capabilities of small businesses throughout the United States, forcing them to make difficult financial, not medical-based, decisions to stop offering tests or close their laboratories altogether. This will severely disrupt localized care, delay turnaround times, drive up costs directly by reducing competition, inhibit the ability of healthcare teams to adapt testing that best meets their patients' needs, and dramatically impair efforts toward quality improvement and innovation. While FDA notes in the proposed rule that it would be the "choice" of the laboratory to not invest resources to meet medical device requirements, it is not a choice. It is simply not financially possible.

The impact will also be felt by some of this country's most prestigious institutions where many LDTs support their innovative approaches to provide care for a range of diseases and conditions and patient populations. For instance, Dr. David Klimstra, former Chair of Pathology at Memorial Sloan Kettering Cancer Center, stated at a Senate Health, Education, Labor, and Pensions Committee hearing in 2016 that if the institution was required to submit their 350 LDTs for FDA approval, there would be no way the institution could afford the cost associated with formal FDA review.⁸ In fact, in response to a question from the Chair of the Committee, he testified that he would close their laboratory. Indeed, using the costs approximated in the impact analysis for FDA review, this institution's estimated one-time cost of compliance over the phaseout period would be an astronomical \$140 million and this is in addition to the resources already devoted to compliance with CLIA, and the New York State Department of Health requirements. The proposed phaseout would require a significant investment of time and resources that would extensively disrupt an institution's ability to maintain its current services, training, research, and clinical care provided to patients. This is not a unique example, but rather one that exemplifies the reality that the proposed rule will make it financially untenable for clinical laboratories, including some of the most innovative in the country, to continue their work.

In the proposed rule, FDA acknowledges that there will be some test and laboratory consolidation and in fact, seems to support eliminating business models that the Agency views as undesirable. Setting aside that influencing market competition is outside the purview of the FDA's mission, the proposed rule fails to address the consequences associated with the subsequent elimination of education and training opportunities for the next generation of clinical laboratorians. If academic medical centers have no choice but to outsource clinical testing if the rule is finalized, there will be limited ability for the future of our workforce to be trained in areas that are vitally important to personalized medicine. The Government Accountability Office (GAO) found the molecular workforce to be quite limited with only approximately 4,700 genetic counselors and 1,240 medical geneticists certified to provide care in the United States in 2020.⁹

⁵ Calculated using data from Table 31 of FDA's impact analysis and FDA's assumption that 1,200 entities will be impacted by the proposed rule.

⁶ See page 110 of FDA's impact analysis.

⁷ Calculated using data from Table 42 of the impact analysis.

⁸ <https://www.govinfo.gov/content/pkg/CHRG-114shrg21906/pdf/CHRG-114shrg21906.pdf>

⁹ <https://www.gao.gov/products/gao-20-593>

Further, these professionals tend to be located near academic medical centers which means there is already limited access to genetics specialists in rural areas. On average, the GAO reports only seven genetic counselors for every 500,000 people and only two medical geneticists per every 500,000 people. To address the looming 20% retirement rate in laboratory personnel, plus the current 13% vacancy rate, over 25 professional organizations formed the Medical and Public Health Laboratory Workforce Coalition this year.¹⁰ Policymakers need to invest in expanding the molecular pathology workforce to meet the demands of our healthcare system which will only grow as precision medicine utilization increases, not implement rules that will reduce training opportunities for these professionals.

Further, the market does not typically result in tests that are developed to allow for efficient care delivery. In contrast, health management organizations with large laboratories leverage laboratory efficiency by consolidating workflows and/or leverage economies of scale to improve the cost-effectiveness of healthcare. LDTs are often implemented in these because the broader economics of healthcare and diagnostics do not provide a market-based solution that takes advantage of the opportunities in an integrated system. Further, within these systems, the integration of laboratory professionals into coordinated care within a health system provides important feedback throughout the system regarding appropriate test utilization, interpretation, follow-up, and global quality improvement. If the proposed rule is finalized, many of these tests will ultimately be outsourced, interfering with patient care even in large health systems.

These are just a few examples of how the immediate and long-term consequences of complying with the proposed rule would decimate the clinical laboratory community, disrupt patient care, and restrict training opportunities. While the effects will be felt in every region of the United States, AMP is especially concerned about the impacts on underserved populations and areas. We find the proposed rule runs counter to the priorities of this Administration to “pursue a comprehensive approach to advancing equity for all, including people of color and others who have been historically underserved, marginalized, and adversely affected by persistent poverty and inequality” as articulated in Executive Order 13985.¹¹ Small laboratories serving these important regions would likely disappear. The number of LDTs at academic medical centers serving as reference testing sites for remote locations would also likely be diminished. Regions that are underserved, currently lack sufficient molecular expertise to care for the populations in those areas, and if the proposed rule were to be finalized, existing disparities will be exacerbated.¹² There is added complexity considering that states have their own requirements regarding in-state versus out-of-state testing and the proposed rule would jeopardize access if laboratories, tests, and the number of professionals in a state were diminished and state requirements could not be met.

We are also concerned about the impact on the pediatric population as many FDA-authorized tests are only intended for adult populations or the specimens that are authorized for use with the test are not the types that are commonly used in children (e.g., gastric aspirates for nucleic acid amplification tests for use in pediatric patients suspected of having tuberculosis¹³). Further, as noted in our comments, we already have extensive workforce challenges in laboratory medicine, especially in certain geographic regions, and the proposed rule would only further

¹⁰ <https://www.mphlcoalition.org/>

¹¹ <https://www.federalregister.gov/documents/2021/01/25/2021-01753/advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government>

¹² Zhou Y. Realizing the Dream of Precision Oncology: A Solution for All Patients. *J Mol Diagn*. 2023;25(12):851-856. doi:10.1016/j.jmoldx.2023.09.001

¹³ See Amplified Mycobacterium Tuberculosis Direct (MTD) Test and Xpert MTB/RIF Assay as examples.

intensify the existing inequalities. It is negligent of the FDA to conclude that any impacts resulting in the closing of laboratories and the reduction in the availability of LDTs in rural and underserved communities is an acceptable exchange for finalizing the policy within this rulemaking, as it does on page 68,013 of the Federal Register publication of the proposed rule.¹⁴ AMP does not find this impact on patient care, especially in rural and underserved communities, to be acceptable.

To some extent, FDA has acknowledged the effect of these burdens by proposing various patchwork solutions. FDA requests comments on whether a longer phaseout period should be extended to small laboratories to defray costs. In particular, FDA evaluated phasing out enforcement discretion over a 10-year period for smaller laboratories and concluded it would “reduce the burden on the affected laboratories by shifting costs into the future.” AMP agrees that special consideration is needed to ensure that laboratory diversity and our workforce are preserved, but delaying costs are nothing more than a shift in time – the costs remain the same and a delay does not prevent the severe impacts on the laboratory community. Further, FDA does not account for the fact that some laboratories with less revenue are associated with large hospital systems that may not meet the definition of a small business and thus, would not be afforded the option of a longer phaseout period.

In addition, FDA asks for feedback on a possible exemption for academic medical centers, but this ignores the equally detrimental effects on healthcare institutions that would not qualify as academic centers. Moreover, the proposed definition fails to meaningfully give these institutions the ability to provide necessary care to patients because it would require patient care, specimen collection, and testing to all occur at the same physical location. This is unreasonable as an academic medical center may encompass several physical buildings on one campus or several physical buildings across local or regional campuses that are part of the same academic institution.

Last, while the idea of grandfathering existing LDTs would reduce costs to laboratories during the phaseout period, laboratories would be unable to make necessary updates and modifications to the test, meaning those tests would be frozen in time unless the laboratories could bear the cost of each FDA review. Because of the costs associated with FDA review and supplementals, the proposed rule creates a strong disincentive to modifying LDTs to provide the most up-to-date, clinically relevant information to patients. The pace of innovation in laboratory medicine is rapid with new insights being gleaned every day and its rapid incorporation into clinical care is exemplified by how often professional guidelines related to genetic testing are updated (e.g., NCCN Clinical Practice Guidelines in Oncology). Under the proposed rule, it is likely that necessary updates to tests would not be readily made. Again, these solutions merely delay the proposed rule’s negative impact on laboratories but do not prevent decreased test access, medically out-of-date LDTs, increased costs, increased time to result, laboratory consolidation, diminished innovation, and patient harm.

Section III: FDA Did Not Fully Comply with the Unfunded Mandates Reform Act

¹⁴ <https://www.govinfo.gov/content/pkg/FR-2023-10-03/pdf/2023-21662.pdf>

As specified by the Unfunded Mandates Reform Act, FDA is required to identify and consider a reasonable number of regulatory alternatives and, from those alternatives, select the least costly, most cost-effective, or least burdensome option that achieves the objectives of the rule. Despite FDA acknowledging that there are harms to the laboratory community, and thus to patient access to care, and offering other regulatory approaches in its impact analysis, the Agency did not select the approach that is least burdensome. While the alternatives posed by FDA would still inappropriately regulate LDTs as medical devices, numerous other options are less burdensome and costly to both laboratories and the Agency. Additionally, improvements to the CLIA program, and how FDA might work cooperatively with CMS to implement a modernized approach to CLIA requirements, was not considered. AMP is disappointed that FDA continues to dismiss this approach and its obligations to work with CMS and the Centers for Disease Control and Prevention (CDC) to best implement the CLIA program. The lack of a CLIA-centric approach is a significant and glaring gap in the proposed rule. AMP agrees that LDTs should be precise, accurate, and meaningfully support patient care, which is why AMP is strongly supportive of robust and modernized CLIA regulations. This program has been tremendously successful since its implementation and it continues to be the foundation for ensuring the quality of laboratories, their personnel, and the services they provide. Rather than building from an existing laboratory regulatory framework, the FDA is proposing to impose additional and, in some respects, duplicative requirements on laboratories. Not only would this cause financial hardship but it would significantly, and pointedly, increase the administrative burden for laboratories and laboratory professionals.

CLIA and the FDA's medical device regulations do not complement each other; rather, CLIA functions to holistically regulate laboratory processes, personnel requirements, the validity of laboratory procedures, and ongoing proficiency testing to ensure that professionals working in clinical laboratories are properly caring for patients. Further, many of the medical device regulations do not translate well to laboratories because they are not manufacturers. Yet, FDA does not propose any changes to remedy how ill-suited the medical devices regulations are to laboratories and LDTs. We summarize our initial analysis of the medical device regulations that FDA proposed CLIA-certified laboratories offering LDTs would need to comply with in the table below.

FDA Regulation	Findings
Design controls under 21 CFR 820.30	<p>AMP's members found that this language does not translate well to laboratories and, the following CLIA regulations serve to ensure LDTs are properly developed:</p> <ul style="list-style-type: none"> ● 42 CFR 493.1241 Test request ● 42 CFR 493.1242 Specimen submission, handling, and referral. ● 42 CFR 493.1252 Test systems, equipment, instruments, reagents, materials, and supplies. ● 42 CFR 493.1253 Establishment and verification of performance specifications.

	<ul style="list-style-type: none"> ● 42 CFR 493.1290 Postanalytic systems. ● 42 CFR 493.1291 Test report.
<p>Purchasing controls (including supplier controls) under 21 CFR 820.50</p>	<p>Under CLIA, laboratories already must define criteria for those conditions that are essential for proper storage of reagents and specimens, accurate and reliable test system operation, and test result reporting. Additionally, professionals must not use reagents, solutions, culture media, control materials, calibration materials, and other supplies when they have exceeded their expiration date, have deteriorated, or are of substandard quality. 42 CFR § 493.1252</p> <p>However, the medical device regulations would expand the responsibility of the laboratory professional to re-verify the quality of any purchased components and materials. Compliance with these FDA medical device regulations would require significant increases in the resources and staff for laboratories. Additionally, FDA's requirement puts liability on laboratory professionals who are not manufacturers but rather, are acting as healthcare providers. The responsibility of ensuring the quality of reagents should be on the supplier.</p>
<p>Acceptance activities (receiving, in-process, and finished device acceptance) 21 CFR 820.80 and 21 CFR 820.86</p>	<p>Many of the FDA terms do not translate well to laboratories using LDTs. As an example, it is unclear how a laboratory might comply with the following: "Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria." Additionally, there is potential overlap with 42 CFR 493.1242 related to specimen submission, handling, and referral.</p>
<p>Corrective and preventative actions (CAPA) under 21 CFR 820.100</p>	<p>CMS requires that any clinical laboratory report patient test result errors to the authorized person ordering the test, maintain a record of those errors, ensure that all complaints and problems reported to the laboratory are documented, conduct investigations of complaints when appropriate, and issue a corrected report. 42 CFR § 493.1291</p>

	<p>Per CLIA, the laboratory's quality systems must include a quality assessment component that ensures continuous improvement of the laboratory's performance and services through ongoing monitoring that identifies, evaluates, and resolves problems. 42 CFR § 493.1200</p> <p>Thus, the CLIA program already requires laboratories to address laboratory errors.</p>
<p>Records requirements under part 820, subpart M</p>	<p>Many of these requirements are analogous to the following:</p> <ul style="list-style-type: none"> ● 42 CFR § 493.1251 Procedure manual. ● 42 CFR § 493.1101 Facilities. ● 42 CFR § 493.1105 Retention requirements. ● 42 CFR § 493.1291 Test report. ● 42 CFR § 493.1283 Test records.
<p>Medical device reporting - 21 U.S.C. 360i(a) through (c) and 21 CFR part 803</p> <p>Correction and removal requirements - 21 U.S.C. 360i(g) and part 806 (21 CFR part 806)</p>	<p>As noted above, laboratories are already expected to comply with requirements associated with taking corrective actions. Additionally, CMS-approved accrediting organizations must notify CMS within 10 days of any deficiency identified in an accredited or CLIA-exempt laboratory if the deficiency poses an immediate jeopardy to the patient or a hazard to the general public. 42 CFR § 493.555</p> <p>It will be difficult for laboratory professionals to parse out what is an error due to the LDT versus an error associated with laboratory processes. As a result, essentially all adverse events will have to be additionally reported to FDA even if the laboratory eventually determines that the error was not due to what FDA considers the “device”.</p> <p>AMP continues to strongly advocate for enhancing laboratory error reporting requirements through a streamlined CLIA modernization approach. It is not necessary to enforce these medical device requirements onto CLIA-certified laboratories offering LDTs.</p>

AMP supports the use of third-party organizations in ensuring the quality of LDTs. In fact, their use is an existing hallmark feature of the CLIA program. Importantly, CLIA has always served as the floor for ensuring testing quality, and many third-party accreditation organizations and states

establish even more rigorous processes for verifying that laboratory tests are accurate and reliable. AMP applauds these efforts and believes that they should continue to act to hold laboratory professionals to high standards. Because of CLIA's ongoing success in using these third-party entities, it is unclear why FDA's involvement via the use of potentially the same third-party entities is required. Again, FDA's proposal adds complexity, duplication, and burden to a system that is already working well.

Section IV: FDA Lacks Resources and Expertise to Implement Proposed Rule

Given FDA's unjustified proposed plan to regulate all LDTs, it is understandable why the FDA might be concerned that the Agency does not have the expertise and resources to handle the additional workload and seeks to resort to the use of outside entities. The additional workload will not only be significantly burdensome and costly to laboratories, but the proposed rule will also be a tremendous burden to the FDA. To illustrate the increase in workload, a recent report released in November 2023 noted that there are approximately 175,000 distinct genetic tests in use for clinical care today in the areas of hereditary disease and oncology.¹⁵ Comparatively, FDA has only authorized approximately 140 human genetic tests to date¹⁶ indicating that FDA's current resources are not nearly sufficient to handle the influx. By FDA's own estimates, they are anticipating that more than 40,000 existing LDTs will need to be reviewed, and an additional 4,000 applications per year afterward. Given that others are reporting that there are 175,000 distinct genetic tests alone, not including infectious disease tests, FDA's approximation of the total number of LDTs that will be required to be reviewed under their medical device framework is concerning, incredibly low. Still, the increase in workload as demonstrated by FDA's flawed data is astronomical. Using data from table 4 of the impact analysis, the percent increase in PMA-related submissions would be 5,767%. For 510(k) premarket notifications, the percent increase would be 830%. And, for de novo classification requests, it would be a 6,091% increase. Even if FDA were to grandfather all existing LDTs, the increase in workload would still be significant, including that PMA-related submissions would increase by 558%.

Thus, the question is not simply whether our healthcare system can withstand the economic burden of the proposed rule, it is also whether the FDA is equipped to handle the increased workload. Well-documented evidence of FDA's limited abilities during the COVID-19 pandemic indicates that the Agency is not. According to an independent assessment, FDA received 3,672 COVID-19 IVD submissions to review between March 2020 and March 2021¹⁷ -- a similar number to the approximately 4,000 new LDTs that FDA would be expected to review per year. Yet, this number of submissions, for just COVID-19 testing, overwhelmed FDA and forced them to prioritize review and contributed to further delays. Not only did FDA fail to review applications related to COVID-19 in a timely manner, FDA announced during town halls that it was also indefinitely pausing the review of applications for non-COVID tests and medical devices during the emergency.

Further, many of our members experienced significant issues associated with the review of their emergency use authorization (EUA) applications for COVID-19 tests. One member shared via our August 2020 survey¹⁸ that FDA required many rounds of questions despite the laboratory

¹⁵ Concert Genetics, "Genetic Test Price Transparency Report." 2023. <http://www.concertgenetics.com/wp-content/uploads/2023/11/Concert-Genetics-2023-Genetic-Test-Price-Transparency-Report-07Nov2023.pdf>

¹⁶ <https://www.fda.gov/medical-devices/in-vitro-diagnostics/nucleic-acid-based-tests#human>

¹⁷ <https://www.fda.gov/media/152992/download>

¹⁸ <https://www.amp.org/advocacy/sars-cov-2-survey/>

only making minor modifications to other authorized assays. Other members shared that, at times, it took weeks for the FDA to even respond to a submission. Another member said that FDA officials were not familiar with the technology in their EUA submission. Members reported that they would comply with a request from FDA only for FDA to shift the goal post again and again. A number of requests were unreasonable; as an example, members were asked to ensure their tests were specific to SARS-CoV-2 and did not produce false results for Middle Eastern Respiratory Syndrome (MERS) despite the fact that it was nearly impossible to obtain MERS positive controls because of the way they are restricted and that MERS was not actively circulating in the United States. Two members from prestigious institutions and, highly regarded laboratories, shared just recently that they are still awaiting their EUA over three years later, despite both submitting their applications in April 2020. While an FDA official noted that out of the first 125 EUA requests reviewed, FDA identified that 66% of those tests had “major issues”¹⁹, we question FDA’s perspective of these “issues” given that our members reported unreasonable and unnecessary requests from the Agency during the emergency. In response to the testing challenges in the early weeks of the pandemic, the Department of Health and Human Services’ National Biodefense Science Board recently released recommendations based on lessons learned during the COVID-19 pandemic and called for an increased ability to use novel diagnostic tests in an epidemic or infectious disease emergency in part by allowing for “the use of laboratory developed testing procedures without employing duplicative regulatory requirements to better leverage the capacity of all types of clinical laboratories.”²⁰

Others have questioned FDA’s expertise regarding genomic technologies. For instance, authors of a publication regarding FDA oversight of research associated with the Newborn Sequencing In Genomic medicine and public Health (NSIGHT) Consortium found that “the transition from evaluating analytic validation to evaluating clinical genomic analyses proved to be a steep learning curve for several FDA reviewers, with clear evidence that the interaction with the NSIGHT groups provided a great deal of insight into this field.”²¹ The authors also experienced problems with FDA review team turnover which “resulted in the need for frequent re-education by the NSIGHT investigators.” Even FDA’s Chief of Staff recently acknowledged that FDA had about 2,000 vacancies to fill as of June 2023 and has challenges recruiting highly trained scientific, medical, and technical staff.²² Thus, AMP believes that for the most part, FDA is sorely understaffed and, if the proposed rule were finalized, FDA would greatly require many more appropriately qualified experts to verify the analytical and clinical validity of all LDTs.

We raise these issues because AMP is concerned about what the COVID-19 pandemic, as an important case study, means for the timely review of lifesaving LDTs in the future. Especially considering that FDA already misses its goals associated with the Medical Device User Fee Amendments (MDUFA) despite companies being required to pay significant fees for prompt FDA review. FDA says in its FY 2022 MDUFA Performance Report that “FDA’s response to the unprecedented COVID-19 public health emergency has impacted its MDUFA performance, resulting in four missed FY 2020 review goals, six missed FY 2021 review goals, and five

¹⁹ <https://www.regulations.gov/document/FDA-2023-N-2177-0121>

²⁰ <https://aspr.hhs.gov/AboutASPR/WorkingwithASPR/BoardsandCommittees/Documents/NBSB-Public-Mtg-Rec-COV19-Lessons-Learned-28Aug2023.pdf>

²¹ Milko LV, Chen F, Chan K, Brower AM, Agrawal PB, Beggs AH, Berg JS, Brenner SE, Holm IA, Koenig BA, Parad RB, Powell CM, Kingsmore SF. FDA oversight of NSIGHT genomic research: the need for an integrated systems approach to regulation. NPJ Genom Med. 2019 Dec 10;4:32. doi: 10.1038/s41525-019-0105-8. PMID: 31839987; PMCID: PMC6904743.

²² <https://www.raps.org/news-and-articles/news-articles/2023/6/fda-chief-of-staff-hiring-is-up,-but-so-are-resign>

missed FY 2022 review goals.”²³ Yet, FDA proposes to usher in the unprecedented workload associated with all LDTs.

Section V: FDA’s Inaccurate Claims about LDT Quality Are Irresponsible

All LDTs should be accurate, precise, clinically relevant, and monitored for continued quality performance, and patients should receive the most appropriate tests and procedures for their medical evaluation and/or clinical condition. It is unacceptable when LDTs do not meet these standards, and it is important that this country continues to have a federal regulatory approach that works toward ensuring that patients are appropriately and effectively cared for. In keeping these values in mind, we find that it is irresponsible of the FDA to make broad claims, asserting that LDTs are low quality and harm patients when, in fact, far beyond the vast majority of laboratory tests successfully contribute to the management of patient care. If there are any concerns about the quality of the majority of LDTs used for patient care, that information would be available based on information acquired by third-party accrediting organizations who must verify that CLIA standards are met, test the proficiency of laboratories at least on a biannual basis, and report to CMS when patients and/or the public are at immediate jeopardy as a result of a laboratory error.

Given the seriousness of the proposed rule’s policy change, it is very concerning that almost all of the evidence cited by the FDA is anecdotal and/or of poor quality. For example, FDA heavily relies upon an article published by Pfeifer and colleagues (2022) on a pilot study of reference samples and experimental *in silico* data to measure the performance of next generation sequencing LDTs among a cohort of clinical laboratories.²⁴ In particular, they evaluated testing of RAS mutations in colorectal cancer, which is recommended by the National Comprehensive Cancer Network (NCCN) for advanced or metastatic disease to determine eligibility for anti-EGFR therapy. The authors describe their findings as suggesting that LDTs do not perform as well as the FDA-authorized test, Praxis Extended RAS Panel CDx. However, upon further evaluation by another expert team²⁵, a plethora of issues and omissions in the Pfeifer et al. study indicate that the pilot-study data should not be the basis of any regulatory decision. Zehir and colleagues (2023) describe issues with the design of the study, which included instructions that led to laboratories not performing their tests as intended when it was validated. This led to missed opportunities for pre-testing evaluation that, in the normal course of testing patient samples in real-world settings, would have prevented the use of specimens that were at risk of false negative results. The study also used standardized samples with variant allele fractions (VAFs) that were lower than the intended limit of detection the LDTs’ were designed for. This impacts whether a variant is reported or not and skewed the results of the Pfeifer et al. publication. Laboratories were only allowed to report VAFs as whole numbers, leading to rounding of results, which contributed to the seemingly poor performance of LDTs. According to Zehir et al., this led to clerical errors that accounted for 12 of 13 errors for one of the laboratories included in the study. Moreover, the pilot samples greatly differed from those most often observed in patients with untreated colorectal cancer in terms of the expected allele

²³ <https://www.fda.gov/media/167825/download?attachment>

²⁴ Pfeifer JD, Loberg R, Lofton-Day C, Zehnbaauer BA. Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics. *Am J Clin Pathol*. 2022 Apr 1;157(4):628-638. doi: 10.1093/ajcp/aqab164. PMID: 34871357.

²⁵ 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.

fraction, indicating that the study was not properly designed to translate well in a real world. The pilot study also included a disproportionately high number of multinucleotide variants (MNVs), which are so rare that there are no examples of them in the American Association for Cancer Research (AACR) Genomics Evidence Neoplasia Information Exchange (GENIE) data set which includes over 14,000 colorectal carcinomas. The authors of the pilot describe how MNVs are so problematic that they end up being reported as individual and/or adjacent single-nucleotide variants (SNVs), but the real-world impact of this would be that a patient's results would still indicate that there is a strong clinical significance for therapeutic decisions.

When the data was reevaluated using well established proficiency testing methods, Zehir et al. found that the overall detection rates of *KRAS* and *NRAS* SNVs and MNVs by SPOT/Dx pilot laboratories were 96.8% (716 of 740) and 81.1% (129 of 159), respectively. Comparatively, in the College of American Pathology (CAP) proficiency testing programs, the overall detection rates for the same SNVs and MNVs were 97.2% (2671 of 2748) and 91.8% (1853 of 2019), respectively. Thus, contrary to the conclusions of Pfeifer et al., laboratory performance for *KRAS* and *NRAS* SNVs in the SpotDx study was excellent and agrees with larger longitudinal data. Additionally, while the variants are rare among cancer patients, the overall detection rate for 5 *KRAS* and *NRAS* MNVs was 97.3% (1161 of 1193) in 2022. While LDTs do perform well when asked to detect these rare variants, Zehir et al. note that there are a number of other FDA-authorized tests that do not include the same rare variants as the Praxis Extended RAS Panel CDx indicating that FDA-authorized tests do not always provide patients with complete information. While Pfeifer et al. produced an interesting thought exercise using an unconventional approach, Zehir et al. concluded that the findings are not generalizable. Nonetheless, FDA uses this problematic study as the basis for its entire cancer assessment in the impact analysis, extrapolating the findings to apply to many cancer types. This flawed approach, in addition to the other issues described below, indicates that the benefits of the proposed rule touted by the Agency are highly erroneous.

FDA also cites another study that evaluated the clinical and economic impact of apparently inaccurate LDTs and an FDA-approved test for the detection of *EGFR* mutations in non-small cell lung cancer (NSCLC) patients.²⁶ However, the authors compared the FDA-authorized cobas® *EGFR* Mutation Test to an LDT developed 10 years ago outside the US and thus, not subject to CLIA regulations. This omission by FDA leads the public to erroneously believe that current regulations are insufficient. Further, the publication presents unclear data, as it appears the assay used to adjudicate differences between the methods was a LDT that was not validated for the specific purpose it was used for in the study. FDA fails to acknowledge the importance of proficiency testing data and also fails to consider a publication by Kim and colleagues (2018) that examined nearly 7,000 proficiency testing responses to demonstrate the LDTs used for *BRAF*, *KRAS*, and *EGFR* testing perform very well, including as compared to FDA-authorized companion diagnostics.²⁷ The authors conclude that both test types exceed 97% accuracy for all three genes combined. The story continues, though, as the data published by Kim et al. reveals that the FDA-authorized tests performed less well evaluating a particular *BRAF* genetic variant, p.V600K. This was widely recognized by laboratory professionals at the

²⁶ Cheng MM, Palma JF, Scudder S, Poullos N, Liesenfeld O. The Clinical and Economic Impact of Inaccurate EGFR Mutation Tests in the Treatment of Metastatic Non-Small Cell Lung Cancer. *J Pers Med.* 2017 Jun 28;7(3):5. doi: 10.3390/jpm7030005. PMID: 28657610; PMCID: PMC5618152.

²⁷ Kim AS, Bartley AN, Bridge JA, Kamel-Reid S, Lazar AJ, Lindeman NI, Long TA, Merker JD, Rai AJ, Rimm DL, Rothberg PG, Vasalos P, Moncur JT. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing. *JAMA Oncol.* 2018 Jun 1;4(6):838-841. doi: 10.1001/jamaoncol.2017.4021. PMID: 29242895; PMCID: PMC6145687.

time, which is why they developed LDTs so their patients with melanoma would no longer miss the opportunity to have access to the lifesaving treatment, vemurafenib. This study also demonstrated that IVDs are often modified based on patient need; 60% of participants using the FDA-authorized test reported adapting their assay from the approved procedure to allow for a greater breadth of sample type, a greater number of tumor types, to accept a lower level of tumor content, and to use instrumentation specific to their laboratory. Importantly, these changes should be validated by each and every laboratory employing them per CLIA regulations. Strategically selecting flawed studies, while simultaneously ignoring well documented evidence of the safety and accuracy of LDTs, calls into question FDA's rationale for the proposed rule.

The Agency also conflates alleged validation issues with companies making false claims about its tests or outright fraud to support rulemaking. AMP shares concerns about false claims and fraudulent tests but referencing media reports such as newspaper articles instead of high-quality evidence is not appropriate to justify such a dramatic and costly expansion in regulation. FDA even stated that it doesn't verify the claims that are being made. In footnote #10 of the proposed rule, which supports an entire paragraph describing multiple complaints, adverse events, etc., FDA says it "has not confirmed the veracity of the allegations or facts in every complaint, report, and allegation." In one instance when a government source is cited in the impact analysis²⁸, FDA references the findings of CMS, which actually demonstrate that CLIA successfully acted as the primary regulator requiring that the laboratory issue a corrective plan or be subject to severe penalties.²⁹

Additionally, FDA review is not always sufficient to ensure quality. For instance, FDA authorized the CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel developed by the CDC on February 4, 2020³⁰ despite the kit that was distributed to public health laboratories being seriously flawed. In a recent report from the Office of Inspector General, it was concluded that CDC had inadequate policies and procedures for developing a COVID-19 test kit.³¹ While CDC has ultimate responsibility for the flaws detailed in this report and for the steps it has taken to address OIG's recommendations, it is imperative that it is recognized that FDA authorization did not prevent the failure.

Theranos is another commonly cited egregious story and one where the FDA also had the opportunity to review the company's processes. On July 5, 2015, FDA authorized Theranos' enzyme linked immunosorbent assay for HSV-1, a clearance that remains active today. That is not to say that FDA did not recognize issues with Theranos months later when it documented issues with Theranos' design procedures, its collection device, and its processes for reviewing customer complaints.^{32,33} Yet, despite FDA having concerns, it was CMS that took action to stop the company's fraud by revoking its CLIA license and issuing penalties.

²⁸ See page 42 of the impact analysis.

²⁹ CMS, Statement of Deficiencies and Plan of Correction (Dec. 29, 2021), available at <https://s3.documentcloud.org/documents/21872905/northshore-clinical-labs-14d0426602-form-cms-2567-12292021.pdf>.

³⁰ <https://www.fda.gov/media/134919/download?attachment>

³¹ <https://oig.hhs.gov/oas/reports/region4/42002027.asp>

³² <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-orgs/documents/document/ucm469395.pdf>

³³ <https://www.forbes.com/sites/sarahhedgecock/2015/10/27/fda-releases-theranos-inspection-reports/www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-orgs/documents/document/ucm469396.pdf>

Other issues with an FDA-authorized assay used for congenital cytomegalovirus saliva screening were demonstrated in a publication by Atwood and colleagues (2023)³⁴. The authors describe data produced by two institutions suggesting that the Alethia CMV Assay Test System has a false positive rate of 4.5–6.2%, which is higher than the 0.2% reported for this assay in FDA claims. In particular, the authors disclose that both sites noted increased positivity rates around July 2022 raising their concerns that an undisclosed manufacturing change affected the assay's performance. This publication emphasizes the important role of laboratory professionals in continuously monitoring the entire testing process. Additionally, it points to the strength of the current regulatory system that relies upon peer review so that the laboratory community can always strive for higher quality patient care.

We also believe there is an existing strong disincentive to updating FDA-authorized test systems given the cost and burden associated with FDA review which contributes to why they often fail to be the best option for providers and their patients over time as new scientific information is acquired and technology advances. For instance, manufacturers do not always modify their device and its associated software so that it continues to comply with safeguards established by the implementing regulations of the Health Insurance Portability and Accountability Act (HIPAA). Consequently, our members have found that FDA-approved and FDA-cleared devices sometimes pose a risk for malware, ransomware, and unauthorized disclosures. One member reported that when their laboratory installs or upgrades software used as part of an FDA-authorized test system, approximately 75% of the time the software has one or more cybersecurity issues. One specific example includes situations where the operating system that runs on the computer that comes with a purchased FDA-authorized device is no longer supported by Microsoft or Linux (depending on the operating system of the device). The result is that the computer is not able to receive and install patches and updates to protect the device or computer against new malware and/or ransomware, leaving it vulnerable and putting the overall network at the institution, and consequently, patient information, at risk.

AMP also believes it is important to remind the public that FDA authorization only means that FDA has evaluated whether or not the test meets the claims made for its intended use. It does not mean that the test incorporates the latest knowledge and/or most clinically accepted understanding of that specific test; whether a test is optimally designed (*e.g.*, interpretive criteria, cutoffs/thresholds, etc.); whether the test is superior/inferior to any other options by any metric (better performance, more cost-effective, faster, etc.); and, whether the test is equitable/inclusive in its design. On the other hand, laboratory professionals make these kinds of assessments every day in their practice, and they incorporate these considerations into their test design and expertly modify and improve the performance of LDTs as needed in a timely and clinically appropriate fashion. The proposed rule fails to consider any of this in its assessment.

It is disingenuous to convey to the public that FDA authorization would deter all harm, and indeed, no single entity could. It is for this reason that AMP instead advocates for a multi-layered approach where CLIA, state, and third-party requirements work in concert with a peer-review-based system and the interest of appropriately trained professionals to provide the best care possible for their patients.

³⁴ Atwood EN, Esper FP, Bailey K, Doud MK, Benton AM, Friesen J, Rodgers MJ, Humphries RM, Rhoads DD, Gaston DC, Wang H. False positive congenital cytomegalovirus saliva screening results with an FDA-approved assay at two institutions. *J Clin Virol.* 2023 Sep;166:105527. doi: 10.1016/j.jcv.2023.105527. Epub 2023 Jun 24. PMID: 37392724.

Section VI: Significant Flaws in FDA's Impact Analysis

There are numerous and significant flaws in the impact analysis of the proposed rule. To start, the number of LDTs used in the analysis is highly inaccurate. FDA makes a central estimate that the proposed rule would impact approximately 80,400 LDTs, and even the Agency's high estimate, 160,800, is likely too low. As noted above, recent reports indicate that there are more than 175,000 genetic tests used in clinical care in the areas of hereditary disease and oncology.³⁵ As noted by the report's authors, this number does not include LDTs that are not marketed externally. Nor does this figure include genetic tests for other disease areas or the thousands of LDTs used in other clinical domains entirely. Therefore, the costs to the laboratory community described in the impact analysis are likely a significant underestimation. Further, FDA does not account for variability in laboratory types and how the proposed rule would more severely impact certain entities over others. FDA assumes that all laboratories are the same, evenly spread across geographic regions, each offering 67 LDTs. This is not nearly realistic. Some laboratories specialize in certain services and others offer a wider array of LDTs using various methods – the burden and costs will vary depending on each laboratory's characteristics.

FDA references the possibility that the market will consolidate in the proposed rule, but the downstream consequences of this on the healthcare system are not factored into the analysis. Assuming FDA's data is correct, over 90% of laboratories will be unable to sustain their current testing services. FDA does not provide an estimation of how this will disrupt local care, nor does it take steps to estimate the reduction in access to care underserved communities would endure. These data are critical to fully understand the economic impact of the proposed rule and FDA should present a complete analysis prior to proceeding with rulemaking.

Further, FDA does not address the impact of testing monopolies created by consolidation and how this could affect the economy, laboratory testing access, and healthcare costs. For instance, consolidation is likely to greatly reduce economic growth spurred from innovation in genetics and genomics. One study by the American Society of Human Genetics (ASHG), found that human genetics and genomics, including as it relates to clinical laboratory testing, contributed \$265 billion to the US economy, 166,000 academic and industry jobs, and \$5.2 billion in direct federal tax revenues in 2019 alone.³⁶ Considering that Administration's focus in promoting competition to support innovation and our economy³⁷, it is not prudent to finalize a rule that does the opposite.

There are numerous case studies demonstrating how testing monopolies harm patient care. For instance, prior to the unanimous 2013 *Association for Molecular Pathology v. Myriad Genetics Inc.* Supreme Court decision, a single company controlled testing for the *BRCA1* and *BRCA2* genes which had profound implications for patient access. For instance, some Medicaid programs did not contract with the company, which meant lower income women in certain states were unable to afford this important and lifesaving hereditary cancer test.³⁸ The testing

³⁵ Concert Genetics, "Genetic Test Price Transparency Report." 2023.
<http://www.concertgenetics.com/wp-content/uploads/2023/11/Concert-Genetics-2023-Genetic-Test-Price-Transparency-Report-07Nov2023.pdf>

³⁶ <https://www.ashg.org/advocacy/the-economic-impact/>

³⁷ <https://www.whitehouse.gov/briefing-room/statements-releases/2023/06/28/bidenomics-is-working-the-presidents-plan-grows-the-economy-from-the-middle-out-and-bottom-up-not-the-top-down/>

³⁸ Association for Molecular Pathology Compl. 21, 24, available at
http://www.aclu.org/images/asset_upload_file939_39568.pdf

monopoly also prevented patients from seeking a second opinion on genetic test results and, in one example, a patient stated in a complaint that they were forced to make major medical decisions without confirmatory testing.³⁹ Testing monopolies also dramatically drive up the cost of testing, further restricting patient access. Before the 2013 Supreme Court decision, sequencing of the *BRCA1* and *BRCA2* genes cost over \$4400 per test.⁴⁰ These situations are not unique to *BRCA1* and *BRCA2* testing and, indeed, a report of the Secretary's Advisory Committee on Genetics, Health, and Society details other instances where testing offered by a sole provider was disruptive to patient care.⁴¹ Upon the Supreme Court's decision in the 2013 case, five companies began offering testing for Hereditary Breast and Ovarian Cancer (HBOC) syndrome, with many more joining the market by 2014.⁴² Today, patients can access hereditary cancer panels that sequence over 80 genes for as little as \$250 and have an array of testing options.⁴³ This is an incredible outcome that was enabled by innovation and competition spurred by the removal of an inappropriate monopoly. Because the Administration is already grappling with high prescription drug costs and implementing policy to restore the affordability of medications, it should consider whether advancing a proposed rule that will recreate testing monopolies and in doing so, dramatically increase the cost of laboratory testing and prevent access to care, is in the best interest of Americans.

Additionally, FDA's impact analysis fails to factor in both the health and non-health costs stemming from laboratories discontinuing certain testing services altogether or if they were never to develop them in the first place. If the proposed rule is finalized, market-based incentives will be required to justify the expense associated with FDA review and, in particular, there will likely be a strong disincentive for developing LDTs for rare diseases given the small populations they would serve. Newborn screening (NBS) is one of the most successful public health programs in history that uses combinations of screening and diagnostic tests for rare diseases making presymptomatic diagnosis, care, and management possible, preventing death or disability, and enabling children to reach their full potential. Currently, all newborn screening tests are LDTs performed by local health departments who typically are not bestowed with large budgets. There are already significant barriers to adding conditions to a newborn screening panel and the proposed rule will add additional challenges to the detriment to patient care.

Diagnostic testing is also pivotal to ending the diagnostic odyssey for patients with rare diseases. As noted by the EveryLife Foundation in a recently published study, patients with rare diseases spend on average, more than 6 years searching for a diagnosis, preventing them from immediately accessing the most appropriate and comprehensive treatment plan for their unique health needs.⁴⁴ For instance, adrenoleukodystrophy (ALD), Pompe, and severe combined immunodeficiency (SCID) are all debilitating diseases that will cause death in children if left untreated. Not only does testing save patients' lives, but the EveryLife Foundation study determined that a timely diagnosis prevents excess costs of \$301,647, \$168,718, and \$517,638

³⁹ ACLU Compl. 23, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf.

⁴⁰ University of Utah Research Foundation et al v. Ambry Genetics, No. 2:2013cv00640 - Document 185 (D. Utah 2014) <https://law.justia.com/cases/federal/district-courts/utah/utdce/2:2013cv00640/89779/185/>

⁴¹ Secretary's Advisory Committee on Genetics, Health, and Society, Department of Health and Human Services. 2010. Gene patents and licensing practices and their impact on patient access to genetic tests.

⁴² Cook-Deegan R, Niehaus A. After Myriad: Genetic Testing in the Wake of Recent Supreme Court Decisions about Gene Patents. *Curr Genet Med Rep.* 2014;2(4):223. doi:10.1007/S40142-014-0055-5

⁴³ <https://www.judiciary.senate.gov/download/george-testimony>

⁴⁴ Everylife Foundation. 2023. The Cost of Delayed Diagnosis in Rare Disease: A Health Economic Study. <https://everylifefoundation.org/delayed-diagnosis-study/#:~:text=About%20the%20Study,in%20avoidable%20costs%20per%20patient.>

per patient for ALD, Pompe, and SCID respectively. Fortunately, many patients with these conditions are diagnosed early as they are, at least to some extent, included in routine NBS in the United States. Other diseases evaluated in the study are not included on the Recommended Uniform Screening Panel (RUSP) as is the case with Fragile X Syndrome (FXS) and Duchenne Muscular Dystrophy (DMD), and regardless of that fact, the study found that a timely diagnosis prevents excess costs of \$94,250 and \$94,913 per patient respectively. Every day, researchers gain better understanding of the genetic causes of diseases, but if the proposed rule were finalized, the prohibitive costs associated with FDA compliance may lead a laboratory to stop offering infrequently used tests for diagnosing rare diseases, or required assays may never be developed. This could be especially true for pediatric specialty hospitals that perform testing at low volumes, making it infeasible to absorb the costs associated with FDA regulation. The FDA also does not address the economic and healthcare impact associated with the loss of tests, such as these, would cease to be offered under such high regulatory burdens.

As stated earlier, we found serious flaws with the literature cited by the FDA in support of the proposed rule, and this is more problematic in the impact analysis. For example, in the section on FDA's cancer extrapolations, FDA defines misdiagnosis as a missed diagnosis or an inaccurate diagnosis and assumes that 50% of misdiagnoses occur after testing with an LDT, as opposed to other methods of diagnosis. This section relies heavily upon a publication by Pfeifer et al. comparing genetic LDTs to an FDA-authorized IVD, as detailed above in Section III of our comments. However, genetic tests are not used primarily for diagnostic purposes in oncology, but rather for characterization of the tumor and treatment identification. Other diagnostic modalities, such as imaging and histology are far more frequently used for diagnostic purposes in oncology, making it unlikely that a cancer patient who receives genetic testing is "missed" and therefore, unable to begin treatment. Thus, it is highly inappropriate to use the findings of Pfeifer et al. to estimate the extent to which LDTs contribute to misdiagnosis which contributes to a significant overestimation of the "benefits" of FDA review. Instead, FDA should have compared individuals who received genetic testing-guided therapy selection to those who did not to appropriately account for how genetic tests are currently used in oncology care.

Finally, and most importantly, the basis for the cancer assessment is called into question because of the seriousness of the errors and limitations of the Pfeifer et al. study itself. As described above in our comments, there are a myriad of issues with how well the study's reference sample represents real-world patients, the study's design, the authors' approach to data collection, and their conclusions. Instead, other published peer-reviewed evidence based on proficiency testing results strongly suggests that LDTs perform excellently including when compared to FDA-authorized assays. Using this single paper as the basis for the assumption that 47% of tests used in care are "problematic" LDTs is deeply flawed, and thus, the entirety of FDA's cancer assessment should be removed from the impact analysis.

Regarding the COVID-19 assessment, we are concerned that FDA uses evidence from a ProPublica publication detailing the fraudulent and deceptive actions of a single nascent laboratory seeking to criminally benefit from the crisis. We have already noted in our comments that FDA review does not prevent fraud. Moreover, it is important to note that the laboratory was not in compliance with CLIA law and regulations as detailed extensively in CMS' 29-page Statement of Deficiencies and Plan of Correction.⁴⁵ Thus, compliance with existing

⁴⁵ CMS, Statement of Deficiencies and Plan of Correction (Dec. 29, 2021), available at <https://s3.documentcloud.org/documents/21872905/northshore-clinical-labs-14d0426602-form-cms-2567-12292021.pdf>.

requirements would have prevented this issue and this situation does not warrant the need for a costly burdensome additional regulatory regime.

However, we agree that the COVID-19 pandemic offers important case studies given the myriad of issues that prevented the most effective use of the laboratory community during the response efforts.⁴⁶ AMP believes it is imperative that FDA also estimate the health and economic costs associated with the lack of testing during the first few months of the pandemic as a result of the Agency's regulatory actions. With the declaration of the public health emergency, FDA issued a policy requiring EUA for LDTs prior to using them clinically.⁴⁷ While under non-pandemic circumstances, FDA review of LDTs was not required, the sudden policy change requiring that laboratory professionals using LDTs comply with medical device requirements created a significant regulatory barrier that led to a dearth of clinical testing in the United States during the critical first few weeks of the pandemic despite laboratories throughout the country having tests validated and ready to deploy. Community spread of COVID-19 was rampant and our healthcare system had no diagnostic tools available to stem its spread in those early days.⁴⁸ Comparatively, South Korea was performing 10,000 tests per day in March 2020.⁴⁹ While there are numerous reasons for the difference in the outcome between the US and South Korea, it is clear that adequate testing contributed, in part, to South Korea's successful approach in stemming the spread of the virus and preventing deaths.^{50,51}

Once laboratories in the United States could implement SARS-CoV-2 LDTs concurrently while applying for an EUA, they responded rapidly. AMP found that experienced academic medical centers were able to develop, validate, and start using their LDTs on average in less than a month from FDA's policy change.⁵² However, while navigating the EUA process, many laboratories reported that FDA set impossible-to-meet requirements, such as requiring an evaluation of more positive samples than confirmed cases in the US early in the outbreak and also validation of their test against MERS or SARS, for which samples were unattainable because they are considered possible bioterrorism agents. In August 2020, almost a third of laboratories reported that they experienced hurdles of this kind while seeking an EUA. Thus, despite FDA's policy changes, significant barriers to obtaining an EUA remained. As Eric Topol, MD stated, "I don't think there's any question that America's original sin was not having a broadly available test by the time COVID-19 was here... It's the original sin that has become our daily tragedy."⁵³

⁴⁶ Konnick EQ, Laser J, Weck KE. The Role of Clinical Laboratories in Emerging Pathogens-Insights From the COVID-19 Pandemic. *JAMA Health Forum*. 2021 Oct 1;2(10):e213154. doi: 10.1001/jamahealthforum.2021.3154. PMID: 36218899.

⁴⁷ <https://www.federalregister.gov/documents/2020/02/07/2020-02496/determination-of-public-health-emergency>

⁴⁸ <https://www.nytimes.com/2020/03/10/us/coronavirus-testing-delays.html>

⁴⁹ https://www.washingtonpost.com/world/asia_pacific/coronavirus-test-kits-south-korea-us/2020/03/13/007f14fc-64a1-11ea-8a8e-5c5336b32760_story.html

⁵⁰ Song S, Choi Y. Differences in the COVID-19 Pandemic Response between South Korea and the United States: A Comparative Analysis of Culture and Policies. *J Asian Afr Stud*. 2023 Mar;58(2):196–213. doi: 10.1177/00219096221137655. Epub 2022 Nov 16. PMID: PMC9669502.

⁵¹ <https://foreignpolicy.com/2022/06/26/coronavirus-pandemic-global-response-devi-sridhar-review/>

⁵² <https://www.amp.org/advocacy/sars-cov-2-survey/>

⁵³ <https://www.theatlantic.com/ideas/archive/2021/03/the-original-sin-of-americas-covid-19-response/618300/>

Additionally, there are other instances when FDA action has deterred the use of important testing approaches during outbreaks. For instance, despite having opportunities to learn from the consequences of restricting test development during the COVID-19 pandemic, FDA published guidance in 2022 placing confines on the use of Mpox LDTs without an EUA. In particular, the FDA guidance prevented the expedient use of rectal swab testing.⁵⁴ Caldera and colleagues at UCLA described their experiences working with FDA to obtain authorization to use rectal swab testing and relayed that FDA's validation requirements were overly onerous, especially in light of the time-restricted scenario of the public health emergency.⁵⁵ This ultimately prevented the laboratory from offering the test for patient care despite the laboratory's rigorous approaches and compliance with third-party accreditation requirements. The outcome likely resulted in delayed care to patients as indicated by the authors' description of patients presenting with Mpox-consistent symptoms and/or known risk for exposure but without apparent lesions. Once again, FDA compromised timely diagnoses to satisfy overly burdensome and unnecessary technical requirements and yet, failed to consider the economic, societal, and public health costs due to lack of available testing from their policies in its impact analysis.

Section VII: Conclusion

AMP remains committed to maintaining and enhancing the oversight of LDTs and appreciates the opportunity to provide these comments in support of its mission to advance the clinical practice, science, and excellence of molecular and genomic laboratory medicine to enable the highest quality health care. Because LDTs are not medical devices, the proposed rule's failure to document a legitimate need for this burdensome regulatory change, and the severely flawed, incomplete, and questionable impact analysis, AMP strongly urges FDA to rescind the proposed rule and instead defer to Congress to establish a streamlined, flexible, and cost-effective pathway forward for updating laboratory testing requirements in a way that continues to protect patients and supports innovation. At a minimum, the impact analysis should be corrected, updated, and released for public comment before FDA proceeds forward so that the Administration may fully understand the true extent of the impact of this rulemaking not only on industry, but on the FDA as well.

Thank you in advance for your consideration of our comments. Please direct any correspondence to Anna Scrimenti, Associate Director, Public Policy and Advocacy at ascrimenti@amp.org.

Sincerely,

Maria E. Arcila, M.D.
President, Association for Molecular Pathology

⁵⁴ https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-monkeypox-tests-address-public-health-emergency?utm_medium=email&utm_source=govdelivery

⁵⁵ Caldera JR, Gray HK, Garner OB, Yang S. FDA trial regulation of laboratory developed tests (LDTs): An academic medical center's experience with Mpox in-house testing. *J Clin Virol.* 2023 Oct 10;169:105611. doi: 10.1016/j.jcv.2023.105611. Epub ahead of print. PMID: 37866092.