UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF TEXAS
GALVESTON DIVISION

ASSOCIATION FOR MOLECULAR PATHOLOGY, and MICHAEL LAPOSATA, M.D., PH.D., Plaintiffs, v. UNITED STATES FOOD AND DRUG ADMINISTRATION, ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES, and XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services, Defendants.	Case No. _____

DECLARATION OF KAREN KAUL, M.D., Ph.D.

I, Karen Kaul, M.D., Ph.D., hereby declare under penalty of perjury as follows:

1. I am the Chair of the Department of Pathology and Laboratory Medicine and the Duckworth Family Chair of Molecular Pathology at NorthShore Hospitals, part of Endeavor Health ("NorthShore") in Evanston, Illinois, where I also serve as Director of NorthShore's Molecular Diagnostics Division. I am a Clinical Professor of Pathology at the University of

Chicago Pritzker School of Medicine, and a Member of Plaintiff Association for Molecular Pathology ("AMP"). I make this declaration in support of the Complaint in the above-captioned case, have personal knowledge of the matters set forth herein, and can and will testify thereto if called upon to do so.

2. I have been practicing medicine at NorthShore since 1992, before which I practiced in the Department of Pathology at the Northwestern Memorial Hospital in Chicago, Illinois from 1988 through 1992. I received my B.A. *magna cum laude* in Chemistry and Biology from Drake University in 1978; my M.D. from Northwestern University Feinberg School of Medicine in 1984; and my Ph.D. in Pharmacology from Northwestern in 1984. I performed my post-doctoral training as a Resident in Anatomic Pathology at Northwestern Memorial Hospital from 1984 to 1988 and concurrently served as a Postdoctoral Fellow at the National Cancer Institute from 1985 to 1986. I am licensed to practice medicine in Illinois, and I am board-certified in Anatomic Pathology by the American Board of Pathology and Molecular Genetic Pathology jointly by ABP and the American Board of Medical Genetics and Genomics.

3. In addition to my membership in AMP, I was a Trustee at the American Board of Pathology (2011-2023) as well as a Member of the College of American Pathologists and Association of Pathology Chairs. I served on the Accreditation Council for Graduate Medical Education Residency Review Committee for Pathology from 2013-2019. I am a past president of AMP and was Editor in Chief of the Journal of Molecular Diagnostics from 1999-2011.

Pathology and the Practice of Medicine

4. Pathologists and our professional laboratory colleagues play a vital role in helping to diagnose a patient's disease or condition through the testing and analysis of bodily samples (including tissue, blood, and/or other cellular material) for biomarkers that are known to be

associated with a particular disease or condition. Together, we seek to provide treating physicians with the most accurate and clinically useful diagnostic information possible, as quickly as possible, so that a patient's care team can have the most accurate diagnosis, plan an appropriate course of care, and initiate timely treatment for our patients. After a patient's formal diagnosis, pathologists work directly with the attending physician(s) to monitor the status of a patient's condition and assist with further diagnostic and treatment recommendations. Although pathologists typically are not a point of contact for patients, they are an integral part of a patient's treatment team and are intimately involved in their patients' care.

5. For example, in my role as Chair of Pathology and Laboratory Medicine at NorthShore, I oversee testing services and procedures that touch every patient in the NorthShore system. Among other things, my practice involves helping to select the most appropriate testing services for a given patient in consultation with the patient's treating physician and my professional laboratory colleagues; performing and supervising analyses of patient samples; reviewing and interpreting the results obtained; communicating those results to the treating physician, always in a formal written report and often through additional oral communications and conferences; and offering consultative services to the treating physician so that he or she can fully understand the results obtained, the methods used, and any limitations, and then evaluate that information in conjunction with their knowledge of the patient's unique characteristics and medical history so that a treatment plan can be tailored specifically for that individual patient. Along with my laboratory colleagues, I work closely with treating physicians before, during, and after laboratory testing to ensure that all questions are addressed and the appropriate pathway forward ascertained.

Laboratory Developed Tests

6. In order to best serve patients, my fellow laboratory professionals and I—like thousands of other pathologists and AMP members—frequently develop, validate, and perform new laboratory processes and procedures for analyzing patient samples (often referred to as "laboratory developed tests" or "LDTs"). These LDTs typically are developed out of necessity because no testing kit is commercially available or because currently available processes or tests do not meet the needs of a specific patient or patient population. Sometimes we create these processes anew; other times, and as explicitly authorized by the federal laws and regulations governing clinical laboratories (commonly called "CLIA"), we modify commercially distributed test kits that have been cleared or approved by the U.S. Food and Drug Administration ("FDA"). In either case, LDTs are developed and validated using a rigorous and highly scientific process in order to address a well-defined clinical need.

7. Working collaboratively—as CLIA specifically directs—my colleagues and I typically begin the LDT development process by identifying clinically relevant biomarkers from peer-reviewed academic, medical, and scientific literature and clinical research. We next apply our scientific and medical training to select the appropriate technical methodologies for assessing that biomarker from patient samples, and then design a scientifically rigorous process for performing the series of controlled steps and processes necessary to interrogate a given sample for the biomarker(s) of interest. It is important to emphasize that designing and developing an LDT does not involve the manufacturing of new machines, implements, accessories, or other tangible goods; instead, we are using well-established technologies, commercially available goods, and standard technical methods to craft a scientifically rigorous process for extracting and analyzing information from clinical samples.

8. Once the LDT procedure has been designed and developed, we must thoroughly and comprehensively validate it before clinical use. To do so, we do an extensive analytic validation so that we fully understand the technical performance of the assay, including such factors as sensitivity and specificity, limit of detection, linear range, whether other diseases, agents or drugs interfere with the method, and more. If all these parameters meet the needs for a clinically reliable and useful assay for the biomarker, we will proceed to a clinical validation. For this we typically obtain a large number of clinical samples ideally analyzed by another laboratory or using another method and conduct extensive analytical testing to ensure that the LDT accurately and reliably detects the biomarker(s) the LDT is designed to identify. We apply statistical evaluation to these data and develop detailed criteria for routine interpretation. We maintain full validation records and reports, as required by CLIA, and those reports routinely are inspected by federally approved laboratory accrediting bodies during the CLIA certification, accreditation, or renewal processes and regular laboratory inspections. We also publish our assays and findings in peer-reviewed literature so that others can comment on and replicate our work.

9. Once an LDT has been fully validated (analytically and clinically), we must codify the complete LDT process in a written protocol that details all materials, methods, steps, and processes for performing the LDT and for interpreting, recording, and reporting its results. This written protocol is maintained by the laboratory for use exclusively within that laboratory, and it must be followed at all times, without variation, unless and until it is modified and the modified LDT is newly verified to ensure its validity (again, as CLIA expressly authorizes). All technical staff review these protocols, and the method is approved for clinical use by the laboratory director before the procedure is clinically available. In accordance with CLIA, we must also perform regular third-party proficiency testing to verify the LDT's ongoing accuracy and reliability. If

proficiency testing results show errors, the laboratory must halt performance of the test. Importantly, the LDT itself never leaves the laboratory and is not sold or distributed to other parties; it is a set of procedures to be performed within the laboratory itself.

10. CLIA-regulated LDTs offer many advantages over commercially distributed test kits that typically are reviewed and approved by the FDA. Because medicine, science, and technology advance at a rapid pace, the development and use of LDTs not only enables clinical laboratories to respond rapidly to emerging needs or public health threats but allows my colleagues and I to modify and improve LDTs for existing diseases or conditions in response to new developments and scientific information. In addition, the flexibility allowed by CLIA enables us to use new diagnostic tests in patients as soon as it is fully validated, and to rapidly incorporate new scientific knowledge into our processes and procedures, which in turn allows us to provide our patients with optimal and highly personalized medical care at the earliest possible opportunity. Put simply, the fact that LDTs are not static allows for significant innovation in a short time frame, and this iterative process—expressly authorized and enabled by CLIA—allows me and my laboratory colleagues to provide patients with the most up-to-date and individually appropriate testing without the extraordinary delays and expense that are inherent in FDA's regulatory review of fixed test kits that are commercially distributed for third-party use.

11. I am trained, board certified, and licensed clinically to perform this work, and am personally and professionally responsible for the accuracy and performance of these assays—just as other physicians are responsible for the clinical care of their patients.

12. The importance of the innovation and timeliness of LDTs cannot be overstated. In many instances, LDTs have saved patients from undergoing highly invasive and risky procedures that can take weeks or months to generate results. For instance, the development of a relatively

simple LDT for Herpes Simplex Virus ("HSV") in the 1990s avoided the need for patients with potential viral encephalitis to undergo a brain biopsy, which—beyond its inherent complexity and extraordinary risks—often took weeks to analyze to determine whether the virus was present in the brain tissue. The development of an LDT for HSV that required only a sample of cerebrospinal fluid (CSF) therefore alleviated extraordinary risks and delays and enabled patients to receive treatment for a condition that can be fatal. Laboratories worked together to ensure accurate results and the data from national proficiency testing shows this. We have many other examples similar to this in which laboratories developed improved tests as LDTs that saved time and cost and generated better outcomes for patients, often long before an FDA approved version of the test was commercially available.

13. Of course, many LDTs—like the HSV test—at some point may be commercialized, mass produced, and then sold as an FDA-approved or FDA-cleared manufactured test kit. But that process takes years to complete and millions (if not tens of millions) of dollars in investments. In the case of HSV, it took nearly 2 decades for an FDA-approved assay to become available. As a result, it is not a commercially viable option for uncommon (let alone rare) diseases or conditions or specific disease variants. And by the time the FDA regulatory process is complete and approval or clearance for a commercially viable test kit is obtained, medicine, science, and technology often have evolved considerably—which can seriously reduce that static test's utility or even render it entirely obsolete. It is my role as a medical professional to evaluate available testing options for my laboratory and offer the best tests for the clinical needs of my patients.

Impact of the LDT Rule

14. The Final Rule challenged in this litigation already has had and will continue to have an array of direct, tangible, and immediately adverse consequences for me, my fellow

laboratory professionals, our laboratories, and most important of all our patients—who will be deprived of access to essential healthcare services that can accurately, efficiently, and promptly aid in the diagnosis of their conditions and allow for the swift initiation of appropriate treatment plans.

15. As the Final Rule makes clear, every LDT that was not already in use prior to the Final Rule's effective date will require FDA regulatory review and clearance or approval no later than May 2028. At that time, prohibitively expensive and time-consuming clinical studies for the FDA—in addition to validation under CLIA—will be necessary for virtually any new LDT, and the FDA's mandatory regulatory review will add years to the clinical launch process for new procedures that otherwise could have been developed and put to use in the laboratory in a timely manner.

16. The extraordinary expense and time associated with FDA regulation means that my fellow pathologists and I ***already*** are being forced to consider whether to continue pursuing LDTs that are currently under development. In so doing, rather than focusing on the medical needs of the patient, the assessment of the financial and time commitment to develop such processes will take priority and dictate our actions. In many cases, tests that would be beneficial to our patients will not be developed because undertaking such submissions to the FDA are not viable; indeed, as a direct result of the Final Rule, we already have stopped development work on multiple LDTs that will not be viable given the length and expense associated with FDA review, and I therefore will not be able to provide those testing services to my patients as a direct result of the Final Rule. Many of my colleagues in the pathology community—including numerous members of AMP—have told me that they likewise have been forced to abandon ongoing LDT development efforts as a direct result of the Final Rule. It is also frustrating to know that if we are forced to send out test

to a reference laboratory because of the cost of submission to the FDA, many of these will still be LDTs done at the outside laboratory (with no better performance than our own LDT).

17. For those LDTs already developed and being used when the Final Rule took effect, my colleagues and I no longer can make the kinds of standard changes we typically might make as a matter of course (*e.g.*, switching from one manufacturer's version of a standard laboratory reagent to another when supply is unavailable, replacing the machinery or other tools used to perform an LDT with updated or upgraded versions, and making other technical changes that are expressly authorized by CLIA). Currently, we can validate these substitutions for certain reagents and equipment in-house. Under the Final Rule, our LDTs will be forced "offline" every time we encounter a supply shortage, and because many LDTs are used for only a few individuals, there will not be a sufficient market to justify putting other standard modifications through the FDA regulatory review process. Over time, the LDTs I have been performing for years to provide my patients with essential medical care will effectively become useless, and I will no longer be able to serve my patients' needs. In short, I—along with the thousands of other pathologists and laboratory professionals who are AMP members—will lose the ability to use scores of well-validated LDT procedures that play a vital role in our practice of medicine.

18. FDA itself has acknowledged the extraordinary adverse effects its Final Rule will have on the practice of medicine and the quality of healthcare in the United States: With some understatement, it admits that subjecting these LDTs to FDA regulation "could lead to the loss of access to safe and effective IVDs on which patients currently rely." 89 Fed. Reg. at 37,293. But while it purports to minimize those adverse effects by announcing a series of so-called "enforcement discretion policies" that it says will minimize the Final Rule's burden, it also makes clear that those policies are illusory: The Final Rule repeatedly declares that my development and

modification of LDT procedures to serve my patients is "illegal," *id.* at 37,295; *id.* at 37,297; says that even these supposed "enforcement discretion policies" remain "subject to change," *id.* at 37,390, and indeed threatens "to pursue enforcement action … at any time." *Id.* at 37,301, 37,304, 37,307. In the 35 years that I have been a licensed doctor, I never previously have been threatened with criminal prosecution by the federal government for engaging in the practice of medicine, let alone for engaging in conduct that CLIA both expressly authorizes and enables. These overt threats will fundamentally transform the nature of my life's work and prevent me—and thousands of other pathologists and laboratory professionals—from providing up-to-date and necessary medical care to the thousands of patients for whom I am currently responsible and, in the future, will be responsible.

19. The Final Rule will have an array of other adverse effects on my practice of medicine. As I emphasized earlier, one of the most important things I do is consult with treating physicians about the LDTs and other laboratory procedures my colleagues and I perform, the results we obtain, and their relevance to a patient's diagnosis and course of treatment. The burdens associated with the Final Rule will seriously impede our ability to do so: Rather than treating patients and working with their doctors, I will be forced to spend countless hours complying with the FDA's vast array of new regulatory mandates.

20. While I fully intend to continue developing new and modifying existing testing procedures despite the Final Rule—though far fewer than I otherwise would—the Final Rule will require me and my laboratory colleagues to devote thousands of hours to overseeing clinical trials and clinical trial data collection, preparing FDA regulatory submissions (which I know from personal experience is a lengthy and time-consuming process), answering questions from FDA (which I also know must be done on strict timetables set by the Agency), and complying with

burdensome FDA regulatory inspections (even though my laboratory already is inspected regularly under CLIA) that can take a laboratory offline for days and invariably impede performance to the extent the laboratory remains operational. And because my laboratory otherwise must satisfy the FDA's Quality System regulation, I also will be forced to spend untold hours overseeing and ensuring compliance with FDA's procedures, documentation, training, and other requirements—not just the largely-overlapping laboratory quality requirements under CLIA.

21. Thus, rather than being able to focus on the development and performance of new and important testing, engaging in vital consultation with attending physicians, and providing essential care to our patients—the very reason I became a medical doctor—the Final Rule will force my colleagues and I to divert our scientific and medical expertise away from patient care to concentrate on the regulatory process. In the meantime, we will be forced to run fewer tests, less efficiently, all to the detriment of our patients.

22. All in all, the LDT Rule is already directly, immediately, and adversely affecting me, my colleagues, and thousands of other pathologists and laboratory professionals by fundamentally transforming the way we have been practicing medicine for decades—all under the duress of threatened criminal prosecution. And perhaps most important of all, it will severely harm our patients, by curtailing access to cutting-edge personalized medical care, stifling the innovation and adaptability at the heart of CLIA, impeding our ability to provide vital consultation to our physician colleagues, and delaying life-saving diagnostic services and patient treatment.

Dated: August 16, 2024

Karen Kaul

Karen Kaul, M.D., Ph.D.