Arguments for and Against

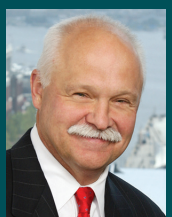
Potential FDA Regulation of Laboratory-Developed Tests and the Effect on Litigation

By Bruce R. Parker and Casey L. Bryant

The proliferation of these tests in more complex and cutting-edge, personalized medicine will ensure that calls for more comprehensive regulations will not go away.

In recent years, personalized medicine has become more attainable through scientific advances, especially in the field of genomics. Using genetic-mapping techniques, laboratories have developed tests that are reported to identify genetic markers for diseases such as cancer and diabetes. Television commercials advertise genetic tests that purportedly allow you to trace your ancestry back hundreds of years. While home genetic testing is undoubtedly an entertaining family project for some, physicians rely on molecular genetic testing for diagnostic and therapeutic decisions. Consequently, it is imperative that the tests have high degrees of sensitivity, specificity, and accuracy. These concerns were articulated in "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies," a U.S. Food and Drug Administration (FDA) publication issued on November 16, 2015. *See* https://www.fda.gov (archived document).

Defense counsel should be aware of concerns about the accuracy of laboratory testing because it is not uncommon for plaintiffs' experts to use the results of poorly validated assays to assert diagnoses of "new diseases" discovered by the plaintiffs' experts. Several such "silicone anti-



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body assays" formed the basis for plaintiffs' experts opining on an autoimmune disease that the plaintiffs' lawyers and the experts created. Unvalidated or poorly validated assays are also used in litigation to claim that they "prove" that a plaintiff was exposed to a chemical that allegedly causes genetic mutations. The recent public collapse of Theranos after it came under scrutiny for the accuracy of its blood test devices has bolstered calls for regulatory oversight of non-FDA approved assays.

A laboratory is permitted to use a newly developed LDT before it has been reviewed by the CMS. Analytical validation under CLIA is reviewed during a laboratory's routine biennial survey.

This article analyzes laboratory-developed tests, or LDTs, which are a specific type of laboratory assay that is not currently regulated by the FDA. We discuss arguments for and against increased FDA regulatory oversight of their development and accuracy and the effect that all this has on personal injury litigation.

A Brief History of the Development of LDTs and Current Regulatory Scheme

The 1976 Medical Device Amendments (MDA) to the Federal Food, Drug and Cosmetic Act (FDCA) authorizes the FDA to regulate the marketing and sale of medical devices. Under the MDA, all medical devices are placed in one of three categories according to the degree of risk that they pose: (1) Class III devices, such as a surgically implanted device, pose the highest risk to consumers and must go through the premarket approval (PMA) process for FDA approval, the most rigorous regulatory process, (covering approximately 47 percent of all medical devices); (2) Class II devices, such as contact lenses or home pregnancy tests, are generally subject to premarket clearance by submitting a 501(k) application to FDA, a quicker and less-stringent process than the PMA process, (covering approximately 43 percent of all medical devices); and (3) Class I medical devices, such as a tongue depressor, pose the lowest risk and are manufactured with limited controls, (covering approximately 10 percent of all medical devices). *See* U.S. Food & Drug Admin., Medical Devices Premarket Approval (PMA): https://www.fda.gov; U.S. Food & Drug Admin., Learn if a Medical Device Has Been Cleared by FDA for Marketing: https://www.fda.gov. In 2010, of the 2,714 medical devices cleared via the 501(k) process, 89 percent were Class II devices. *See* Dept. Health Human Serv. Office Insp. Gen., FDA's Clearance of Medical Devices Through the 510(k) Process (OEI-04-10-00480) (Sept. 2013).

LDTs do not neatly fit within the category of a medical device as defined under the MDA. The FDA defines a LDT as an in vitro diagnostic test that is designed, manufactured, and used (but not sold to third parties) within a single laboratory. LDTs have become increasingly more complex, and their uses more publicly available, than they were just a decade ago. In 2014, the FDA estimated that there were approximately 11,000 LDTs manufactured in 650 laboratories across the country. *See* Notification and Reporting for Laboratory Developed Tests, 79 Fed. Reg. 59,779 (Oct. 3, 2014) (draft guidance). LDTs were first used in the narrow context of detecting an analyte (such as checking glucose or cholesterol levels using a blood sample). The more sophisticated—and potentially more problematic for patients—LDTs have now evolved into detecting various DNA variations using a single blood sample to diagnose and recommend treatment options for life-threatening genetic diseases. *See* U.S. Food & Drug Admin., Laboratory Developed Tests: https://www.fda.gov.

While the 501(k) clearance process is the most common pathway to market for medical devices, some LDT manufacturers have proactively sought approval via the PMA process, perhaps attempting to gain a competitive edge should the FDA require similar LDTs to complete the PMA process down the line. For example, in September 2014, Myriad Genetic Laboratories applied for PMA for its breast cancer gene test, BRACAnalysis, and was approved by the FDA in December 2014. *See* U.S. Food & Drug Admin., Premarket Approvals (PMAs) Medical Device Database: https://www.fda.gov.

The Centers for Medicare and Medicaid Services (CMS) has historically and currently regulates laboratories under Clinical Laboratory Improvement Amendments (CLIA), 42 U.S.C. §263a. The Clinical Laboratory Improvement Amendments regulations are focused on monitoring analytical validity of laboratory tests. This means that a CLIA review considers whether a test detects what it is supposed to detect. A laboratory is permitted to use a newly developed LDT before it has been reviewed by the CMS. Analytical validation under CLIA is reviewed during a laboratory's routine biennial survey. The College of American Pathologists (CAP) has been approved by the CMS as an accreditation organization for all laboratories subject to CLIA requirements and has been delegated authority to have members conduct laboratory inspections. *See* College of American Pathologists (CAP) Approval as Accreditation Organization for Clinical Laboratory Improvement Amendments, 80 Fed. Reg. 16,395 (Mar. 27, 2015).

Inspection is a condition for the laboratory's continued CLIA certification. The Clinical Laboratory Improvement Amendments regulations do not address clinical validity, meaning, does a test result identify, measure, or predict the presence or absence of a clinical condition or predisposition? In contrast, tests that are submitted to the FDA for PMA approval will be assessed for their clinical validity. Consequently, while CLIA may ensure that an LDT accurately measures a biomarker that it is designed to measure, it does not tell a patient or physician if the biomarker being measured has any clinical significance.

The FDA's First Steps in Regulating LDTs

The FDA first announced its authority to regulate LDTs in 1992 with its release of a draft document asserting that the tests were subject to the same regulatory scheme as other in vitro diagnostic tests. *See, e.g.*, Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation (Draft Compliance Policy Guide) (Aug. 3, 1992). The FDA historically

exerted its authority potentially to regulate LDTs as in vitro diagnostic tests because they have been considered medical devices subject to oversight by the FDA under the MDA. Many representatives in the laboratory industry have consistently disputed that LDTs fall under the definition of "devices" subject to FDA regulation. (See more details below). The FDA historically has exercised what it has called "enforcement discretion." What this means is that while the FDA claims that it has the authority to regulate LDTs, it can also lawfully decline to regulate such tests. *See* Analyte Specific Reagents, 62 Fed. Reg. 62,243 (Nov. 21, 1997) (codified at 21 C.F.R. 809, 864) (stating, "If future developments in laboratory technologies or marketing of in-house developed tests indicate that additional regulation is necessary to provide an appropriate level of consumer protection, FDA may reevaluate whether additional controls over in-house developed tests are warranted.").

Although the "FDA has generally not enforced premarket review and other applicable FDA requirements because LDTs were relatively simple lab tests and generally available on a limited basis," the agency has targeted specific LDTs that have generated public safety and consumer rights concerns. U.S. Food & Drug Admin., Laboratory Developed Tests, *supra*. For example, in November 2013, the FDA issued a warning letter about a particular genetic-testing kit being sold directly to consumers, specifically mentioning the "potential health consequences that could result from false positive or false negative assessments" for BRCA-related genetic risk. *See* U.S. Food & Drug Admin. Warning Letter to 23andMe, Inc., Doc. No. GEN1300666 (Nov. 22, 2013): https://www.fda.gov. While LDTs are not generally marketed to consumers directly, the manufacturer contended that the consumer submitted a sample collection swab via the tub provided in the testing kits to the laboratory, which was exclusively responsible for testing and analyzing results. However, this year, the FDA announced its approval for the first direct-to-consumer test to report on three specific BRCA1/BRCA2 breast cancer gene mutations, which uses the patient's saliva sample, based on testing data reviewed through the de novo premarket review pathway for low-to-moderate-risk devices. *See* Press Release, U.S. Food & Drug Admin., FDA Authorizes, with Special Controls, Direct-to-Consumer Test that Reports Three Mutations in the BRCA Breast Cancer Genes (Mar. 3, 2018).

In 2006, the FDA published draft guidance announcing its intent to regulate a subset of tests (in vitro diagnostic multivariate index assays) that would include some LDTs. The FDA supplemented its 2006 draft guidance with an additional proposal the following year, which was met with strong criticism from laboratories and ultimately was never finalized. *See* U.S. Food & Drug Admin., In Vitro Diagnostic Multivariate Index Assays Draft Guidance (July 26, 2007): https://www.fda.gov. Rather than abandoning its intent to regulate subsets of in vitro diagnostic tests, the FDA announced that "it [was] time to reconsider its policy of enforcement discretion over LDTs," citing concerns "that some diagnostics critical for patient care may not be developed in a manner that provides a reasonable assurance of safety and effectiveness." *See* Public Meeting Notice on Laboratory Developed Tests Oversight, 75 Fed. Reg. 34,463, at 34,464 (June 17, 2010). In 2010, the FDA held a two-day meeting to solicit input on LDT regulation from interested stakeholders and articulated its rationale behind more comprehensive regulation, including that LDTs were increasingly being marketed directly to consumers online. The range of feedback that the FDA received at the meeting was considered by the agency to develop draft guidance on the regulatory oversight framework and reporting, which, on July 31, 2014, it announced to Congress its intent to publish. *See* Letters from Sally Howard, FDA Deputy Comm'r, to Sen. Tom Harkin & Rep. Fred Upton (July 31, 2014).

FDA 2014 Draft Guidance on LDT Regulation

In October 2014, the FDA issued two draft guidance documents. *See* U.S. Food & Drug Admin., FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) Draft Guidance (Oct. 3, 2014): https://www.fda.gov; U.S. Food and Drug Admin., Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (Oct. 3, 2014): https://www.fda.gov.

Dr. Jeffrey Shuren, Director of the Center for Devices and Radiological Health, testified on behalf of the FDA during a September 2014, congressional hearing that the FDA regulation would target "high and moderate risk LDTs, and phase-in premarket review requirements for this subset over 9 years using a public process that includes expert advisory panels, as even recommended by the lab community." *21st Century Cures: Examining the Regulation of Laboratory-Developed Tests: Hearing before the Sen. Subcomm. on Health of the Comm. on Energy and Commerce*, 113th Cong. (2014) (Sept. 9, 2014 statement of Jeffrey Shuren).

The FDA historically exerted its authority potentially to regulate LDTs as in vitro diagnostic tests because they have been considered medical devices subject to oversight by the FDA under the MDA.

Despite Dr. Shuren's attempts to pacify those critical of the FDA regulation that the 2014 draft guidance would not stifle innovations in personalized medicine or subject all LDTs to FDA regulation, the proposed FDA regulatory framework was quite complex and comprehensive. The FDA also encountered significant criticism for its failure to undertake a "formal economic analysis" of the direct costs imposed on taxpayers and laboratories as a result of LDT regulation. *See 21st Century Cures Roundtable: Spurring Innovation, Advancing Treatments, & Incentivizing Investment,* 113th Cong. (2014) (Aug. 22, 2014 statement of Dr. Glen Hortin, Quest Diagnostics)

Under the FDA's proposal, almost every LDT would be subject to some measure of enforcement, with the exception of those used solely for forensic purposes and certain tests used in connection with organ, stem cell, and tissue transplantation. All other LDTs would be subject to a risk-based classification system, ranging from I as the

lowest risk, to III as the highest risk, to determine the degree to which a particular LDT was regulated. The proposed regulations could include premarket approval related to safety and efficacy, quality reviews, and postmarket surveillance requirements, including, among other things, uniform adverse event and false positive reporting requirements. *See* U.S. Food & Drug Admin., Framework for Regulatory LDTs Oversight, *supra*. Class III LDTs would be subjected to the more stringent PMA process, Class II LDTs would be required to submit a 501(k) application, and Class I LDTs would be subject to FDA discretion for approval through the 501(k) application. The draft guidance also included continued CLIA review of laboratory testing processes, which some criticized as indicative of the dual regulatory scheme over LDTs that FDA was attempting to promulgate.

Instead of abandoning FDA oversight of lab-developed tests, the 2017 draft bill proposed a risk-based classification system for all in vitro diagnostic tests, not just LDTs, but it would require premarket approval for high-risk lab-developed tests.

Despite overwhelming pushback on the 2014 draft guidance, especially from laboratories, the FDA forged ahead with increasing oversight of LDTs up until the 2016 presidential election. On November 18, 2016, undoubtedly in response to the imminent change in administration and the anticipated pullback in government regulations, the FDA announced that it no longer intended to institute comprehensive regulation of LDTs, at least in the short term. *See* Zachary Brennan, FDA Delays Finalization of Lab-Developed Test Draft Guidance, Regulatory Affairs Prof'ls Soc. (Nov. 18, 2016): https://www.raps.org.

Continuing in the direction of delaying immediate regulation, in January 2017, the FDA circulated a paper for discussion about its "evolved" position on LDTs, while making clear that the paper did not "represent the formal position of FDA" and was not enforceable. *See* U.S. Food & Drug Admin., Discussion Paper on Laboratory Developed Tests (LDTs) (Jan. 13, 2017): https://www.fda.gov. That document indicated that the FDA had adopted a somewhat softer position from the position in previous draft guidance documents and conveyed that the FDA was not inclined to push back on the newly elected administration's reluctance to increase any government regulations. For example, it suggested "grandfathering" existing and traditional LDTs to exempt them from the most stringent aspects of FDA regulation as well as additional time before FDA premarket approval requirements would be phased in for all the applicable LDTs. Despite the FDA's indication that it sought "to appropriately balance patient protection with continued access and innovation," the FDA's rationale in publishing the 2017 discussion paper remained unclear, however, because it left the question of whether the FDA would proceed with the formal rulemaking process for LDTs up in the air. *Id.* Further, the discussion paper answered few, if any, questions about how certain provisions would work, including adverse event reporting requirements based on when certain LDTs were developed. In short, the 2017 discussion paper left even more questions unanswered about how the FDA intended to proceed with LDT regulation.

A Recent Alternative Legislative Proposal

In March 2017, U.S. Representatives Larry Bucshon and Diana DeGette introduced a "discussion draft" of the Diagnostic Accuracy and Innovation Act (DAIA), which would create a classification system for in vitro clinical tests (IVCTs), including LDTs. *See* Zachary Brennan, Diagnostics: Bipartisan Duo Offers Bill to Alter Regulations, Regulatory Affairs Prof'ls Soc. (Mar. 27, 2017): https://www.raps.org; The Diagnostic Accuracy and Innovation Act: Advancing Innovation and Safety for Patients in Diagnostics, U.S. Congressman Larry Bucshon (2017) (summary): https://bucshon.house.gov. Instead of abandoning FDA oversight of lab-developed tests, the 2017 draft bill proposed a risk-based classification system for all in vitro diagnostic tests, not just LDTs, but it would require premarket approval for high-risk lab-developed tests. It also would require postmarket adverse event reporting. *Id.*

The preemption provision in Section 590(G) of the proposed bill is broader than the current provision under Section 360(k) of the MDA. While the MDA preemption provision prevents state regulations that differ from the MDA's requirements for the "safety and effectiveness of the device," the draft bill preempts all state requirements that differ from "any requirement related to the development, manufacture, labeling, distribution, sale, or use of an in vitro clinical test."

Unlike previous proposals, the draft bill would establish a new center in the FDA, the Center for In Vitro Clinical Tests, to regulate LDTs, and perhaps most significantly, in vitro clinical tests would not be regulated as devices, drugs, or biologics. As a result, the draft bill would eliminate a problem that currently exists: laboratories that use a test in-house only escape regulation because the test qualifies as an LDT, while companies that seek to develop test kits for sale to laboratories or health-care providers are burdened with the regulatory process. It also would "create a new user fee program… [although] user fees will not be the primary funding source for the new regulatory structure (*i.e.*, user fees will be capped at 30 percent)." *Id.* According to the discussion draft, the FDA would regulate "the design, development, and validation of an IVCT as well as the production of an IVCT for distribution to another facility or third party." *Id.* The bill would also allow the CMS to "delegate inspection and certification" processes. *Id.* There would be a phase-in period under the bill, requiring that new regulations be promulgated within three years of enactment, and compliance would be mandatory within two years of that date.

The Debate over the FDA's Authority to Regulate LDTs

Although some laboratories claim that the FDA does not have the authority to regulate LDTs, in the past, the FDA has claimed that it does.

Some Laboratories Claim that FDA Does Not Have Authority to Regulate LDTs

Whether the FDA has statutory authority to regulate LDTs has been disputed since the FDA first asserted such authority in 1992. Citizen Petitions filed by Hyman, Phelps & McNamara (in 1992), the Washington Legal Foundation (in 2006), and the American Clinical Laboratory Association (in 2013), one of the most ardent opponents of FDA regulation of LDTs, have all asserted that the FDA lacks statutory authority to regulate LDTs under the Food, Drug, and Cosmetic Act (FDCA). LDT manufacturers (led by the American Clinical Laboratory Association) argue that the definition of "device" as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article" in Section 201(h) of the FDCA describes objects. They contend that LDTs represent a laboratory's proprietary *procedure* and knowledge for performing a given test, which is outside the FDCA's "device" definition. In addition, they contend that because laboratories do not commercially distribute LDTs, they do not meet the requisite criteria for FDA regulation. Lastly, laboratories generally argue that the authority to regulate such tests has been delegated to the CMS under CLIA, and an additional regulatory scheme imposed by the FDA would be duplicative and confusing.

The FDA Claims Statutory Authority to Regulate LDTs

The FDA has opposed these claims about proprietary procedures and knowledge and has consistently interpreted its authority under the FDCA, and specifically the MDA, to encompass LDTs as medical devices. For example, in response to Hyman Phelps & McNamara's Citizen Petition, filed in 1992, which argued that the FDA lacked the statutory authority to regulate in-house assays, in an August 12, 1998, letter responding to the petition, the FDA asserted that under Section 709 of the FDCA, if an "ingredient" crosses state lines, then the interstate commerce requirements for federal regulation are met.

To support its claim to have regulatory authority, the FDA asserted that "Section 201(h) of the FDCA defines medical devices to include in vitro reagents (21 U.S.C. 321(h))" and defines in vitro diagnostics as "those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions" (in 21 C.F.R. §809.3(a)). Given that in-house assays depend on reagents to diagnose a disease, the FDA concluded that "home brew" tests, another term used to refer to LDTs, were medical devices under the FDCA.

Despite claims that the "FDA [was] improperly asserting jurisdiction over these CLIA-regulated in-house assays," the agency has argued that it has regulatory authority over LDTs in conjunction with CLIA, and its authority to regulate LDTs has not been assigned to the CMS. Petition of Washington Legal Foundation, Docket No. FDA-2006-P-0149 (Sept. 28, 2006): https://www.regulations.gov. In response to the Washington Legal Foundation's Citizen Petition, the FDA, in a response letter, asserted that Congress intended to regulate different areas under CLIA and the FDCA and that CLIA was enacted due to Congress' concern over the "quality of the human element in the provision of testing services, *i.e.*, whether laboratory personnel were performing their jobs in a setting and in a manner that ensured accurate test results" for cervical cancer testing. Citizen Petition Denial Response from FDA CDRH to Washington Legal Foundation (WLF), Docket No. FDA-2006-P-0149 (July 31, 2014): https://www.regulations.gov. Indeed, the FDA's sporadic enforcement against specific LDTs, such as an October 2007 warning letter to EXACT Sciences regarding its DNA test for colorectal cancer screening, supports the FDA's consistent statements that its authority to regulate LDTs has not been delegated exclusively to CMS. *See* U.S. Food & Drug Admin., Warning Letter to EXACT Sciences Corp. (Oct. 11, 2007) (archived document): https://www.fda.gov. The conflicting views on whether the FDA has authority to regulate LDTs, or whether such authority belongs to the CMS alone, could be ultimately sorted out in litigation.

The FDA is not necessarily alone in arguing that it has authority to regulate LDTs. Genentech submitted a Citizen Petition on December 5, 2008, encouraging the FDA to go much further than it had proposed in terms of issuing comprehensive LDT regulations. *See* Petition of Genentech, Inc., Docket No. FDA-2008-P-0638 (Dec. 5, 2008): https://www.regulations.gov. Genetech cited *Clinical Reference Lab., Inc. v. Sullivan*, 791 F. Supp. 1499, 1509 (D. Kan. 1992), *aff'd in part, rev'd in part sub nom. United States v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026 (10th Cir. 1994), for the proposition that the "FDCA and CLIA are not inconsistent" and that "CLIA does not preempt the FDA's authority to regulate" laboratories. *Id.* This aligns with the FDA's April 16, 2015 announcement that it would form an FDA–CMS Task Force on Laboratory-Developed Test Quality Requirements to identify "areas where collaboration may realize greater oversight efficiency and produce the greatest benefit to patients, providers, and laboratories." Jeffrey Shuren & Patrick H. Conway, FDA and CMS Form Task Force on LDT Quality Requirements, FDA Voice blog (Apr. 16, 2015): https://blogs.fda.gov/FDAvoice. In arguing that FDA regulations should be applied uniformly to all diagnostic tests, Genentech cited *Bracco Diagnostics v. Shalala*, 963 F. Supp. 20, 27–28 (D.D.C. 1997), holding that the FDA's failure to regulate all diagnostic tests with the same standards could be seen as arbitrary and capricious. *Id.*

The conflicting views on whether the FDA has authority to regulate LDTs, or whether such authority belongs to the CMS alone, could be ultimately sorted out in litigation.

Genentech describes a current problem with the gaps in a discretionary approach to FDA enforcement regarding diagnostic tests in that diagnostic test kits produced and marketed by companies are required to meet costly and time-consuming premarket approval requirements, while assays manufactured by clinical laboratories can be marketed without going through the FDA regulatory maze. It is quite possible that two diagnostic tests in this scenario could target the same biomarker, creating

disparate barriers to market entry simply based on the company or the laboratory developing the test.

Although the FDA agreed with many of the principles outlined by Genetech in favor of regulating LDTs, in the July 14, 2017, letter, it denied Genetech's request that it issue new regulations for the tests, stating that "new regulations are not required for FDA to modify its policy of enforcement discretion with respect to LDTs." Citizens Petition Denial Response from FDA CDRH to Genetech, Docket No. FDA-2008-P-0638: https://www.regulations.gov.

Assessing the Potential Impact of FDA Regulation of LDTs

During the years of stakeholders waiting for the FDA to finalize its guidance on LDT regulation, there has been much speculation about the effects of the proposed regulation. Proponents of FDA regulation have identified examples of the public safety concerns that they argue favor regulating the validity and reliability of LDTs. In conjunction with the FDA's publication in November 2015 of "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies," mentioned above, Dr. Peter Lurie, the FDA's then-Associate Commissioner for Public Health Strategy and Analysis, articulated some of the safety concerns arising from unregulated LDTs. *See* Peter Lurie, Why FDA Should Oversee Laboratory Developed Tests, FDA Voice blog (Nov. 16, 2015): https://blogs.fda.gov/FDAvoice.

For example, Dr. Lurie explained that LDTs that produce false positives for ovarian cancer diagnostic tests can be especially harmful because women who receive those false positive results may go through the invasive and unnecessary procedure of having their ovaries removed. On the other hand, Dr. Lurie cautioned that LDTs that produce false negatives could result in patients not seeking the critical care that they needed to treat or cure a life-threatening disease, such as diagnostic tests that fail to detect levels of human epidermal growth factor receptor 2 (HER2), which are associated with the growth of breast cancer cells. Patients undergoing chemotherapy for breast cancer and who received false negatives from diagnostic tests would then forgo drugs specifically designed to target HER2, which Dr. Lurie estimated was possible in about 20 percent of the tests available at that time. The FDA's November 2015 publication estimated that the social cost per false-negative HER2 test result was $775,278. While the case studies presented by the FDA represent the most extreme known examples of LDT failings, the universe of the tests with questionable validity is largely unknowable in large part because the majority of the tests do not have to report adverse events or undergo premarket review.

Dr. Shuren previously expressed the overarching concerns regarding the clinical validity of LDTs on which many patients rely for diagnosis and treatment options. Jeffrey Shuren, Curbing Risk, Not Medical Innovation, in Personalized Medicine," FDA Voice blog (July 31, 2014): https://blogs.fda.gov/fdavoice. While acknowledging the important role that LDTs serve in personalized medicine, Dr. Shuren expressed the FDA's belief that it was possible to "appropriately balance assuring that patients and providers receive safe and effective tests with promoting innovation." *Id.* He also articulated the position of those in favor of FDA regulation that a lack of oversight, and essentially allowing laboratories to develop their own tests without completing the approval process that manufacturers must undergo, "stifles innovation by creating disincentives for conventional manufacturers to invest in developing new, medically important tests." Id.

Supporters of FDA regulation, including AdvaMedDx, a trade association of medical device manufacturers historically and currently subjected to FDA oversight, agree with Dr. Shuren that innovation in personal medicine is discouraged when traditional manufacturers with the resources and human capital to develop high-quality and potentially life-saving tests must pay a higher cost and wait longer to take their tests to market than laboratories producing tests on a smaller scale with no FDA oversight or delays in marketing their tests. In addition, they argue that health-care providers will be in a better position to make recommendations on patient care because LDTs marketed by laboratories would no longer be able to make claims about their validity and accuracy without going through the same premarket approval process that manufacturers face. Even well-intentioned laboratories may lack the resources or experience to identify issues in their testing process without standardized oversight by the FDA. Arguably, any issues with an LDT's performance might not be detected for years after the tests are marketed to physicians because laboratories are subject to inspection for recertification every two years. The counter to this argument is that manufacturers that choose to seek approval from the FDA for the assays that they develop can then sell their assays to other laboratories. By doing so, they can recapture their cost of seeking regulatory approval. Conversely, laboratories that developed their tests are not permitted to sell the assays to other laboratories.

The most ardent opposition to LDT regulation has come from smaller laboratories and academics, who argue that it disadvantages them compared with larger companies that have the resources and institutional knowledge to complete the FDA premarket approval process successfully. Those opposing FDA regulation claim that it would have the effect of stifling innovation, which is exactly what the FDA argues would happen if just larger manufacturers were subject to more rigorous enforcement. From a risk-aversion perspective, smaller laboratories have expressed fears that classifying LDTs as medical devices would open the floodgates to lawsuits based on strict liability claims, as opposed to the negligence theories on which plaintiffs have historically had to rely in suing laboratories over LDTs. They also fear the expense and delays that they would face if subjected to the rigorous PMA process for higher-risk lab-developed tests.

Effect on Litigation: The Practitioner's Perspective

Although it would depend on the type of regulation and the specific language enacted, laboratories could find that they have more effective defenses to personal injury litigation, *e.g.*, preemption, if their tests are subject to PMA approval. *See Riegel v. Medtronic*, 552 U.S. 312 (2008) (finding that the PMA process for the medical device manufacturer's balloon catheter established federal "requirements" under the FDCA, thereby preempting state requirements). As discussed, if passed, the Diagnostic Accuracy and Innovation Act would potentially provide an even broader scope of preemption for LDTs that are required

to undergo the PMA process. While the doctrine of parallel claims does not provide complete immunity from civil lawsuits, pursuing a personal injury action against the developer of an assay that has gone through a PMA process would be less attractive than asserting claims against an LDT that does not have the benefit of express preemption.

In addition, FDA regulation of LDTs would help undermine expert causation opinions that are predicated on the results of bogus assays that have been created for litigation purposes. *Daubert* challenges to opinions based on the results of such assays would be strengthened if the assays could be shown not to have complied with FDA regulations.

Such FDA regulation could also help dispense with some of the "junk science" tests relied on by plaintiffs' causation experts. Defendants have traditionally been forced to spend considerable time and money disputing the validity of these tests that have either not been subject to independent review or were "validated" by laboratories that used questionable testing techniques. The uniform enforcement of FDA premarket approval for LDTs would curtail plaintiffs' ability to rely on expert testimony based on self-serving and clinically unreliable assays.

FDA regulation of these tests could remove obstacles for defendants refuting causation claims, especially in toxic tort cases. In light of the recent advancements in genomics, some courts have relied on genetic-testing evidence to exclude plaintiffs' experts' testimony. For example, in *Bowen v. E.I. Du Pont de Nemours & Co., Inc.*, the court accepted the results of a recently developed genetic test that showed a genetic mutation, rather than the defendant's fungicide, caused the plaintiff's birth defects and excluded the plaintiff's proposed causation testimony. 2005 WL 1952859, at *7 (Del. Super. Ct. Aug. 5, 2005), *aff'd*, 906 A.2d 787 (Del. 2006). Having more genetic tests subject to FDA approval would provide defendants with more options for showing alternative causation and bolster the credibility of the evidence on which defendants rely in challenging plaintiffs' experts' causation opinions.

As illuminated in the citizens petitions in response to the FDA's draft guidance on LDTs, the FDA's authority to regulate the tests under the existing framework will likely face legal challenges. Proponents of more uniform regulation could also challenge the FDA's discretion not to regulate certain tests while subjecting other tests screening or diagnosing similar markers to the delay and expense of premarket approval as arbitrary.

What Is on the Regulatory and Litigation Horizon?

The FDA's November 2016 announcement that it was essentially putting comprehensive reform of its enforcement of LDTs on hold signaled the beginning of even more uncertainty on the regulatory horizon. Since Dr. Scott Gottlieb became the new FDA Commissioner in May 2017, he has expressed a willingness to address the complex enforcement issues related to a range of medical products. During a speech in March 2018, Dr. Gottlieb explained that the FDA recognizes that "LDTs are not a mom-and-pop industry anymore" and is concerned that tests "that haven't been properly validated present serious risks." Remarks by Scott Gottlieb, M.D., Comm'r, Food & Drug Admin., at the Am. Clinical Lab. Ass'n Annual Meeting, (Mar. 6, 2018) (as prepared): https://www.fda.gov. Dr. Gottlieb also highlighted the FDA's flexible approach to reviewing next-generation sequencing, which involves a single test that is able to detect many genetic mutations, including "qualify[ing] third party databases that could be used to help establish clinical validity," as evidence that the FDA is making the premarket review process for LDTs more efficient. *Id.* During another earlier speech, in September 2017, Dr. Gottlieb also shed some light on the FDA's future plans for LDT regulation. Remarks by Scott Gottlieb, M.D., Comm'r, Food & Drugs Admin., at the AdvaMed (MedTech) Conference (Sept. 26, 2017) (as prepared): https://www.fda.gov. He referenced the FDA's creation of a premarket certification program, called Pre-Cert, through which the FDA will be a certifier of select firms seeking to market digital health tools, and he previewed that "this construct could form part of the framework for a modern legislative approach to LDTs." *Id.*

Proponents of legislative action to institute LDT regulation hope that the Diagnostic Accuracy and Innovation Act will continue to make its way through the legislative process. Various stakeholders have now had the opportunity to comment on the draft of the act released by Representatives DeGette and Bucshon. The laboratory community has generally been more receptive to the draft bill and has expressed support for its distinct regulatory framework for LDTs, as opposed to past FDA proposals, which some claim have "inappropriately suggested regulation of LDTs as 'medical devices'" under the FDCA. Letter from Julie Kahni, Pres., Am. Clinical Lab. Ass'n, to Reps. Larry Bucshon & Diana DeGette. U.S. House Comm. on Energy and Commerce (Mar. 21, 2017) (commenting on Diagnostic Accuracy and Innovation Act discussion draft): http://www.acla.com. Even with a positive reception among some stakeholders, the Diagnostic Accuracy and Innovation Act is likely still years away from making it through the legislative process.

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What remains certain in the midst of confusion and competing positions on addressing the regulatory scheme for LDTs is that debate on this issue will continue for the foreseeable future. The proliferation of these tests in more complex and cutting-edge, personalized medicine will ensure that calls for more comprehensive regulations will not go away. As stakeholders await inevitable administrative or congressional action on this issue, they are left hoping that the process allows for full participation of voices from the diagnostic industry and a careful balancing of concern for patient safety with the need for continuing investment in advancements in personalized medicine. FD