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The Wild, Wild West of Laboratory Developed Tests

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Abstract

Since the 1950's, scientists have built novel technologies to screen for genetic diseases and other biological irregularities. Recently, researchers have developed a method called "liquid biopsy" (as opposed to a standard tissue biopsy) that uses a liquid sample (e.g., blood) to non-invasively spot biomarkers indicating different types of cancers in the patient's body. While the U.S. Food and Drug Administration (FDA) has fully cleared a small number of liquid biopsy tests under its rigorous and expensive review process, most biotech companies have instead followed a less restrictive regulatory path through the Centers for Medicare and Medicaid Services (CMS), which label the devices as "laboratory-developed tests" (LDTs).

Despite Congress' initial passage of LDT designation in the 1980's, LDT regulation remains akin to the "Wild West," with ongoing questions about which agency is actually in charge of LDTs. While FDA initially claimed regulatory control over LDTs, it has (until recently) left discretion to CMS. Therefore, some unscrupulous companies have tried to abuse the gray regulatory area by marketing potentially misleading scientific

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claims about their LDTs, comparing them to FDA-approved tests. Competitors with fully-approved tests are furious and have sued under federal Lanham Act claims. Because of Congress' repeated failures to pass a law addressing these claims and modernize the regulatory path for all in-vitro diagnostic tests, the FDA has proposed its own rules amending its regulatory authority to reign in most diagnostic tests.

This Note therefore suggests a multi-faceted approach to address the issue of regulating LDTs and their potentially misleading claims by (1) revising failed Congressional bills to allow regulatory and industry compromise, (2) applying certain circuit court decisions on Lanham Act claims to questionable facts in a company's advertisements, and (3) narrowly expand the FDA's regulatory power to all liquid biopsy tests before gradually expanding to all LDTs. Although LDTs may benefit the healthcare sector by offering novel tools to identify rare diseases, the federal government must develop an approach that both protects private parties and the general public and balances the need for research and development of life-saving diagnostic tests.

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INTRODUCTION

Medical diagnostic companies are developing revolutionary methods to diagnose different diseases—particularly cancer—from a simple blood draw rather than an invasive tissue sample called a biopsy.[1] These new diagnostics, which are termed liquid biopsies,[2] offer the promise of helping identify cancer at an early stage, potentially making the disease easier to treat and, hopefully, cure.[3] But liquid biopsies also may prove unreliable due to the small amount of tumor DNA in a patient's bloodstream, potential false positives, and lack of clinical significance.[4]

Notably, these new tests do not always fall under the U.S. Food and Drug Administration's ("FDA") regulatory purview.[5] For example, many liquid-biopsy based cancer tests are marketed as Laboratory Developed Tests ("LDTs") for "research use only."[6] Because LDTs lack the same degree of FDA scrutiny as traditional 510(k)-approved tests, companies have made bold, even potentially false, claims about their tests.[7]

For instance, in the early 2000's, Theranos, a one-time Silicon Valley unicorn biotech startup, claimed it had developed

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1. *See generally* Geoffroy Poulet et al., *Liquid Biopsy: General Concepts*, 63 ACTA CYTOLOGICA 449 (2019); *see also* Christopher B. Seaman, *Patent Eligibility and Cancer Therapy*, 79 WASH. & LEE L. REV. 453, 457–58 (2022) (describing the use of testing for cancer by collecting circulating tumor DNA in a person's bloodstream).

2. *See infra* Part I.B.

3. *See Using Liquid Biopsy for Early Cancer Detection,* MT. SINAI, https://perma.cc/2KG6-73TM (last visited Mar. 19, 2024).

4. *See infra* Part I.B.2.b; *see also* Behind the Bench Staff, *Cancer Heterogeneity and Liquid Biopsy,* THERMOFISHER SCI.: BEHIND THE BENCH (Aug. 29, 2022), https://perma.cc/CP4B-A4Z5.

5. *See What FDA Does and Does Not Regulate,* FDA, https://perma.cc/UP99-6F94 (last updated Oct. 19, 2017) (detailing elements like certain animal-specific diagnostic tests kits outside the agency's regulation).

6. *See Laboratory Developed Tests*, FDA, https://perma.cc/R3DL-REN2 (last updated Jan. 18, 2024) (describing LDTs as diagnostic tests designed, manufactured, and used within a single laboratory); *see also infra* Part II.B.

7. *See infra* Part III.B.2 (noting potential risks of claims made by Guardant Health and Natera about their tests).

diagnostic tests that could perform quickly and accurately using very small amounts of blood, all using compact automated devices.[8] After a series of medical errors and regulatory investigations exposed Theranos's platform as fraudulent, the company eventually shuttered operations.[9] Theranos's biggest problem—besides its blatant attempt to evade FDA scrutiny and defrauding investors[10]—involved the company's tests that it incorrectly claimed could accurately diagnose rare diseases actually "caused immediate jeopardy to patient" health "and safety."[11] Theranos diagnostic tests' inaccurate results placed patients at two major risks.[12] First, the company's tests could produce a false positive for a disease like colorectal cancer (CRC), causing patients to undergo rigorous treatment such as chemotherapy, only to later find out they never had the disease.[13] Second, the test could produce a false negative result,

8. Arielle Duhamie-Ross, *US Government Says Theranos Lab Poses "Immediate Jeopardy to Patient Safety"*, THE VERGE (Jan. 27, 2016), https://perma.cc/B5AH-RKLN (noting that Theranos repeatedly failed lab safety inspections by both the Centers for Medicare and Medicaid and the FDA, despite claiming back then that the findings did "not reflect the current state of the lab" and its technology).

9. *Id.*; *see also* JOHN CARREYROU, BAD BLOOD: SECRETS AND LIES IN A SILICON VALLEY STARTUP (Alfred A. Knopf ed., 2018**).** Through whistleblower revelations and Carreyrou's investigative work, the Wall Street Journal reported that more than 200 of the tests that Theranos deceptively advertised did not actually work on its specially developed "Edison" machine. Further the few tests that did work produced flawed and unreliable results. *See* EQS Editorial Team, *Elizabeth Holmes and the Theranos Case: History of a Fraud Scandal,* INTEGRITY LINE, https://perma.cc/ZXX5-SADB (last updated Nov. 22, 2023) (analyzing why the medical startup's technology failed to work properly).

10. *See* United States v. Holmes, No. 18-CR-00258, 2020 WL 6047232 at *2, *14 (N.D. Cal. Oct. 13, 2020) (noting the company defrauded multiple federal agencies and investors and placed patients at risks through its misleading advertisements). The district court eventually found Holmes guilty on four counts of defrauding investors and sentenced to 11 years in federal prison in 2023. *See* Natalie Neysa Alund, *Ex-Theranos CEO Elizabeth Holmes To be Released from Prison Two Years Early,* USA TODAY, https://perma.cc/C7UJ-6ZQ8 (last updated July 12, 2023).

11. Duhamie-Ross, *supra* note 8.

12. Kezia Parkins, *The Theranos Saga: A Wake-up Call for the Lab-Developed Test Market,* MED. DEVICE NETWORK (Jan. 25, 2022), https://perma.cc/TG57-EVQQ.

13. *Id.*

which failed to identify the disease until it was too late to deliver effective treatment (i.e., the patient ultimately died).[14]

Theranos's tests posed such a massive risk because they fell into the category of LDTs, which the FDA currently exercises little to no control over.[15] Because Theranos designed and used a test in a single lab, the company could market the tests without the FDA's approval.[16] The Theranos drama initially sparked a renewed interest in protecting the public against LDTs and other potentially faulty laboratory-based tests.[17] Congress, however, has failed to act, with proposed legislation that would grant the FDA greater regulatory authority over LDTs stalling without a floor vote.[18] More recently, the FDA has responded to Congress's failure to pass laws by issuing its own proposed rules on LDTs.[19]

Failing to hold companies like Theranos liable for potentially misleading claims about LDTs indicates worrisome implications for both the future of life sciences advertising and public safety. By marketing LDTs with potentially false or misleading claims, unscrupulous companies place patients in danger of an inaccurate diagnosis or inappropriate treatment.[20] Either failure can lead to significant patient harm and even death. Because the federal government cannot currently hold biotech companies liable for misleading accuracy claims about LDTs, this Article proposes a solution that increases the FDA's

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14. *Id.*

15. *See infra* II.B (detailing FDA's currently limited regulatory powers on LDTs).

16. *Id.*

17. *See infra* Parts II.A, IV.A (summarizing Congress' initial response that ultimately failed due to intense industry lobbying).

18. *See* Michael Dobias, Opinion, *Congress Must Close the Theranos Lab Test Loophole,* THE HILL (July 18, 2022), https://perma.cc/26ZX-GNEN; *see also* S. 4348, 117th Cong. (2022).

19. *See infra* Part II.C (noting the FDA's recent efforts to seize control of LDT regulation with its Sept. 2023 proposed rules).

20. *See* Kathy Talkington *Changes in Diagnostic Test Policies Help Reduce Risks for Patients,* PEW CHARITABLE TRS. (Jan. 19, 2023), https://perma.cc/LVH2-V7LP (noting that LDTs "have become widespread and increasingly complex, and are used for a variety of diseases, including cancer, exposing more people to potential harm from unreliable or misleading test results").

regulatory abilities to protect public health and safety while also increasing access to reliable diagnostic tests.

Part I of this Note begins by introducing the current standard for diagnostic testing, especially for cancer detection (biopsy), before discussing how an emerging technology called "liquid biopsy" has the promise to help spot cancers.[21] This Part also discusses liquid biopsy's advantages, areas for improvement, and potential clinical application in colorectal cancer.[22] Next, Part II reviews the ability of federal agencies—including the FDA and Centers for Medicare & Medicaid Services (CMS)—to regulate claims that companies developing LDTs make about their products.[23] Part III outlines the Lanham Act's[24] history and shows how private businesses have used the statute to protect their products while suing other parties for false claims.[25] Part III then highlights a current circuit split on applying the Lanham Act to scientific claims.[26] It then examines the potential ramifications of a current case, *Guardant v. Natera*,[27] regarding two parties who are suing one another for allegedly misleading claims about LDTs.[28] In Part IV, the Note reviews legislative efforts to pass the Verifying Accurate Leading-edge IVCT Development Act ("VALID Act"),[29] which would increase the FDA's power over LDTs and *in-vitro* diagnostic tests.[30] Because the VALID Act is unlikely to be enacted in its current form, Part V of this Note critically evaluates three potential solutions: (i) a legislative path involving a narrower version of the VALID Act; (ii) a judicial path embracing the Fifth Circuit's interpretation of the Lanham Act to cover misleading claims relying on scientific data as actionable statements of fact; and (iii) an administrative path

21. *See infra* Part I.
22. *See infra* Part I.B.
23. *See infra* Part II.
24. 15 U.S.C. § 1125.
25. *See infra* Part III.A.
26. *See infra* Part III.B.
27. 580 F. Supp. 3d 691 (N.D. Cal. 2022).
28. *See infra* Part III.B.2.
29. H.R. 4128, 117th Cong. (2022).
30. *See infra* Part IV.

expanding the FDA's power to liquid biopsy-specific, high-risk LDTs.[31]

I. TESTING AND IDENTIFYING CANCER BIOMARKERS

Diagnostic tests using cancer biomarkers[32] can be incredibly valuable. When used correctly, the tests can help clinicians determine whether their patients have cancer, a disease that affects millions of Americans.[33] When not used properly, however, tests like Theranos's that falsely claim to detect traces of cancer in a person's body can instead pose massive risks to a patient's long-term health.[34]

This Part will first discuss the history and traditional standards of *in-vitro* diagnostic tests for cancer detection.[35] Next, it will talk about "liquid biopsy" tests, an emerging field that uses a patient's liquid sample rather than tissue, and its promise to improve the traditional standard of cancer testing by spotting the disease at its earlier stages without requiring invasive surgeries.[36]

A. *Traditional Standards for Detecting Cancer*

Historically, researchers and companies have developed tests to diagnose cancer using FDA-approved methods such as tissue sampling, X-ray, and *in-vitro* diagnostic testing.[37] The

31. *See infra* Part V.

32. *See Focus Area: Biomarkers*, FDA, https://perma.cc/CES2-SZ5T (last updated Sept. 6, 2022) (describing biomarkers as "characteristics that are objectively measured as indicators of health, disease, or response to an exposure or intervention, including therapeutic interventions").

33. *See* Sonya Collins, *2024—First Year the US Expects More than 2M New Cases of Cancer*, AM. CANCER SOC'Y (Jan. 17, 2024), https://perma.cc/H3ZJ-GV5B (noting that while the risk of cancer has steadily declined over the past 30 years, medical experts expect to diagnose greater than two million cases of cancer and find over 611,000 deaths attributable to the disease in 2024).

34. *See* Duhamie-Ross, *supra* note 8.

35. *See infra* Part I.A.

36. *See infra* Part I.B.

37. *See How Cancer Is Diagnosed,* NAT'L CANCER INST., https://perma.cc/NE8D-NZ9C (last updated Jan. 17, 2023) (detailing methods such as lab tests, imaging tests, CT scans and x-ray machines, MRI, nuclear scans, PET scans, and ultrasounds).

FDA defines an *in-vitro* diagnostic test ("IVD") as reagents, instruments, and systems intended to diagnose diseases or other conditions.[38] IVDs use biological samples extracted from a patient's body and include "supplies and instructions for collecting, preparing, and testing" a biospecimen (e.g., cells, tissues, and DNA floating in a person's bloodstream).[39] These methods screen for, diagnose, and monitor the patient's cancer progression during and following treatment.[40] Current cancer diagnostic tests gather both tissue and liquid samples, searching for biomarkers indicating the presence of cancer.[41]

Though highly informative, traditional biopsies have several drawbacks.[42] First, due to their invasive nature, tumor biopsies pose significant health risks, including internal bleeding, extreme pain, and deadly infections.[43] In addition, clinicians also find certain cancers like leukemia difficult to access, making it difficult, if not nearly impossible, to perform a tissue biopsy.[44] In response, researchers have developed new, non-invasive and accurate methods to identify cancer tissue, including liquid biopsies.

B. *Liquid Biopsy Testing*

While the traditional standard for cancer testing has relied on invasive procedures that extract pieces of a patient's body tissue to spot cancer, a new method of non-invasive cancer testing has emerged in the clinical space that currently complements, and one day may replace, tissue biopsies: a liquid

38. 21 C.F.R. § 809(3)(a) (2022).

39. Wendy Schroeder, *So, I Asked Myself, "What's a Lab Developed Test?"*, 20 J. HEALTH CARE COMPLIANCE 27, 27 (2018).

40. *See Cancer Blood Tests: Lab Tests Used In Cancer Diagnosis,* MAYO CLINIC, https://perma.cc/V8DH-KX87 (last updated Mar. 9, 2024) (explaining the general lab tests identifying cancer biomarkers and how a patient can understand the different results).

41. *See How Cancer Is Diagnosed, supra* note 37 (noting that the test involves a biopsy, where a doctor removes a sample of abnormal tissue and looks at it under a microscope, running other tests as well).

42. *Liquid Biopsy: Promises and Problems,* AM. ASS'N FOR CANCER RSCH.: CANCER RSCH. CATALYST (Aug. 13, 2018), https://perma.cc/5KNB-23XV.

43. *Id.*

44. *See Bone Marrow Biopsy and Aspiration*, MAYO CLINIC (Dec. 1, 2022) https://perma.cc/HLW9-3A25.

biopsy. A "liquid biopsy" refers to real-time detection and analysis of tumor cells or tumor cell products released into the blood or other body fluids by cancer.[45] While researchers have identified several tumor cell products to help detect cancer, cell-free circulating-tumor DNA ("ctDNA") has emerged as the most promising analyte for screening cancer in its earliest stages.[46]

When used properly, liquid biopsy based LDTs can act as a powerful source of information for cancer screening.[47] Initially, LDTs served "a limited number of patients" who lived close to the laboratories developing the tests for purposes like spotting viral biomarkers for the COVID-19 coronavirus and measuring levels of lead in the bloodstream.[48] Today, however, LDTs assume a more pivotal role in medical decision-making, including applications for genetic testing and personalized medicine.[49] Experts now estimate that U.S.-based laboratories administer roughly 75,000 distinct LDTs.[50] Numerous companies hope to capitalize on this innovation by developing liquid biopsy tests relying on ctDNA.[51]

In the remainder of this Subpart, the Note will explain how liquid biopsy tests work by analogizing the technique to searching for invasive species of fish.[52] The Note will then highlight the technique's advantages, acknowledge certain

45. When a tumor cell detaches from the primary site and floats through the bloodstream, it may eventually latch onto another organ or location in the human body. This is known as "metastasis" and remains the main cause of cancer-related deaths. Klaus Pantel et al., *Liquid Biopsies: Potential and Challenges,* 148 INT. J. CANCER 528, 529 (2020).

46. *Id*.

47. *See Examples of Essential Laboratory-Developed Tests,* ASS'N FOR DIAGNOSTICS & LAB'Y MED., https://perma.cc/PBM4-4B4W (last accessed Mar. 19, 2024) (noting that effective LDTs are used for a variety of diagnostic purposes, including blood sampling for cancer tests that detect the full range of known certain cancer mutations, in a single laboratory setting).

48. *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market*, PEW CHARITABLE TRS. (Oct. 22, 2021) [hereinafter *Role of Lab-Developed Tests*], https://perma.cc/Y58B-3VJ8.

49. *Id*.

50. *Id*.

51. *See infra* Part I.B.3.

52. *See infra* Part I.B.1.

hurdles before full clinical implementation, and its potential applications for CRC.[53]

1. Invasive Species: How Spotting Asian Carp Mirrors Finding ctDNA

To better understand the potential power of ctDNA and liquid biopsy testing, imagine a person's body as the continental United States, their bloodstream as the Mississippi River (covering much of the central United States), and ctDNA as invasive Asian carp.

Asian carp are a quickly-growing invasive species of fish that are voracious eaters and outcompete native species, leaving a trail of environmental degradation and destruction in their wake.[54] Envision batches of Asian carp entering the Mississippi River from the Gulf of Mexico at estuaries (primary sites) like New Orleans's Lake Pontchartrain. Over time, smaller groups swim upstream, invading the river's hundreds of tributaries that span as far west as Missouri and east as Pennsylvania. While scientists face difficulties spotting the initial group that spread through the Mississippi River, they can track and eventually eradicate the invasive species from traveling farther north by sampling different carp and comparing their genetics at different locations. After sampling the number of fish and their genetic sequences, scientists have a better grasp of the scope and scale of the "infection" and can start treating the problem at primary and secondary invasion sites.

Like the Asian carp in a river, ctDNA initially starts in a primary tumor site within the human body, such as bone marrow or the colon.[55] The tumor eventually sheds pieces of its DNA in the patient's body.[56] Researchers collect a patient's blood sample, run different analyses, and spot traces of the tumor with

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53. *See infra* Part I.B.2.a–b.

54. *Invasive Carp*, U.S. DEP'T AGRIC., https://perma.cc/6RLB-Z496 (last visited Mar. 19, 2024).

55. *See* Olatunji B. Alese et al., *Circulating Tumor DNA: An Emerging Tool in Gastrointestinal Cancers*, AM. SOC'Y CLINICAL ONCOLOGY EDUC. BOOK 279, 279 (2022) (noting that ctDNA comes from primary or metastatic cancer cites).

56. Jason Zhu & John Strickler, *Clinical Applications of Liquid Biopsies in Gastrointestinal Oncology*, 7 J. GASTROINTESTINAL ONCOLOGY 675, 675 (2016).

ctDNA.[57] Importantly, ctDNA accounts for anywhere from 0% to more than 50% of all cell-free DNA in a patient's bloodstream.[58] This means researchers can use ctDNA in a person's bloodstream to identify irregular DNA patterns that can lead to cancer.[59] Based on the specific biomarker, researchers can then determine what type of cancer shed the ctDNA and screen to see if the tumor exists at the primary site.[60] To spot ctDNA biomarkers and identify a patient's tumor, researchers have developed two major enrichment methods: polymerase chain reactions ("PCR")[61] and next-generation sequencing (NGS)[62]. Using either method, researchers can find traces of tumors like colon cancer without using invasive, painful, and potentially disease-causing traditional biopsies that extract tissue from deep within a patient's body.[63]

2. Advantages and Weaknesses of Liquid Biopsies

Analyzing ctDNA offers several critical advantages versus standard tissue biopsies and other methods. For example,

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57. *Id.*

58. *See* Todd Morgan, *Liquid Biopsy: Where Did it Come From, What Is It, and Where Is It Going?*, INVESTIGATIVE & CLINICAL UROLOGY 139, 141 (2019) (highlighting ctDNA's clinical utility).

59. *Id.*

60. *See infra* Part I.B.2.b.

61. A polymerase chain reaction (PCR) involves rapidly amplifying millions to billions of copies of a specific segment of DNA. PCR uses short synthetic DNA fragments to select a segment of the genome to amplify and then several rounds of DNA synthesis to amplify that segment. When used for cancer detection, the process can amplify specific biomarkers indicating the source and type of cancer. *See Polymerase Chain Reaction (PCR)*, NATL. HUMAN GENOME RSCH. INST., https://perma.cc/X5PM-GMG5 (last updated Mar. 7, 2024).

62. Next-generation sequencing (NGS) uses a DNA amplifier to quickly bind DNA strands, which then are organized and bound to one of the four DNA. *See* Athinka Gkazi, *An Overview of Next-Generation Sequencing*, TECH. NETWORKS (Mar. 17, 2021), https://perma.cc/EW5F-E4Q2 (last updated Dec. 19, 2023). Subsequently, the fluorescent signal bound to the nucleotide is read at each cluster, then washed away. *Id.*; *see also* Pantel, *supra* note 45 (finding that certain targeted NGS methods can detect multiple rare mutations in ctDNA simultaneously, while untargeted approaches can detect novel, clinically relevant genomic aberrations without needing information about the primary tumor).

63. *See* Alese et al., *supra* note 55, at 280 (elaborating on the advantages and disadvantages of various assays for ctDNA analysis).

ctDNA provides a personalized snapshot of the patient's disease status.[64] CtDNA also shows increased sensitivity for detecting cancers early, especially compared to methods like X-rays or CT scans that may fail to spot extremely small tumors.[65] CtDNA is also non-invasive and reproducible; meanwhile, a tissue biopsy requires an invasive (and often painful) surgery to extract tumor tissue.[66] Further, ctDNA can give an accurate picture of the tumor's genetic profile.[67] So far, the FDA has approved at least one ctDNA assay for drug treatment purposes, with more expected in the next three to five years.[68]

Widespread adoption of ctDNA analysis faces three major hurdles before it can effectively enter the clinical space. These hurdles include: (1) dealing with the wide variety of cancer biomarkers, (2) a massive variety of cancer stage growth, and (3) a lack of prospective data.[69]

First, the cancer mutation must exist in the primary tumor's genome[70] for the test to identify ctDNA in the blood sample.[71] Consider the Asian carp metaphor: while scientists can identify carp along the Mississippi's tributaries from DNA in the water, they cannot always confidently confirm the exact carp species. Similarly, while CRC has certain genes that commonly mutate as part of its profile, none mutate all of the time.[72] Researchers therefore cannot always confirm whether

64. *See* Yingli Sun et al., *Circulating Tumor DNA as Biomarkers for Cancer Detection*, 15 GENOMICS, PROTEOMICS & BIOINFORMATICS 59, 59 (2017) (highlighting on the clinical advantages of ctDNA over CTCs and other liquid biopsy analytes).

65. *Id.*

66. *Id.*

67. Morgan, *supra* note 58, at 140.

68. *See FDA Approves Foundation Medicine Blood Test as CDx for Rozlytrek,* GENOMEWEB (Jan. 4, 2023), https://perma.cc/ZMD6-GV89 (noting that the company's test still requires all patients with a negative test to undergo a tissue biopsy due to the concern of false negative results).

69. *See* Yingli, *supra* note 64, at 59 (acknowledging critical challenges with liquid biopsy methods before it can enter the clinical space).

70. The genome is the entire set of DNA instructions found in a cell, containing all the information needed for a person to develop and function. *Genome,* NAT'L HUMAN GENOME RSCH. INST., https://perma.cc/7XWG-LRM7 (last updated Mar. 7, 2024).

71. Zhu, *supra* note 56, at 676.

72. *Id.*

the ctDNA indicates the true presence of CRC or another cancer type.[73] Further, the quantity of ctDNA is linked to the tumor in a non-linear manner, which means researchers often struggle to measure the amount of ctDNA in early-stage cancers.[74] After patients undergo treatment, any tumor remnants like ctDNA exist in extremely small fractions, making it challenging to find amid the vast background of the normal DNA in a blood sample.[75]

Applying the Asian carp analogy, not enough scientists and nets exist to screen for and catch fish repeatedly in the entire Mississippi River after treating for the first invasion. Instead, the invasive carp population may return after the initial eradication. Only then can scientists identify and contain the fish population in later stages and minimize its effects on the river's ecosystem.

Lastly, researchers lack sufficient data from prospective studies that directly compare liquid biopsy assays and standard tissue-based tests, limiting their actual clinical benefit in cancer's earliest stages.[76] Instead, ctDNA holds the most clinical benefit for patients with advanced metastatic disease because it can spot certain mutations previously identified with tissue biopsies at earlier stages.[77] Still, researchers believe ctDNA is a promising tool for cancer detection, particularly for monitoring for disease recurrence and progression.[78]

Despite challenges with satisfying the accuracy needed for clinical use, ctDNA-based liquid biopsy tests might remove the need for invasive needles and help doctors make smart treatment decisions after cancer surgery, especially in the case

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73. *Id.*

74. *Id.*

75. *See* Isabel Heidrich et al., *Liquid Biopsies: Potential and Challenges*, 148 INT'L J. CANCER 528, 541 (2020) (noting that single mutations in patients with advanced disease is "less demanding than assessing the broad panel of mutation in early-stage patients with low amounts of ctDNA").

76. *See* Zhu, *supra* note 56, at 676, 682 (noting additional smaller barriers to clinical access, including the lower clinical sensitivity and specificity, as well as despite the fact that "while liquid biopsies may give us the ability to detect mutations, we still lack effective drugs for many genomic" mutations).

77. *Id.*

78. Maxim Freidin et al., *Circulating Tumor DNA Outperforms Circulating Tumor Cells for KRAS Mutation Detection in Thoracic Malignancies,* 16 CLIN. CHEM. 1299, 1304 (2015).

of colorectal cancer ("CRC").[79] Researchers have found that ctDNA biomarkers are effective for minimal residual disease ("MRD")[80] purposes in CRC, which involves checking to see if the tumor has returned after treatment.[81] CtDNA can also help researchers predict which drugs will best eradicate a patient's colorectal cancer.[82] Thus, post-treatment screening with ctDNA may improve overall survival for colorectal cancer patients.[83]

II. 510(K) VERSUS LDTS: CLASHING REGULATORY PATHWAYS

Biotech companies can obtain approval to market liquid biopsy tests through two potential regulatory pathways: (1) a full regulatory path through the FDA that may secure 510(k)-clearance (e.g., Natera's Signatera test),[84] or (2) a commercially limited, less expensive, and minimal regulatory route through CMS (e.g., Guardant's Reveal assay).[85] Neither agency can conclusively claim regulatory control over LDTs, however, because of disagreements regarding ambiguous statutory language and different test validation requirements for market approval.[86] This regulatory uncertainty poses a

79. *See* Pantel, *supra* note 45, at 540 (highlighting that almost 900,000 colorectal cancer deaths occurred in 2018 alone).

80. MRD refers to residual tumor cells or biomarkers in the body after local or systemic cancer treatment**.** *See* Yan Peng et al., *Circulating Tumor DNA and Minimal Residual Disease (MRD) in Solid Tumors: Current Horizons and Future Perspectives*, FRONTIERS IN ONCOLOGY (2021). Its activation promotes tumor metastasis and tumor cell attachment in other parts of the patient's body. *Id.*

81. Frank Diehl et al., *Circulating Mutant DNA to Assess Tumor Dynamics*, NATURE MED., Sept. 2008, at 985, 990; *see also What Is Cancer Recurrence?*, AM. CANCER SOC. (Dec. 2, 2012), https://perma.cc/FWG6-SUUP (explaining that relapse occurs when the tumor redevelops in another portion of the body after treatment when standard methods fail to detect it).

82. *See* Zhu, *supra* note 56, at 577 (touting ctDNA's use for "monitoring for the development of molecular resistance").

83. *Id.*

84. *Premarket Notification 510(k)*, FDA, https://perma.cc/JN4N-8GBH (last updated Dec. 5, 2023).

85. *See* Elizabeth Cairns, *Guardant Steps into a New Arena*, EVALUATE (June 22, 2021), https://perma.cc/KPH7-EJXF (describing Guardant's recent foray into colorectal cancer recurrence with the launch of the Guardant Reveal assay).

86. This will likely be the case unless the FDA's recently proposed rules are finalized. *See infra* Part II.C.

growing danger to public safety and limits protection against unreliable tests.

This Part first walks through the FDA's review process for diagnostic companies seeking full regulatory approval for their tests before marketing the product.[87] Next, it discusses the problematic approach that some companies have used to avoid the expensive and time-intensive process of FDA approval by instead relying on CMS's less rigorous standards.[88] Finally, it elaborates on the FDA's recent drive to establish its control over LDTs and end the historical enforcement discretion policy.[89]

A. *Playing It Safe and Reliable: The 510(k) Path*

The FDA has established a clear regulatory framework for traditional IVD tests.[90] Until recently, however, the agency has failed to assert regulatory power over LDTs, causing a massive growth in unregulated tests in the last decade.[91]

The FDA regulates the development, approval, and marketing of new devices under the Federal Food, Drug, and Cosmetic Act ("FD&C Act").[92] Thus, a company hoping to market a medical device in the U.S. must submit a premarket 510(k) document to the FDA for "commercial distribution".[93] Based on the device's complexity, the sponsor must first demonstrate in the 510(k) document that the new device is "substantially equivalent" to a "predicate device".[94] Then, before marketing the

87. *See infra* Part II.A.

88. *See infra* Part II.B.

89. *See infra* Part II.C.

90. *See In-Vitro Diagnostic Device Labeling Requirements*, FDA, https://perma.cc/4BMZ-JZBZ (last updated July 7, 2023) (addressing the regulatory route and labeling requirements that biotech companies must follow to receive FDA approval and subsequently commercialize their tests).

91. *See infra* Part II.B.

92. 21 U.S.C. §§ 301–399i.

93. *See* 21 C.F.R. § 807.07 (2022) (detailing information required for each pre-market notification, including submissions supported by clinical data); *see also Premarket Notification 510(k), supra* note 84.

94. *See How to Find and Effectively Use Predicate Devices*, FDA (Sept. 4, 2018), https://perma.cc/U59W-RA68 (elaborating that a predicate device is a "legally marketed device to which equivalence is drawn" to, but claiming one's device meets "substantial equivalence" does not require that the devices must be identical); *see also* Etienne Nichols, *Understanding FDA Cleared vs Approved vs Granted for Medical Devices*, GREENLIGHT GURU (Jan. 16, 2023),

device, each submitter must "receive an order, in the form of a letter," from the FDA finding that the device meets certain requirements, such as: (1) clinical results showing that the new diagnostic poses no more risk than the predicate device, and (2) the test's data indicates its clinical accuracy and utility.[95] 510(k) approval thus indicates that the new device can be marketed and used as safely and effectively as a device already on the market.[96]

As part of the 510(k) process, companies voluntarily sign up for a program called the "Breakthrough Devices Program" to "provide healthcare providers with timely access to the devices by speeding up their development, assessment, and review."[97] This program offers testing companies an opportunity to interact with the FDA's experts while commercializing their tests, ultimately providing the companies with feedback and prioritized review of their submissions.[98] Liquid biopsy companies like Natera have followed this route to buttress their clinical results while working on a 510(k) submission.[99] Unfortunately, the FDA's regulatory options—whether companies seek 510(k)-certification status or Breakthrough Device Designation—only cover either fully-commercialized assays or those that are "provide for more effective treatment or

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https://perma.cc/N7RD-MFHB (explaining the specific requirements for the different classifications of medical devices, based on their level of risk to the public and novelty).

95. 21 U.S.C. § 360(k); *see also Premarket Notification 510(k)*, *supra* note 84 (pointing out that the similarly legal market devices are those that do not violate the FD&C Act).

96. *See Premarket Notification 510(k)*, *supra* note 84 (explaining that a device that is substantially equivalent it has the same intended use and other relevant factors).

97. *Breakthrough Devices Program,* FDA, https://perma.cc/ZFP2-N493 (last visited Mar. 22, 2024).

98. *Id.*

99. *See In Brief This Week: Natera, Genome Diagnostics, Veracyte, and More*, GENOMEWEB (May 10, 2019), https://perma.cc/BC3K-55LD (highlighting that the FDA granted Natera's assay "Breakthrough Device Designation" status and that the company has begun clinical trials as part of its plan to commercially launch the test).

diagnosis of life-threatening or irreversibly debilitating diseases".[100]

B. *Dodging the Ball: LDTs and "Research Use Only"*

In contrast to the FDA's 510(k) route, some companies have instead opted to pursue a cheaper and quicker route to commercialize their tests.[101] Specifically, firms developing liquid biopsy tests—such as Guardant and its "Guardant Reveal"[102]—have pursued a cheaper, yet allegedly commercially-limited, route by offering their test as an LDT. This route offers LDT companies a loophole that bypasses certain regulatory requirements for fully-approved tests: namely, the FDA does not review or approve tests developed and used in a single lab.[103]

After Congress enacted the 1976 Medical Device Regulation Act,[104] which amended the FD&C Act to regulate medical devices including IVDs, the FDA has generally declined to directly enforce this statute's provisions with respect to LDTs.[105] Until recently, the agency has left enforcement discretion for LDTs as a matter of general practice to CMS.[106]

The FDA defines the term *laboratory developed test* as an IVD that is designed, "developed, and manufactured" out of a

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100. *Breakthrough Devices Program: Guidance for Industry and Food Drug Administration Staff,* FDA, https://perma.cc/M2ET-J6TG (last updated Apr. 14, 2023).

101. *See Laboratory Developed Tests*, *supra* note 6 (pointing out that LDTs present high risks than IVDs because of their lack of clinical evidence).

102. *See Guardant Health Receives Medicare Coverage for MRD Liquid Biopsy in Stage II and III Colon Cancer*, GENOMEWEB (Aug. 2, 2022), https://perma.cc/6RL4-5YX7 [hereinafter *Guardant Health Receives Medicare Coverage*] (noting that Guardant's Reveal assay, as an LDT, has received CMS local coverage determination for stage II-III colorectal cancer patients).

103. *See* Dobias, *supra* note 18 (emphasizing that companies still have the opportunity to "market high-risk" LDTs without "FDA review because the outdated rules that have been in place for decades allow it").

104. 21 U.S.C. § 360(c).

105. FDA, FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS (LDTS) 5 (2014) [hereinafter FRAMEWORK].

106. *Id.* at 6–7; *see also Laboratory Accreditation Program,* COLL. AM. PATHOLOGISTS, https://perma.cc/ULB3-5W3Y (walkthrough of the requirements a company's laboratory must meet to receive the designation to market LDTs).

single Clinical Laboratory Improvement Amendments of 1998[107] ("CLIA")-certified laboratory that "is intended for clinical use."[108] CMS regulates laboratories under the CLIA system, which defines a clinical laboratory as a facility that examines materials "derived from the human body" information to diagnose, prevent, or treat any disease.[109] While the College of American Pathologists ("CAP")[110] governs the accreditation, inspection, and certification requirements of these labs, the specific CLIA requirements address the laboratory's testing process.[111] Under CLIA, CMS accreditors do not evaluate the test's analytical validity before marketing, nor do they examine its clinical validity.[112] In other words, while a CLIA accreditor confirms that the test spots a specific biomarker, it does not assess whether the test accurately diagnoses the disease allegedly linked to the biomarker. As more LDTs claim to detect several diagnosable diseases, this causes concern because LDTs do not have to comply with quality system regulations.

In contrast, CMS does not restrict claims made about the efficacy of LDTs developed by CLIA-certified, CAP-accredited labs.[113] Rather, advertisements about an LDT's clinical claims are subject to review by a different federal agency—the Federal

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107. *See* 42 U.S.C. § 263(d) (enumerating the different standards that a laboratory must meet to receive a certificate, such as maintaining a quality assurance and control program to ensure the test's reliability and use only qualified personnel to conduct examinations).

108. *See* FRAMEWORK, supra note 105, at 6.

109. 42 U.S.C. § 263(a).

110. *See* CLIA Program: Announcement of the Re-Approval of the College of American Pathologists (CAP) as an Accreditation Organization Under the Clinical Laboratory Improvement Amendments of 1988, 86 Fed. Reg. 16371 (Mar. 29, 2021) (highlighting CMS' re-approval of CAP as the accreditation organization for purposes of establishing clinical laboratories' compliance with CLIA requirements in all specialties and subspecialties until 2027).

111. *See About CLIA*, CDC, https://perma.cc/WE58-NYWM (last updated Aug. 6, 2018) (describing the federal standards applicable to U.S. facilities that test human samples for "health assessment or to diagnose, prevent, or treat disease").

112. *See* FRAMEWORK, *supra* note 105, at 7 (acknowledging that the accreditor examines issues such as the "accuracy with which the test identifies, measures, or predicts the presence or absence" of a medical condition or predisposition in the patient).

113. AMANDA SARATA, CONG. RSCH. SERV., IF11389, FDA REGULATION OF LABORATORY-DEVELOPED TESTS (2022), https://perma.cc/JV7Z-YHKG (PDF).

Trade Commission (FTC)—and must carry a disclaimer that the FDA has not cleared nor approved the test.[114]

Today, LDTs are developed in laboratories that apply components and instruments that are not legally marketed for clinical use and often require high-tech instruments to generate results.[115] When used properly, LDTs can assist in patient care, particularly for patients with medical conditions that lack a commercially-approved test.[116] However, CMS approval of LDTs is not without concerns. In particular, the FDA has identified several regulatory gaps and risks associated with CMS's LDTs approval process, including: (1) inadequate clinical validation, (2) disparate evidentiary rigor in competitive product spaces, and (3) manufacturer claims that are not supported by scientific data.[117] The FDA has argued that some LDTs can place patients in serious jeopardy due to their complexity, nationwide reach and higher risks.[118] Even worse, certain competitors allegedly take advantage of IVD manufacturers conducting research to validate their tests for pre-market review by not following the same standards to support similar claims for their LDTs.[119] For

114. Antionette Konski, *FDA Regulation of Laboratory Developed Tests: Benefit or Unnecessary Burden?*, JDSUPRA (Feb. 5, 2013) https://perma.cc/6MQA-5TXQ.

115. *See* FRAMEWORK, *supra* note 105, at 10–11 (noting that the FDA is concerned that LDTs that do not use legally marketed reagents can lead to "inaccurate, unsafe, ineffective, or poor quality" results).

116. *See Oversight of Laboratory Developed Tests*, ASS'N FOR DIAGNOSTICS & LAB'Y MED. (Oct. 1, 2020), https://perma.cc/D5NZ-MKLU (noting that LDTs play a critical role in responding to world health crises, such as HIV and the COVID-19 pandemic).

117. *See* FDA OFF. OF PUB. HEALTH & STRATEGY, THE PUBLIC HEALTH EVIDENCE FOR FDA OVERSIGHT OF LABORATORY DEVELOPED TESTS: 20 CASE STUDIES 3–4 (2015) https://perma.cc/4LDX-2F2Z (PDF) (highlighting that such issues, along with deficient adverse event reporting, lack of premarket review of performance data, and lack of transparency, can undermine progression in precision medicine).

118. *See Laboratory Developed Tests*, *supra* note 6 (emphasizing that the agency is aware of faulty LDTs that could have led to colon cancer patients being exposed to inappropriate therapies or not getting effective therapies, which could lead to illness and death).

119. *See* FDA OFF. OF PUB. HEALTH & STRATEGY, *supra* note 117, at 4 ("Under the status quo, manufacturers have every incentive not to seek FDA clearance/approval, and the public is thus denied the advantages and improvements in scientific rigor the research and review process ensures."); *see also Role of Lab-Developed Tests, supra* note 48 (noting that while an estimated "3.3 billion in vitro diagnostic tests—both FDA-reviewed and

example, Guardant Health currently offers its Guardant Reveal as an LDT for "research use only".[120] Understandably, companies pursuing 510(k)-clearance like Natera are eager to sue when their competitors make perhaps misleading or unsupported scientific claims without potential fear of regulatory or legal repercussion.[121]

In light of LDT's exponential growth and their dangers for unauthorized clinical uses, the FDA initially announced in 2010 that all LDTs would be subject to agency oversight.[122] To assert its regulatory authority over LDTs, the FDA published draft guidance in 2014 describing how the agency intended to regulate diagnostic laboratories like medical device manufacturers under the FD&C Act.[123] However, a number of healthcare professionals, patient advocates, medical institutions, pathology departments, and companies in the healthcare industry quickly opposed the "one-size-fits-all" approach to regulating LDTs.[124] After two years of industry feedback, the FDA announced in 2016 that it would postpone work on the guidance, at least temporarily killing the proposal.[125]

LDTs—are run every year," it is unclear exactly how often LDTs are used or their exact clinical purpose).

120. *See Guardant Health Receives Medicare Coverage*, *supra* note 102 (providing details about Medicare coverage of Guardant's Reveal assay while still only being offered as an LDT).

121. *See infra* II.B.2 (discussing Natera and Guardant's suit about misleading medical claims).

122. *Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments*, FDA (June 17, 2010), https://perma.cc/PDY4-JTLQ.

123. FRAMEWORK, *supra* note 105.

124. *See* Turna Ray, *FDA to Finalize LDT Guidance Amid Uncertainty on Number of Genetic Tests Impacted*, GENOMEWEB (Feb. 4, 2016), https://perma.cc/2YP9-4WTN (highlighting that several medical groups contend that the "FDA oversight of LDTs would be burdensome on industry" and several suspect that the regulatory burden "may be bigger than what the agency is estimating").

125. Turna Ray, *FDA Holding Off on Finalizing Regulatory Guidance for Lab-Developed Tests*, GENOMEWEB (Nov. 18, 2016), https://perma.cc/5JWF-8U74.

C. *FDA's Recent Attempt to Reign in LDTs: Proposed September 2023 Rules*

To respond and potentially curb the "Wild West" antics of LDTs on the healthcare sector, the FDA proposed a new rule in September 2023 that would amend regulations and increase the agency's powers over IVDs.[126] The FDA contends that the LDTs should be held to the "same standards as other tests, while helping to ensure test makers have the flexibilities they need to continue innovating and developing tests critical to the advancement of public health."[127] This rulemaking would amend the definition of "in vitro diagnostic products" in the Code of Federal Regulations to state that IVDs are "devices" under the FD&C Act, "including when the manufacturer of these products is a laboratory."[128] As noted above, the FDA is concerned that patients could start unnecessary treatment, or delay or forego proper treatment altogether, based on inaccurate test results, which may lead to increased morbidity and mortality.[129] By doing so, the FDA implicitly is admitting it has not strictly enforced its current rules, allowing an enormous market to create tests offered as LDTs.

Under the new rule, the FDA is proposing a policy where the agency anticipates a five-stage, four-year phaseout process

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126. *See* Press Release, FDA, FDA Proposes Rule Aimed at Helping to Ensure Safety and Effectiveness of Laboratory Developed Tests (Sept. 29, 2023), https://perma.cc/T7UA-CBNT; *see also* Thomas M. Burton, *Is Lab Testing the 'Wild West' of Medicine?,* WALL ST. J. (Dec. 10, 2015), https://perma.cc/HV99-TLXF (describing the dynamic between the FDA and lab-developed test providers as a "Wild West" of medicine).

127. *See* Press Release, *supra* note 126.

128. Medical Devices; Laboratory Developed Tests, 88 Fed. Reg. 68006 (proposed Oct. 3, 2023) (to be codified at 21 C.F.R. § 809.3); *see also* 88 Fed. Reg. 68031 (noting that the regulation would read "[T]hese products are devices as defined in section 201(h)(1) of the [FDCA] and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory.").

129. *See supra* Part II.A. For example, the FDA is concerned that IVDs offered as LDTs developed by Guardant Health could have led to patients with cancer being exposed to inappropriate therapies or not getting effective therapies. *See* Press Release, *supra* note 126 (noting that a growing number of clinical diagnostic tests are being offered as lab-developed tests without proven assurances that they actually provide valuable and reliable results to patients).

for its general enforcement discretion approach toward LDTs.[130] The phaseout would cause laboratory-manufactured IVDs to generally fall under the same enforcement approach as other IVDs following the issuance of the policy.[131] In Stage One, the FDA would end the approach to medical device reporting ("MDR") and removal reporting.[132] In Stage Two, the agency would cease requirements for device registration and listing requirements, device labeling, investigational use, and other requirements not covered by the rest of the phaseout stages.[133] In Stage Three, the FDA will stop the approach for quality system regulation requirements.[134] In Stage Four, the agency would cease the approach for premarket review requirements for high-risk IVDs. In Stage Five, the FDA will finally end the approach for premarket review requirements for moderate- and low-risk IVDs requiring premarket submissions.[135] However, in Stages Four and Five the FDA would not anticipate enforcing IVDs offered as LDTs after a company has filed a timely premarket submission, at least until the FDA completes its review.[136] After the phaseout period, the FDA would expect IVD makers to satisfy the same requirements as current IVD manufacturers, other than when the lab can leverage certain requirements under CLIA.[137]

However, the FDA's proposal notes that certain tests that it never aimed to regulate using the current enforcement discretion policy—like direct-to-consumer genetic ancestry tests lacking dedicated participation with a licensed healthcare professional and tests for public health emergencies (like the

130. *See* Medical Devices; Laboratory Developed Tests, *supra* note 128.

131. *Id.*

132. Gregory H. Levine et al., *Regulation Without Legislation: FDA Proposes Rule to Regulate Laboratory Developed Test and End Historical Enforcement Discretion Policy*, ROPES & GRAY (Oct. 3, 2023), https://perma.cc/42LB-N28T.

133. *Id.*

134. However, for tests that satisfy the FDA's 1976 definition of LDTs, the agency will only expect compliance with certain elements of the quality system regulation, namely (1) design controls, (2) purchasing controls, (3) acceptance activities, (4) corrective and preventive actions, and (5) records requirements. Levine et al., *supra* note 132.

135. *Id.*

136. *Id.*

137. *See* Press Release, *supra* note 126.

COVID-19 pandemic)—will still be regulated as before under CLIA.[138] Aware of the interplay between the FD&C Act and CLIA regulatory schemes, the FDA anticipates addressing CLIA-certified laboratories differently as it shuts down the enforcement-discretion approach to regulating tests and other medical devices.[139] Further, the FDA proposes that certain LDTs and IVD categories will not be affected by the phaseout at all and continue to be subject to enforcement discretion.[140] Instead, the FDA will only apply the phaseout policy to IVDs offered as LDTs by labs that meet CLIA certification *and* meet the regulatory elements under CLIA to perform complex testing (even if these tests are not designed, manufactured, and used within a single laboratory).[141] In sum, the FDA's proposed rule envisions that it would advance "responsible innovation by both laboratory and non-laboratory IVD manufacturers" by assuring the safety and effectiveness of IVDs offered as LDTs *and* remove financial disincentives for non-manufacturers.[142]

Unsurprisingly, the agency has faced industry pushback regarding its newly-proposed rules on LDTs. During the agency's Notice and Comment period, several groups—including 89 organizations in an October 31, 2023 letter—representing clinical laboratories and scientists requested a 60-day extension of the comment period.[143] Since the agency's comment deadline

138. *See* Medical Devices; Laboratory Developed Tests, *supra* note 128.

139. *See id.*

140. *See* Elizabeth Hillebrenner, Assoc. Dir. for Sci. and Regul. Programs, Ctr. for Devices and Radiological Health, Webinar on the FDA's Proposed Rule Regarding Laboratory Developed Tests, Oct. 31, 2023, (PDF) https://perma.cc/TF2R-2VDR (noting that tests that meet 1976-Type LDTs, Human Leukocyte Antigen (HLA) tests, forensic tests, and Public Health Surveillance Tests will not be affected by the Phaseout Policy).

141. *Proposed Rule on Laboratory-Developed Tests Takes Center Stage*, COOLEY (Nov. 29, 2023), https://perma.cc/B494-VYMN.

142. *See* Hillebrenner, *supra* note 140.

143. *See* ASS'N FOR DIAGNOSTICS & LAB'Y MED. et al., *Request for an Extension to the Comment Deadline to the Rulemaking Docket No. FDA 2023-N-2177, Medical Devices: Laboratory Developed Tests* (Oct. 31, 2023), https://perma.cc/WV37-WJ34 (PDF) (highlighting that similar efforts to regulate IVDs in markets like the European Union dealt with risks of diagnostic shortages due to lack of grace periods for certain device types and ultimately other consequences like lack of sharing informatics pipelines)*; see also* Adam Bonislawski, *FDA Moving Quickly on LDT Rulemaking as 2024 Elections, 2027 User Fee Renewal Loom*, 360DX (Nov. 15, 2023), https://perma.cc/J7TB-MQMD (noting that the FDA held firm to its sixty-day

on December 4, 2023, users have posted nearly 7,000 comments on the Federal Register's webpage expressing concerns regarding the proposed rule's impact on the clinical lab industry.[144] Industry groups like American Clinical Laboratory Association ("ACLA") have sharply rebuked the FDA's unilateral approach to regulate LDTs, arguing that LDTs are not medical devices and the new rule exceeds the agency's statutory powers.[145] Further, industry groups are concerned that even if the FDA promulgates the proposed rule and implements the phaseout policy, the four-year timeframe will be insufficient for the industry to transition.[146]

Prior to the FDA's recent push last fall, biotech companies have taken advantage of the regulatory clash diagnostic tests by using limited marketing methods to develop and commercialize LDTs lacking adequate clinical evidence.[147] Private companies and industry groups have thus used the Lanham Act in litigation or to advocate for Congress to pass legislation to address fraudulent claims about LDTs.[148]

III. ISSUES WITH LDTS AND UNSCRUPULOUS CLAIMS

Despite the increased demand and use of LDTs, the U.S. legal system has not yet developed a comprehensive approach to evaluate the veracity of marketing material promoted by companies developing the tests. As discussed in more detail below, one possibility for intervention is to raise a claim for false or misleading statements of fact under the Lanham Act. Initially

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period because of the "extensive background of public comment on this topic and the public health benefits of proceeding expeditiously").

144. *See* Medical Devices; Laboratory Developed Tests, *supra* note 128.

145. *FDA Issues Proposed Rule for Regulating Lab-Developed Tests*, AM. HEALTH L. ASS'N (Oct. 6, 2023), https://perma.cc/9BAQ-JQEC; *see also* PR Newswire, *ARUP Laboratories Urges FDA to Withdraw Proposed Rule Regulating Laboratory-Developed Tests*, YAHOO! FIN. (Nov. 29, 2023), https://perma.cc/ULB6-AM7H (arguing that the rule would decrease access to safe testing since "staggering compliance costs would force many laboratories to stop offering some LDTs, which would disproportionately affect patients with rare diseases, underserved populations, and children").

146. *Proposed Rule on Laboratory-Developed Tests Takes Center Stage*, *supra* note 141; *see also Response*, *supra* note 143 (discussing delay, modification or new genetic tests).

147. *See infra* Part III.B.2.

148. *See infra* Part III.A.

passed in 1946, the Act creates a federal law of unfair competition and false and misleading advertising.[149] More recently, some lower federal courts have applied the Lanham Act to claims about the efficacy and safety of healthcare products and services.[150] However, federal courts have split on whether the Lanham Act extends to scientific studies (which form the crux of any LDT's marketing efforts), let alone to claims between LDTs and FDA-approved tests.[151]

This Part will first discuss the Lanham Act's history and how private parties have succeeded in applying it to false claims.[152] It will then evaluate a circuit split between the Second and Fifth Circuit about applying the Lanham Act to scientific material. Finally, it will discuss a pending federal case under the Lanham Act that deals with allegedly false and misleading claims regarding a liquid biopsy LDT.[153]

A. *Lanham Act and False Claims*

Initially passed by Congress in 1946 with the purpose to "regulate commerce" by "prevent[ing]" fraud and deception,"[154] the Lanham Act was narrowly interpreted as "forbidding only 'passing-off,' or the infringement or unauthorized use of a trademark."[155] Courts have since expanded the Act's scope: it now serves as a vehicle for preventing infringement of trade dress, common law marks, and most importantly, false advertising (including product disparagement).[156] Specifically,

149. *See infra* Part III.A; *see also* Christopher B. Seaman, *Reconciling the Lanham Act and the FDCA: A Comment on Chris Hurley's Note*, 75 WASH. & LEE L. REV. 647, 655–56 (2018) (summarizing the Lanham Act's evolution).

150. *See infra* III.B.

151. *See infra* III.B.1.

152. *See infra* III.A.

153. *See infra* III.B.2

154. Lexmark Int'l, Inc. v. Static Control Components, Inc., 572 U.S. 118, 131 (2014) (quoting 15 U.S.C. § 1127 (2012)).

155. Ethan Horwitz & Benjamin Levi, *Fifty Years of the Lanham Act: A Retrospective of Section 43(a)*, 7 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 59, 59–60 (1996).

156. RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 9; *see also generally* Bruce P. Keller, *"It Keeps Going and Going and Going": The Expansion of False Advertising Litigation Under the Lanham Act*, 59 LAW & CONTEMP. PROBS. 131 (1996).

Congress provided a cause of action for false advertising by initially incorporating into § 43(a) the words "any false description or representation,"[157] and tried to reintroduce a general federal law of unfair competition in response to *Erie Railroad Co. v. Tompkins*.[158]

Following § 43(a)'s revision in 1988, the Lanham Act now establishes a civil cause of action against a commercial speaker who expresses a "false or misleading representation of fact"[159] that "misrepresents the nature, characteristics, or qualities of goods, services, or commercial activities.[160] Because the terms "false or misleading description of fact" and "false or misleading representation of fact" were initially new to § 43, they were subject to much judicial interpretation.[161] However, this prong of § 43 generally covers statements that are literally false, as well as statements that, while literally true, create false impressions.[162]

Federal courts have adopted slightly different versions of a multifactor test first established in *Skil Corp. v. Rockwell Int'l Corp.*[163] to analyze false advertising claims under § 43(a). The factors include: (1) that the defendant made false statements of fact about either product (later extended to defendant's product *or the plaintiff's* product),[164] (2) the advertisements actually deceived, or have the tendency to deceive, a substantial segment

157. Until amended in 1988, § 43(a) stated that "any person who shall affix . . . any false description . . . including words . . . tending falsely to describe . . . the same, and shall cause such goods . . . to enter into commerce . . . with knowledge of the falsity of such designation of . . . [description] shall be liable to a civil action." 15 U.S.C. § 1125 (1988).

158. 304 U.S. 64 (1938).

159. Trademark Law Revision Act of 1988, Pub. L. No. 100-677, 102 Stat. 3935 (effective Nov. 16, 1989); *Id.* at § 1125(a)(1).

160. *Id.* at § 1125(a)(1)(B).

161. Horwitz & Levi, *supra* note 155.

162. *See* S.C. Johnson & Son, Inc. v. Clorox Co., 241 F.3d 232, 238 (2d Cir. 2001) (noting that § 43 covers ads that are "literally false," or despite being literally true, are likely to mislead and confuse the public). For example, even though it is true that a figure skater who earned first place in a two-person competition finished "almost in last place," the statement clearly misleads the listener. The statement creates a false impression such that if the speaker did not share any additional information, the listener could not figure out that the skater also won the competition.

163. 375 F. Supp. 777 (N.D. Ill. 1974).

164. *See supra* note 162 and accompanying text.

of their audience, (3) the deception is likely to influence the purchasing decision, (4) the defendant causes the false statement to enter interstate commerce, and (5) the plaintiff has been or is likely to be injured because of result of false statements, by diverting sales or damaging the goodwill of its products.[165] Moreover, a plaintiff must prove all five requirements and cannot "mix and match statements, with some satisfying one Lanham Act element and some satisfying others."[166] Courts have applied the test to a variety of advertisements in different sectors, including the fast food industry,[167] alcohol,[168] and, less frequently, scientific claims.[169]

While not about scientific claims, the Ninth Circuit has held that that plaintiffs have at least two ways to demonstrate a competitor's test is false or misleading under the Lanham Act. In *Southland Sod Farms v. Stover Seed Co.*,[170] the court held that to show falsity within the meaning of the Lanham Act, a plaintiff can prove that an advertising claim based on product testing is "literally false" by attacking the validity of the defendant's test.[171] Alternatively, the plaintiff can attempt to show that its competitor's tests are contradicted or "unsupported by other scientific tests."[172]

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165. *Skil Corp.*, 375 F. Supp. at 782; *see also* Ill. Tool Works, Inc. v. RustOleum Corp., 955 F.3d 512, 517 (5th Cir. 2020); Merck Eprova AG v. Gnosis S.P.A., 760 F.3d 247, 255 (2d Cir. 2014).

166. Verisign, Inc. v. XYZ.com L.L.C., 848 F.3d 292, 299 (4th Cir. 2017); *see also* Pizza Hut, Inc. v. Papa John's Int'l, Inc., 227 F.3d 489, 495 (5th Cir. 2000) (emphasizing that the "failure to prove the existence of any element of the prima facie case is fatal").

167. 227 F.3d 489, 496 (5th Cir. 2000) (noting pizza chain plaintiff did not have a "false advertising" claim because the challenged statement amounted to puffery).

168. *See* MillerCoors, L.L.C., v. Anheuser-Busch Companies, L.L.C., 385 F. Supp. 3d 730, 733 (W.D. Wis. 2019) (noting that a competitor's Super Bowl advertisements about alleged use of corn syrup in beer likely deceived "a substantial segment of consumers" into believing the beer company's product actually contained corn syrup).

169. *See infra* note 173.

170. 108 F.3d 1134 (9th Cir. 1997).

171. *Southland Sod Farms,* 108 F.3d at 1139.

172. *Id.*; *see also* Castrol, Inc. v. Quaker State Corp., 977 F.2d 57, 62–63 (2d Cir. 1992) (emphasizing that a product's superiority claims explicitly based on test or studies can be proven false by shown the tests did not establish the proposition that they were cited for).

However, most federal courts have struggled to apply the Lanham Act broadly to advertising claims when the advertisements at issue directly rely on scientific material**.** Only three circuit courts have established clear standards—though even these standards differ—when applying the Lanham Act to scientific material used for advertising purposes. The wide discrepancy among courts has triggered a circuit split. While the Second Circuit—and to an extent the Seventh Circuit—has chosen a more deferential approach regarding any scientific material integrating peer-reviewed studies, the Fifth Circuit instead has found that scientific material used in fliers and advertisements is readily subject to the Lanham Act.[173] Furthermore, no circuit court has directly applied the Lanham Act to scientific data and marketing material comparing LDTs and 510(k)-approved tests. However, a series of cases applying the Lanham Act has shed some light on what federal courts may ultimately conclude regarding applying the Lanham Act to LDTs.

B. *Circuit Split: Applying Lanham Act Claims to Scientific Research*

While federal courts have usually avoided imposing liability for broad scientific opinions, some circuit court cases may help indicate what route the federal court system will follow regarding LDTs and their risks, at least for liquid biopsies.[174] In this Subpart, the Note will first explain and analyze the current circuit split between the Second and Fifth Circuit as how to interpret and apply the Lanham Act to scientific claims made by advertisers.[175] The Subpart will then conclude with a discussion

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173. *Compare* ONY, Inc. v. Cornerstone Therapeutics Inc. 720 F.3d 490, 498 (2d Cir. 2013) (holding that a publication of peer-reviewed studies cannot be challenged under the Lanham Act unless the study is clearly fraudulent), *and* Underwager v. Salter, 22 F.3d 730, 736 (7th Cir. 1994) ("Scientific controversies must be settled by the methods of science rather than by the methods of litigation."), *with* Eastman Chem, Co. v. PlastiPure, Inc., 775 F.3d 230, 236 (5th Cir. 2014) ("Advertisements do not become immune from Lanham Act scrutiny simply because their claims are open to scientific or public debate. Otherwise the Lanham Act would hardly ever be enforceable."); *see also infra* Part III.B.2.

174. *See infra* Part III.B.1.

175. *See infra* Part III.B.1.a–b.

about a case out of the U.S. District Court for the Northern District of California called *Guardant v. Natera*[176] where both sides have argued in favor of either the Second or Fifth Circuit's interpretation of the Lanham Act.[177]

1. Circuit Split: Scientific Opinion v. Statements of Fact

When dealing with unscrupulous companies and their marketing claims, the Second and Fifth Circuits have disagreed over when and how to apply the Lanham Act to marketing material sourced from scientific data.[178] Specifically, the courts have attempted to distinguish between "non-actionable scientific opinions" and "actionable statements of fact."[179]

a. Second Circuit

The Second Circuit has held that published peer-reviewed studies are exempt from liability under the Lanham Act unless the defendant's study results are clearly fraudulent.[180]

ONY, Inc. v. Cornerstone Therapeutics, Inc. involved two major competing producers of FDA-approved "surfactants," biological substances that line the surface of human lungs and help underdeveloped infants breathe.[181] Hiring physicians to present the results of its comparison study, the defendant eventually published the results in a peer-reviewed journal article and subsequently issued a press release touting its conclusions.[182] The plaintiffs sued under the Lanham Act, claiming the article contained several flawed statements about the competing products.[183] The plaintiff also took issue with subsequent promotional use of the conclusion in the article.[184]

176. 580 F. Supp. 3d 691 (N.D. Cal. 2022).

177. *See infra* Part III.B.2.

178. *See* discussion of cases *infra* Part III.B.1.a–b.

179. *Eastman*, 775 F.3d at 232.

180. *ONY*, 720 F.3d at 490.

181. *See id.* at 492–94 (noting that the defendants in that case conducted a study comparing the relative efficacy of the competing products and claimed that their own product was more effective than the plaintiffs).

182. *Id.* at 494–95.

183. ONY, Inc. v. Cornerstone Therapeutics Inc., 720 F.3d 490, 495 (2d Cir. 2013).

184. *Id.*

After the district court granted the defendant's motion to dismiss, the plaintiff appealed to Second Circuit, arguing that false scientific claims printed in a publication can be "defamatory or represent false advertising if known to be false when made."[185] However, the Second Circuit hesitated to agree with the plaintiffs, reasoning that courts "are ill-equipped to undertake to referee such controversies."[186] Instead, the court considered that the debate of scientific "ideas plays out in the pages of peer-reviewed journals," and the scientific public reviewing the study's results acts as an informed jury.[187] Therefore, the court held that scientific conclusions and opinions that an author draws from a peer-reviewed study's data are not actionable for a claim of false advertising under the Lanham Act, even if allegedly misleading.[188]

b. Fifth Circuit

In contrast to the Second Circuit, the Fifth Circuit has held that promotional statements derived from scientific material are not exempt from Lanham Act liability.[189] In *Eastman Chemical Co. v. Plastipure,*[190] the plaintiff initially developed a plastic resin that it sold to water bottle manufactures.[191] Capitalizing on recent consumer concern that certain water bottles could contain a harmful ingredient called "BPA", the defendants developed a plastic resin that they claimed was

185. *Id.* at 495–96.

186. *Id.* at 497.

187. *Id.*

188. *Id.* at 498; *see also* Underwager v. Salter, 22 F.3d 730, 733 (7th Cir. 1994) ("More papers, more discussion, better data, and more satisfactory damages—not larger awards of damages—mark the path toward superior understanding of the world around us."). Further, the Second Circuit's decision acts similarly to the FTC's now-rescinded "Mirror Image Doctrine," where the Commission would not proceed against advertising claims promoting the sale of books and other publications (like studies) if: (1) the advertising expressed the author opinion's or directly quotes the work, (2) the advertising "discloses the source of statements quoted or derived from the contents of the publication," and (3) the advertising "discloses the author to be" the source of opinions. 36 Fed. Reg. 13,414 (July 21, 1971).

189. Eastman Chem. Co. v. PlastiPure, 775 F.3d 230, 236 (5th Cir. 2014).

190. *Id.* at 236.

191. *Id.* at 233.

"BPA-free."[192] The defendants published an article in a peer-reviewed journal that summarized their results of testing more than 500 commercial plastic water bottles.[193] Before official publication, however, the defendants distributed a sales brochure at trade shows that suggested that bottles containing the plaintiff's resin contained significant levels of the toxic material.[194]

The plaintiffs sued under the Lanham Act, alleging the defendants' brochure was misleading.[195] After the district court granted the plaintiff's motion for a preliminary injunction, the defendants appealed to the Fifth Circuit, arguing that the lower court's decision was incorrect because their statements "were scientific opinions, rather than actionable facts."[196] Highlighting that the brochure's data mirrored *ONY's* study data,[197] the appellants argued that the information was within the realm of scientific debate rather than legal debate.[198]

The Fifth Circuit rejected the appellants' argument, finding that their data had morphed into "commercial advertisements and [was] directed at customers," rather than for scientific discourse.[199] The court noted that even if it had agreed with the *ONY* decision, this case was still distinguishable for two critical reasons.[200] First, the court emphasized that the Second Circuit addressed the article's secondary distribution "in the context of a state law" claim, *not* a Lanham Act claim.[201] In addition, the Court pointed out that the promotional use in *ONY* was limited to "a press release" summarizing the article's conclusions, while the promotional materials in *Eastman* demonstrated a clear market message derived from the study.[202] The Court

192. *Id.*

193. *Id.*

194. *Id.* at 233–34.

195. *Id.* at 234.

196. *Id.*

197. 720 F.3d 490 (2d Cir. 2013).

198. Eastman Chem. Co. v. PlastiPure, 775 F.3d 230, 235–36 (5th Cir. 2014).

199. *Id.* at 236.

200. *Id.* at 237.

201. *Id.*

202. *Id.* at 237 ("The different results reflect the difference between presenting an article's conclusions and transform[ing] snippets of a paper

emphasized that "advertisements do not become immune from Lanham Act scrutiny simply because their claims are open to scientific or public debate."[203]

The Ninth Circuit has not addressed the dangers of misleading scientific claims. However, a case in the U.S. District Court for the Northern District of California between biotech companies may present such an opportunity.[204]

2. Guardant, Natera, and Wild LDTs

A pending case, *Guardant v. Natera*, is a clear example capturing some of the legal issues involved with the development, promotion, and application of liquid biopsy testing in clinical medicine.[205]

In *Guardant Health v. Natera*, two cancer testing firms sued each other for false claims about their respective liquid biopsy-based CRC detection tests.[206] Both companies have recently developed and commercially launched liquid biopsy tests that—while slightly different in their approaches—monitor for CRC growth after treatment.[207] Clinicians use Guardant's "Reveal"[208] test for patients with

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which never mentions [the plaintiff and its products] . . . by name . . . into commercial advertisements.").

203. *Id.* at 236.

204. Guardant v. Natera, 580 F. Supp. 3d 691, 695 (N.D. Cal. 2022).

205. *See Guardant Health Sues Natera for False Advertising, 'Misleading' Oncologists About MRD Tests*, PRECISION MED. ONLINE (May 28, 2021), https://perma.cc/MHD2-YXQM (describing Guardant's initial suit against Natera).

206. *Guardant*, 580 F. Supp. 3d at 695; *see also* Molika Ashford, *In Ongoing False Advertising Suit, Judge Allows Natera Counterclaims Against Guardant Health,* GENOMEWEB (Jan. 20, 2022), https://perma.cc/3UGF-3QYE (elaborating on the court's decision to deny, in part, Guardant's motion to dismiss Natera's counterclaims).

207. Cancer recurrence occurs when a "small number of cancer cells survive" after initial treatment and "were too small to show up in follow-up tests." *Recurrent Cancer: When Cancer Comes Back,* NIH NAT'L CANCER INST., https://perma.cc/W79B-2ZM6 (last accessed Mar. 19, 2024).

208. *See* Molika Ashford, *Guardant Health Begins First Foray into Early-Stage Cancer with Commercial MRD Test Launch*, GENOMEWEB (Feb. 26, 2021), https://perma.cc/V5TE-SVDL (describing Guardant's research and commercial plans after launching the Guardant Reveal assay).

genetic mutations who may potentially benefit from adjuvant[209] therapy like immunotherapy.[210] According to Guardant, if Reveal is used repeatedly over time, the test "detect[s] emerging cancer recurrence earlier than" current standard-of-care tools.[211] In contrast, clinicians have used Natera's "Signatera" test to track tumor-specific mutations in a patient's bloodstream.[212] In this test, after selecting the most common mutations, the user collects blood samples every three months and sequences the samples to identify the biomarkers.[213] While Natera's test is currently under FDA review,[214] Guardant's Reveal test has been approved by CMS for Medicare and Medicaid patients, increasing the company's access to a wider pool of patients grappling with CRC.[215]

In the current lawsuit, Guardant alleged that Natera had misled healthcare providers about the performance of Guardant's soon-to-launch Guardant Reveal test[216] Because Guardant had hoped that its Reveal assay would compete against Natera's "Signatera" test, Guardant claimed that Natera's advertising insinuated that Guardant Reveal was "inaccurate and/or insensitive" and inferior to Signatera, which

209. See *Adjuvant Therapy*, NIH NAT'L CANCER INST., https://perma.cc/B2AR-X4ZJ (last accessed Mar. 19, 2024) ("Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.").

210. *Guardant Health Sues Natera for False Advertising, 'Misleading' Oncologists About MRD Tests*, GENOMEWEB (May 28, 2021) [hereinafter *Guardant Health Sues Natera*], https://perma.cc/3BD7-QZ67.

211. *Id*.

212. *See* NATERA, A PERSONALIZED TUMOR-INFORMED APPROACH TO DETECT MOLECULAR RESIDUAL DISEASE WITH HIGH SENSITIVITY AND SPECIFICITY 1 (2020) , https://perma.cc/25CZ-PYLJ (PDF) [hereinafter A PERSONALIZED TUMOR-INFORMED APPROACH] (highlighting the assay's analytical results).

213. *Id*. at 2.

214. *Premarket Notification 510(k), supra* note 84.

215. Medicare administrative contractor Palmetto GBA agreed in 2022 to cover the cost of Guardant's "Guardant Reveal" for Medicare patients with Stage II or III CRC following therapy. *See Guardant Health Receives Medicare Coverage for MRD Liquid Biopsy in Stage II and III Colon Cancer,* PRECISION MED. ONLINE (Aug. 2, 2022), https://perma.cc/8V3J-RQ2X (describing Guardant's recent foray into colorectal cancer recurrence with the launch of the Guardant Reveal assay and approval by CMS).

216. Complaint ¶¶ 56–70, Guardant Health, Inc. v. Natera, Inc., No. 3:21-CV-04062 (N.D. Cal. May 27, 2021).

it alleged violated, *inter alia*, the Lanham Act.[217] Natera countersued, claiming that Guardant's own advertisement (touting Reveal) relied on a fraudulent study[218] and "inaccurate descriptions of the data and methodology."[219]

In January 2022, the U.S. District Court for the Northern District of California struck down Natera's request for declaratory judgment on Guardant's Lanham Act claims.[220] However, the Court did find that Natera also sufficiently pled several of its allegations regarding Guardant's study under the Lanham Act to move the case forward.[221] Each party subsequently submitted motions for summary judgment addressing how the opposing party's scientific opinions and advertisements either meet or fail to establish a claim under the Lanham Act.[222] While the District Court has issued an order granting in part and denying in part both parties' cross motions for summary judgment, its official decision is currently under seal.[223] In addition to seeking recovery and punitive damages, both parties will attempt to argue at trial whether the opposing side should be liable for false advertising under § 43(a) as well

217. Guardant v. Natera, 580 F. Supp. 3d 691, 695 (N.D. Cal. 2022).

218. *See* Aparna R. Parikh et al., *Minimal Residual Disease Detection Using a Plasma-Only Circulating Tumor DNA Assay in Colorectal Cancer Patients,* 21 CLINICAL CANCER RES. 5586, 5589 (2021) (using Guardant's assay for cancer surveillance).

219. *Guardant*, 580 F. Supp. 3d at 702.

220. *Id*. at 713.

221. *See id*. at 713–14 (holding that several statements Guardant made about its test's sensitivity and specificity, ability to detect cancer in its earliest stages, and other information was dubious enough to allow Natera to sue for false advertising).

222. *See, e.g.*, Natera, Inc.'s Mot. Summ. J., Guardant Health, Inc. v. Natera, Inc., No. 3:21-CV-04062 (N.D. Cal. Oct. 14, 2022), ECF No. 219 Ex. 1; Guardant Health, Inc.'s Mot. Summ. J., Guardant Health, Inc. v. Natera, Inc., No. 3:21-CV-04062 (N.D. Cal. Oct. 21, 2022), ECF No. 229.

223. Order Granting in Part and Denying in Part Parties' Cross Motions for Summary Judgment, Guardant v. Natera, No. 3:21-CV-04062 (N.D. Cal. Mar. 22, 2023), ECF No. 326.

downplaying their own likelihood of liability.[224] The case is currently set for trial on March 11, 2024.[225]

Admittedly, *Guardant* is a single case involving two startups fighting about the misrepresentation of claims regarding liquid biopsy tests.[226] However, the novel legal issue in this case serves as a microcosm of a much larger issue because it is the first to address alleged false claims regarding LDTs. This case's ultimate decision will be a warning sign to companies debating whether to fully commercialize their test under 510(k) or skirt costs and regulatory requirements by following the LDT route. The lack of clear and effective civil remedies may affirm the sector's Wild West approach to what LDT-focused companies can claim and still avoid the FDA's watchful eye. Critically, a company offering a test as an unregulated LDT[227] may generate claims that impact the health of patients who are eager to try these technologies.[228] The average individual does not understand the immediate dangers of inaccurate results.[229] As starkly illustrated by the unfortunate patients duped by Theranos,[230] this can lead to medical catastrophes.

To resolve the conflict between federal agencies' regulation of LDTs and biotech companies' Lanham Act Claims, members of Congress have proposed legislation that they believe will also stem the tide of fraudulent accuracy claims. The next Part

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224. Joint Pretrial Conference by Guardant Health, Inc. and Natera, Inc. at 7-23, Guardant Health v. Natera, No. 3:21-CV-04-062 (N.D. Cal. June. 7, 2023), ECF No. 362.

225. Case Management Scheduling Order, Guardant Health, Inc. v. Natera, Inc., No. 3:21-CV-04062 (N.D. Cal. Oct. 3, 2023), ECF No. 417.

226. *See Guardant Health Sues Natera for False Advertising, supra* note 205 (noting a narrow focus solely on tests for cancer detection tests).

227. *See infra* Part II.B.

228. *See* Schroeder, *supra* note 39, at 27 (examining how the FDA grapples with LDTs as *in vitro* diagnostic tests, as well as the dangerous implications of evolving technology marketed as LDTs).

229. While one could argue that doctors involved as an "learned intermediary" when prescribing the diagnostic tests, this is outside the scope of this Note. For more analysis on the "learned intermediary doctrine," *see* Russell G. Thornton, *The Learned Intermediary Doctrine and Its Effects On Prescribing Physicians,* NAT'L LIBR. MED. (July 2023), https://perma.cc/GE6T-CMVE (examining the responsibilities of physicians to warn the user of the risks of the products they recommend as a basis for product liability-related tort claims).

230. *See supra* Part I.

discusses and analyzes recently-proposed legislation called the VALID Act in depth.

IV. CONGRESS' PROBLEMATIC SOLUTION: THE VALID ACT

In reaction to disputes between federal agencies and pending lawsuits between biotech companies, Congress has considered newly-proposed legislation to protect citizens from false claims related to LDTs. In this Part, the Note will first introduce how Congress has attempted to respond to the incongruities between the FDA's and CMS's regulatory powers and outline a newly-proposed bill called the VALID Act.[231] The Note will then examine the debate between the legislation's supporters, who insist that the bill should increase the FDA's power further, and industry detractors who fear the legislation will—among other concerns—limit commercial and academic growth.[232]

A. *The VALID Act and Risk Categories*

Since 2018,[233] members of Congress have introduced several versions of the VALID Act to establish regulatory control over LDTs.[234] Formally co-introduced by House Representatives Diana DeGette and Larry Bucshon in 2021, the bill would establish a framework granting the FDA greater authority to regulate diagnostic tests.[235] By creating a new product class dubbed "*in vitro* clincal tests" ("IVCTs") containing both IVDs and LDTs, the VALID Act would grant the FDA both pre- and

231. *See infra* Part IV.A. The full title of the proposed legislation is the Verifying Accurate Leading-Edge IVCT Development ("VALID") Act of 2021. S. 2209, 117th Cong. (2021).

232. *See infra* Part IV.B.

233. H.R. 4128, 117th Cong. (2021).

234. See *Legislators Release New Draft Bill Incorporating FDA Ideas for Diagnostics Regulation*, 360DX (Dec. 10, 2018), https://perma.cc/6UMY-5AF8 (announcing the initial drafting of a federal act to create a new category of IVDs).

235. *See Congress Introduces VALID ACT for Diagnostics Regulation,* 360DX (Mar. 5, 2020), https://perma.cc/6RVA-9UV5 (elaborating that the bill would "resolve longstanding questions over [the] FDA's authority to regulate LDTs").

post-market authority over both test categories.[236] While the FDA has historically relied on CMS to enforce discretion of LDTs under its CLIA process,[237] the agency has often maintained that "it has the authority to regulate the tests."[238]

Since its 2018 inception and repeated revisions based on FDA and stakeholder feedback, the VALID Act's new risk-based framework places all diagnostic tests, irrespective of their prior status, into low-, moderate-, and high-risk IVCT categories.[239] Each category would determine what type of review the LDT would need to follow at the FDA.[240] First, low-risk IVCTs would include those where an "undetected inaccurate result . . . would cause only minimal or immediately reversible harm and would lead to only a remote risk of adverse patient impact."[241] The FDA would subject these low-risk tests to less scrutiny, in addition to qualifying for pre-market review exemptions.[242]

In addition, the VALID Act includes a "moderate-risk" category that involves tests that a biotech company lacks "mitigating measures" in response to an inaccurate result.[243] The moderate-risk category would also include tests that cause "only non-life-threatening injury [or] reversible injury" or a significant delay in necessary treatment."[244] The test would also have "a reasonable risk of adverse impact on patient or public health from an undetected inaccurate result."[245] Companies

236. *See* Ciara Curtin, *ACMG Survey Finds Laboratory Geneticists Have Concerns Over Proposed Changes to LDT Regulation*, 360DX (Mar. 25, 2022), https://perma.cc/L6TQ-5RBE (noting that under a risk-based framework, existing IVDs and LDTs on the market would be grandfathered into the program).

237. *See supra* Part II.B.

238. Adam Bonislawski, *FDA Control of LDTs Looms as Momentum Builds for VALID Act,* 360DX (Mar. 16, 2022), https://perma.cc/DV79-49GY.

239. Daniel Kracov et al., *The VALID Act & 21st Century Cures 2.0: What Industry Needs to Know*, ARNOLD & PORTER (July 2, 2021), https://perma.cc/97SU-KQHY.

240. *Id*.

241. Rachel Sachs, *FDA User Fee Reauthorization: Contextualizing the VALID Act*, HEALTH AFFS. FOREFRONT (June 23, 2022), https://perma.cc/5HZF-5C4B.

242. *Id*.

243. *Id*.

244. *Id*.

245. Sign-On Letter re VALID Act, to U.S. Senators (July 6, 2022), https://perma.cc/8MJ8-BS36 (PDF).

would need to commercialize these types of tests through a "technology certification" pathway that requires the company to show it has "appropriate internal test validation procedures" and tweak said tests without undergoing FDA review.[246] In other words, the moderate-risk category would involve an abbreviated version of pre-market review, as opposed to no review.

Finally, under the VALID Act, "high-risk" LDTs—which would be subject to full pre-market review—include tests where "an undetected inaccurate result" has the "substantial likelihood to result in serious or irreversible harm of health to a patient."[247] High-risk LDTs can also likely "result in the absence, significant delay, or discontinuation of life-supporting" medical treatment and "sufficient mitigating measures" to identify the risks do not exist.[248] Several liquid biopsy tests (including both Guardant and Natera's tests) would likely fall into this category, as failing to diagnose a person's cancer status can lead to painful and unnecessary treatment, and at worst, a preventable death.

Importantly, several pre-market approval exemptions would shield certain types of IVCTs that may appeal to biotech companies worried about the VALID Act's potential implications. Exemptions to the VALID Act include tests that are: (1) developed and introduced before the bill is passed and meets certain requirements; (2) are low-risk tests; (3) solely for public health surveillance; (4) covered by a technology certification issued under the bill; (5) manual and low volume (performed less than five times per year); or (6) have received a humanitarian exemption or emergency use authorization (e.g., for pandemics).[249]

Unfortunately, the only exception for "high-risk" tests would exist when companies demonstrate that "mitigating measures" to prevent, detect, or otherwise actually mitigate the risk of inaccurate results.[250] Legislators and the FDA likely

246. Deborah Borfitz, *Diagnostics World News—Current Perspectives on the VALID Act*, FRIENDS CANCER RSCH. (Aug. 30, 2022), https://perma.cc/4FMY-R9EG.

247. Kracov et al., *supra* note 239.

248. *Id.*

249. H.R. 4128, 117th Cong. (2021).

250. Kracov et al., *supra* note 239.

included this exemption in response to biotech companies that complained about the original Act's more restrictive terms. These firms develop novel genetic tests for rare conditions that often lack a comparable 510(k)-approved test.[251]

B. *Supporters and Detractors*

While the VALID Act describes risk categories and potential exemptions in excruciating detail, the healthcare industry has responded to the VALID Act with mixed reactions. Some patient advocacy organizations and biotech companies agree that the FDA should hold more power over LDTs, while other groups heavily invested in LDT technology unsurprisingly oppose the Act.[252]

Supporters believe that under current laboratory standards, LDTs are not adequately overseen, placing patients in harm's way.[253] Industry proponents like the Friends of Cancer Research and the American Cancer Society Cancer Action Network believe that the VALID Act creates a clear, modern regulatory framework that ensures "any test, no matter where it is developed, meets the same quality and performance standards."[254] Patient advocacy groups also argue that the VALID Act would ensure that healthcare providers and patients can trust the "results of a test no matter where it is assembled or performed."[255] Importantly, clincal decision-making relies on the accuracy and validity of clinical tests, which CMS's current CLIA process lacks for LDT approval.[256] Without any significant

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251. *Id.*

252. *See* Bonislawski, *supra* note 238 (pointing out that national groups like the American Clinical Laboratory Association, representing national lab companies like LabCorp, has several reservations that it is seeking to address with Congress).

253. *See Pew and 17 Organizations Urge Congressional Committees to Consider Valid Act,* PEW CHARITABLE TRS. (June 30, 2021) [hereinafter *Pew and 17 Organizations*], https://perma.cc/ZX76-UU7D (advocating for widespread reform in regulating LDTs).

254. *See* Jeff Allen and Lisa Lacasse, *Better Lab Test Standards Can Ensure Precision Medicine Is Truly Precise*, STAT NEWS (Nov. 30, 2022), https://perma.cc/J52U-XQVB (noting that the VALID test is good for "industry, laboratories, providers, and most importantly, patients," especially in the context of screening for cancer and subsequently fighting it).

255. *Pew and 17 Organizations*, *supra* note 253.

256. *See* Part II.B.

reform, supporters fear that under-regulated LDTs will continue to impair clinical decision-making, especially for patients at high risk of genetic diseases like CRC.[257]

In contrast, detractors have raised multiple concerns regarding the VALID Act's actual utility and success in the medical space. First, parties have argued the new bill would create an "onerous and complex system" that alters the "way that laboratory testing is regulated," stifling competition and limiting access to patient care.[258] They believe that bill would force some laboratories attempting to commercialize their tests to consolidate their testing menu, as the current version of the bill would favor "larger clinical labs" that have undergone stricter state-level approval processes.[259]

Critics have also argued that the VALID Act lacks clarity in key areas and definitions within its actual text. For example, they contend that proposed definitions in the Act's risk categories create ambiguity that makes it impossible to understand the implications on provisions on laboratory medicine."[260] They also note that the bill's text apparently creates an "unpredictable regulatory process and ambiguities" that drastically differ from the FDA's standard requirements for 510(k)-cleared tests.[261]

Finally, detractors fear that the FDA lacks adequate resources to meet the obligations under the VALID Act. They highlight that during the COVID-19 pandemic, the FDA struggled to review the volume of submitted applications for emergency use authorization approval ("EUA").[262] Comparing

257. *Pew and 17 Organizations*, *supra* note 253.

258. AM. SOC'Y FOR CLINICAL PATHOLOGY ET AL., *supra* note 245, at 2.

259. *See* Elise Reuter, *Testing Overhaul Faces a 'Narrow Pathway' to Pass Before Year End, Industry Groups Say*, MEDTECH DIVE (Oct. 20, 2022), https://perma.cc/BQ5P-RCSB (noting that states like New York have stricter approval process that larger clinical labs have the resources to pass through and thus are not as concerned with the VALID Act as small labs or startups).

260. AM. SOC'Y FOR CLINICAL PATHOLOGY ET AL., *supra* note 245, at 3.

261. *Id.*

262. Under § 564 of the FD&C Act, the FDA may authorize unapproved medical products as part of an "Emergency Use Authorization" (EUA) approval for use to diagnose or treat life-threatening situations in emergency situations, such as the COVID-19 pandemic. *See Emergency Use Authorization,* FDA, https://perma.cc/TNS8-XEH2 (last updated Feb. 2, 2023) (walking through the requirements a company must follow to receive EUA approval).

the delays that the healthcare space faced due to the FDA's inability to review almost 2,200 EUA requests between March 2020 to April 2021, critics believe that the agency will continue to struggle approving future LDTs, which they estimate to be as many as 160,000 in 2021 alone.[263]

As of March 26, 2024, members of Congress have failed to pass a new version of the VALID Act.[264] While the FDA will likely encourage a reintroduction of the bill through the House's Energy and Commerce Subcommittee on Health, VALID Act 2.0's future ultimately remains uncertain. In response to the VALID Act's failures, the FDA has moved forward by drafting and issuing proposed rules of its own to reign in unruly and dangerous LDTs.[265]

C. *The FDA's Response to VALID Act Faces Hurdles*

Stalled legislation in Congress has not prevented the FDA from acting to expand its control over diagnostic tests. While the FDA anticipates promulgating a finalized version of the proposed rules in April 2024, the agency's phaseout policy will likely face multiple obstacles before implementation and enforcement.[266] For example, at the federal level, the FDA's proposed rules will likely face hurdles such as policy and legal responses from the three branches of government and *ultra vires* claims under the Administrative Procedure Act.[267] In addition, the FDA almost certainly will continue to face industry

263. AM. SOC'Y FOR CLINICAL PATHOLOGY ET AL., *supra* note 245, at 4.

264. House Representative Larry Bucshon introduced the most recent version of the VALID Act through the Energy and Commerce Committee in March 2023. However, it has appeared to have stalled after being referred to the Subcommittee on Health. *See* H.R. 2369, 118th Cong. (as referred to the S. Comm. on Health, Apr. 7 , 2023).

265. *See* discussion *supra* Part II.C. (FDA's recent 2023 regulatory efforts).

266. Steve Tjoe & Matt Wetzel, *FDA Targets April 2024 for Laboratory Developed Test (LDT) Final Rule,* GOODWIN: LIFE SCIENCES PERSPECTIVES BLOG (Dec. 8, 2023), https://perma.cc/4MUS-A7PP (noting the FDA's April 2024 target final action date).

267. APA § 706(2). "Ultra vires" is a term used to determine whether a federal agency is acting within the limits set by the enabling act. *See* KRISTIN E. HICKMAN, UNDERSTANDING ADMIN. LAW 80 (Carolina Acad. Press, 7th ed. 2022) (elaborating as to when the APA expressly permits a court to "determine whether an agency is functioning within its jurisdiction").

opposition to its plans to phase out the LDT enforcement-discretion policy.[268]

First, Congress may attempt to reign back the FDA's regulatory powers and pass a bill that regulates both LDTs and IVDs. However, the FDA views the issue of misleading LDTs with heightened urgency based on Congress' repeated failures to pass versions of the VALID Act.[269] Still, Congress may see the FDA's proposed rules as an overstep of their regulatory powers and thus intervene on the public's behalf. Hypothetically, the FDA may actually be issuing potentially strict rules with a mid-2024 deadline to spur Congress to act and finally pass an improved version of the VALID Act. By charging ahead with rules that industry players have complained about, perhaps the FDA is issuing Congress a wake-up call to help protect the public from the dangers of LDTs. If Congress actually recognizes the FDA's potential overreach and passes a revised version of the VALID Act before the April 2024 deadline (while highly unlikely), the FDA may then relent and hand off the reigns over to Congress, believing it has finally done its job protecting the public.

Importantly, any attempt to enacted the FDA's proposed LDT policy would likely need support from the U.S. president and their administration following the 2024 elections.[270] Lacking this support would hinder the FDA's ability to prioritize LDT regulation in terms of both policy and financial resources.[271] Experts believe that the FDA is rapidly moving on LDT rulemaking in part because past presidential administrations have effectively nullified the agency's efforts to regulate LDTs by guidance.[272]

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268. *See* Part II.B (detailing FDA's initial attempts to float a draft risk-based framework for regulating LDTs back in 2014 & 2017 and ultimate cessation due to substantial opposition).

269. *See* Part IV.A.

270. *Proposed Rule on Laboratory-Developed Tests Takes Center Stage*, *supra* note 141.

271. *See Proposed Rule on Laboratory-Developed Tests Takes Center Stage*, *supra* note 141.

272. *See* Bonislawski, *FDA Moving Quickly on LDT Rulemaking as 2024 Elections, 2027 User Fee Renewal Loom, supra* note 143 (arguing that former president Donald Trump's rise to office in 2016 effectively neutered the FDA's efforts to regulate LDTs by guidance, and that given this political history, the

If the newly-proposed rules are established later this year, unhappy industry groups may raise legal challenges and sue the FDA in federal court, arguing the agency's actions are an overreach of its statutory authority under the FD&C Act. Any legal challenge would likely create obstacles to the FDA's goals of timing and implementation of the new rule in 2024 and beyond.[273] For example, parties may claim that the agency violated the Administrative Procedures Act[274] by ignoring their requests to extend the notice and comment period past the December 5, 2023 deadline, despite the ongoing warnings that groups have publicly raised in the past decade.[275] Parties like the ACLA may also bring suit (and are potentially already telegraphing their legal strategy) by claiming that LDTs are not subject to any FDA authority because they fall outside the scope of "devices."[276] Further, if *Chevron*[277] is struck down or at least tailored down this year, the FDA's interpretation of the FD&C Act to consider LDTs as devices will not receive any judicial deference.

However, even in the recent past, the FDA has faced substantial industry pushback when promulgating similar

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agency will try to incorporate the new rule into the Code of Federal Regulations before November 2024).

273. *See Proposed Rule on Laboratory-Developed Tests Takes Center Stage*, *supra* note 141.

274. 5 U.S.C. § 555.

275. *See* Am. Health Ass'n, Comment Letter on Proposed Rule to Categorize Laboratory Developed Tests as Medical Devices (Dec. 1., 2023), [hereinafter Comment Letter on Proposed Rule] https://perma.cc/P8FA-YATK (highlighting concerns such as increased costs to academic centers and regional hospitals unable to compete with larger players that are able to afford financial burdens placed on the new rules).

276. *See id.* (arguing that legislation like the VALID Act is the only approach for FDA to have a role in regulating LDTs, and thus the agency's "unilateral imposition of device law is misguided").

277. *See* Chevron U.S.A. Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 865 (1984) (holding that an agency's reasonable interpretations of a statute that it administers is entitled to judicial deference); *see also FDA Proposes Regulation of Laboratory Developed Tests and Sets up Collision Course with Major Questions Doctrine*, SIDLEY AUSTIN (Sept. 29, 2023), https://perma.cc/P8JG-GYBP (noting that the FDA's proposed rules places it on a "collision course with the 'major questions' doctrine" that "requires that administrative agencies point to 'clear congressional authorization' when they claim the power to make decisions of vast economic and political significance").

rulemaking to protect public health.[278] In 1996, the FDA attempted to regulate tobacco for the first time under powers that it claimed was granted under the FD&C Act, arguing that tobacco met the Act's definitions of "drug" and "device."[279] The FDA promulgated a strict administrative rule to curb the sale of tobacco to minors, which was immediately challenged by tobacco companies up to the Supreme Court.[280] In response to the Court's decision in *FDA v. Brown & Williamson Tobacco Corp.*,[281] Congress enacted the Family Smoking Prevention and Tobacco Control Act ("TCA") in 2009, which established a broad framework for regulation designating the FDA as the central authority to regulate the manufacture, distribution, and marketing of cigarettes and any other form of tobacco it considers to be a "tobacco product."[282]

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278. *See* SCOTT BURRIS ET AL., THE NEW PUBLIC HEALTH LAW: A TRANSDISCIPLINARY APPROACH TO PRACTICE AND ADVOCACY 188 (Oxford Univ. Press, 2d ed. 2023) (highlighting that federal agencies like the FDA often face questions of overstepping their boundaries when they "try to regulate products or activities that have previously gone unregulated").

279. *See* Matthew R. Herington, *Tobacco Regulation In the United States: New Opportunities and Challenges*, 23 HEALTH L. 13, 14 (2010) (noting that the FDA saw that cigarettes and smokeless tobacco were "combination products" consisting of a drug [nicotine] and a delivery device); *see also* Scott Burris et al., *supra* note 278 ("The Food, Drug, and Cosmetic Act . . . said nothing specific about the regulation of tobacco . . . but it provided the FDA with broad authority to regulate 'drugs' and 'devices' that were 'intended to affect the structure or any function of the body.").

280. Herington, *supra* note 279; *see also* FDA v. Brown & Williamson Tobacco Corp. 529 U.S. 120, 156 (2000) (finding that "Congress has persistently acted to preclude a meaningful role for *any* administrative agency in making policy on the subject of tobacco and health" and that "it is plain that Congress has not given the FDA the authority that it seeks to exercise here." (emphasis in original)).

281. 529 U.S. 120 (2000).

282. *See* John D. Blum, *Tobacco Product Warnings in the Mist of Vaping: A Retrospective on the Public Health Cigarette Smoking Act,* 23 CHAP. L. REV. 53, 74–75 (2020) (highlighting the three regulatory pathways for approval of new tobacco products by the FDA in combination with its powers under the FD&C Act, including pre-market approval, modified risk tobacco product category, and a substantial equivalence plan for predicate products on the market before March 2011). Still, the FDA has dragged its feet in developing new tobacco rules— even when required by statutory obligation under the TCA—and only issued new proposed rules in 2019. *See id.* at 79 (noting that the agency finally began crafting a proposed rule on graphic cigarette warnings after a district judge found it failed to justify its delay "in the face of public health and welfare interests").

Admittedly, not all LDTs are at the same risk if FDA's new rules are promulgated later this year. As noted earlier, the FDA is more concerned about new LDTs are that are more complex and difficult to tease out actionable results for patients.[283] Genetic tests that biotech companies like Natera and Guardant develop and commercialize, which provide potentially life-changing information (if accurate), are outside the scope of the original 1976 CLIA amendments.[284] Therefore, the higher the risks that the LDT poses to public health based on their designed and advertised uses (such as liquid-based cancer screening), the more likely the FDA (and other agencies) will investigate their claims.

In contrast to companies who develop FDA-approved tests and follow strict regulatory protocols, companies who develop LDTs and do not need to follow as strict rules may avoid accountability for making misleading claims if other circuits apply the Second Circuit's deferential reasoning.[285] Thus, the federal government must rapidly tackle the potential dangers LDTs pose to public health, whether that involves passing legislation that increases the FDA's regulatory power or allowing the FDA to enforce its current administrative powers, even if it must rely on previous federal judicial decisions.

V. MULTI-FACETED SOLUTIONS

Because unregulated claims about LDTs pose dangers to both private parties and public health, the federal government must identify a multi-faceted solution that considers both legal impacts and healthcare policy. This Part analyzes three potential options: (1) revising the VALID Act so that both the FDA and industry players can compromise on its contents; (2) directly applying the Lanham Act to claims made by both parties to resolve questionable factual claims; and finally (3) narrowly increasing the FDA's regulatory power over IVDs to all liquid biopsy assays (including LDTs) before gradually opening the door to high-risk LDTs.

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283. *See supra* Part II.B (noting the FDA's ongoing concerns about complex diagnostic tests).

284. *See supra* Part II.A (noting the discrepancy between original 1976 CLIA amendments and the enormous complexity of genetic tests today).

285. *See supra* Part III.B.2.

Because of its potential broad impact across the healthcare industry, the federal government should tackle unregulated LDTs by interweaving at least two of the listed solutions. Among them, a legislative option that tweaks the proposed VALID Act will best resolve what biotech companies can claim in LDT-based advertisements because it will overhaul how the FDA regulates diagnostic tests and removes current loopholes.[286] By reforming how the FDA and CMS regulate tests (increasing the FDA's power), the agency would successfully require biotech companies like Guardant to present higher quality data for their tests and ultimately protect patients.

Because the biotech industry has challenged and resisted Congress's attempts to pass the VALID Act, the next most successful and likely efficient path is a judicial approach, which will help promote safe public access to these lifesaving tests. Although federal courts have not yet acknowledged LDT-based Lanham Act claims, they should hold companies liable for their test's dangerous claims before it causes patient harm. Specifically, the *Guardant* court should follow the Fifth Circuit's reasoning in *Eastman*[287] and find that the Lanham Act covers all claims relying on scientific data—including liquid biopsy-based LDTs—because the use of scientific data in a promotional setting should be subject to basic truth-in-advertising standards.[288] By relying on the U.S. District Court for the Northern District of California's (and the Fifth Circuit's) reasoning as a steppingstone, Congressional supporters could emphasize the risk of LDTs to both private competitors and the public and thus modify the VALID Act accordingly.

To gain some footing if the Lanham Act-based judicial approach struggles, the federal government should next follow an administrative route and incrementally allow the FDA to bare some regulatory teeth by lassoing in certain LDTs. Rather than the FDA establish sweeping coverage of all LDTs under its purview, the agency should expand by only regulating liquid biopsy-based LDTs at first. The FDA could adopt certain steps and learn from the federal government's actions during other

286. *See supra* note 103 and accompanying text (highlighting dangers that companies like Theranos could potentially cause with misleading material).

287. 775 F.3d 230 (5th Cir. 2014).

288. *See supra* note 165 and accompanying text.

nationwide initiatives involving genomic concerns—such as its actions during the COVID-19 pandemic—to promote safe public access to these innovative yet risky tests.

While Congress, federal agencies, and private industry players clash about the proper way to classify LDTs and regulate their marketing claims, biotech companies charge ahead to develop tests that likely pose significant harm to the public.[289] To resolve the dangerous loopholes with current regulation, Congress must work efficiently with administrative and industry parties before their inaction places even more patients' health in significant jeopardy.

A. *Pass Narrow and Strict Version of the VALID Act*

The preferred route for reform is to draft a version of the VALID Act that both the FDA and industry labs agree will help best protect the public safety while increasing their access to the innovative tests. If Congress enacts a revised version of the VALID Act, the legislation will render legal decisions about what biotech companies can claim in their LDT advertisements moot.[290] Increasing the FDA's regulatory power will allow the agency to reclassify both Natera's and Guardant's tests as IVCTs.

As noted above,[291] a brief window of opportunity may exist for LDTs like Guardant's Reveal assay under the VALID Act. Specifically, Reveal may fall under a class of tests that were "first offered for the clinical use before the date of enactment" and meet certain CLIA certifications.[292] If true, Guardant would not be required to fully comply with the VALID Act's strictest provisions. In addition, Guardant, acting as an IVCT developer with a grandfathered test, could modify the test as long as it does not alter the clinical or analytical validity or compromise the test's use or safety.[293] However, the test would still need to

289. *See supra* Part II.B.

290. *See supra* Part IV.

291. *See supra* Part IV.A.

292. Sachs, *supra* note 241.

293. *See id.* (emphasizing certain loopholes companies developing LDTs could use).

comply with the Act's other requirements, such as labeling, listing, and registration.[294]

Further, if Guardant offers its test with "any false or misleading analytical or clinical claims," or if it is "probable" that Guardant's test will "cause serious adverse health consequences," the FDA will clarify that Guardant's tests must meet these other statutory requirements.[295] In addition, if the FDA finds that Guardant has significantly modified the test, lacks sufficient scientific evidence touting its abilities, or that it has made any fraudulent claims about the test, then the agency may potentially revoke the test's grandfather exemption.[296]

While several industry players and medical institutions oppose the VALID Act for multiple reasons,[297] the federal government could introduce provisions that both sides would find agreeable. A VALID Act provision that helps subsidize the costs to research and develop LDTs, depending on the specific public need, may incentivize more industry organizations to work with Congress and federal health agencies.[298]

While critics worry that the legislation would immediately impact their commercial process, this is (for the most part)

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294. *See id.* (noting that provisions specifically aimed at detecting and mitigating potential adverse events include (587E), (587L), and (587M)).

295. *Id.*

296. *See* James A. Boiani & Megan Robertson, *The VALID Act: Senate Action Brings FDA Regulation of LDTs Closer to Fruition*, NAT'L L. REV. (May 20, 2022), https://perma.cc/9FZN-QHMD (highlighting that while the test's exemption could be revoked due to its dangerous health risks, companies like Guardant would still "have one year from the date the listing system becomes available to come into compliance").

297. *See supra* Part IV.B (raising multiple potential consequences with the VALID Act's implementation, including the fear that the bill would require smaller labs to produce higher quality and large studies, costs that they claim would hurt innovation).

298. In 2023, the Biden Administration coauthored an agenda on a government approach to advance biotechnology and biomanufacturing based on input by federal agencies including HHS per Exec. Order 14081. In the agenda, HHS emphasized establishing public-private partnerships between the NIH and industry leaders to improve early detection and develop precision multi-omic medicine (patient-specific testing and treatment) that cancer-specific LDTs fall under the umbrella of for diagnosing rare diseases. *See* U.S. Dep't Health & Hum. Servs., *Biotechnology and Biomanufacturing R&D to Further Human Health*, *in* BOLD GOALS FOR U.S. BIOTECHNOLOGY AND BIOMANUFACTURING: HARNESSING RESEARCH AND DEVELOPMENT TO FURTHER SOCIETAL GOALS 37, 39–41, 44, (2023),https://perma.cc/E76Q-EVQF (PDF).

inaccurate because the VALID Act provides integral safeguards for certain LDTs. First, the Act's "grandfather provision" allows current LDTs to operate as normal under the existing framework.[299] The VALID Act's provisions will also gradually kick in over a period of five years, allowing LDT developers some initial breathing room to adapt to the new regulations.[300] For example, the Act requires the FDA to hold public meetings and promulgate certain regulations forming the base of clinical applications under the VALID Act.[301] These meetings will allow LDT developers to voice their concerns in real-time with the government, who will likely take the issues into consideration and update future promulgations.

Admittedly, due to industry pushback against the current VALID Act,[302] Congress's attempts will probably lead to a watered-down version lacking real teeth for administrative enforcement. Therefore, a judicial route will likely (and realistically) instead ameliorate the issue, at least as a temporary option before Congress and the healthcare industry compromise on a solution.

B. *Adopt the Fifth Circuit's Reasoning*

If Congress fails to pass the VALID Act, the next best alternative is to adopt a judicial route based on the Fifth Circuit's analysis in *Eastman*[303] finding statements about LDTs to be actionable under the Lanham Act.[304] By demonstrating the potential damages that misleading claims based on unregulated scientific material can cause to private industry players, Congress should analogize the dangers of misleading claims to public safety as well. While the issue of false claims specific to liquid biopsy tests has only appeared in *Guardant v. Natera*,[305]

299. AM. SOC'Y FOR CLINICAL PATHOLOGY ET AL., *supra* note 245, at 3.

300. Sachs, *supra* note 241.

301. Sachs, *supra* note 241.

302. *See supra* Part IV.B.

303. Eastman Chem. Co. v. PlastiPure, Inc., 775 F.3d 230, 236 (5th Cir. 2014).

304. While both the Second Circuit and Fifth Circuit also discuss important issues about the First Amendment and freedoms of commercial speech regarding scientific material, those issues are outside the realm of this Note.

305. 580 F. Supp. 3d 691 (N.D. Cal. 2022).

the Fifth Circuit's *Eastman* ruling establishes that *any* commercial statement relying on scientific data is subject to the Lanham Act, especially if it promotes the advertiser's product or denigrate its competitor's product.[306]

In contrast to the Second Circuit's broad protection for scientific data,[307] the Fifth Circuit reasoned that companies cannot couch their advertising's potentially misleading claims in scientific opinion.[308] Enjoining statements that would theoretically "embrace one side of an open scientific debate" may limit "academic freedom and inhibit the free flow of scientific ideas."[309] However, deliberately interpreting and translating data via advertisements that consciously paint a company's product in a better light than its competitors would unfairly damage the competitor's reputation. Non-actionable scientific literature is indeed "more closely akin to matters of opinion" that peer-reviewed journals "where the scientific public sits as the jury"—should instead review.[310] However, once the biotech company creates broad and likely inaccurate statements derived from non-actionable scientific literature, private parties should have the right to use Lanham Act to review these claims.

Importantly, akin to the advertisements made by *Eastman*'s defendants, only the statements that Natera and Guardant produced in their advertising, promotion, or offering to sell the tests should be scrutinized under the Lanham Act.[311] For example, Natera can attempt to show that Guardant's marketing statements falsely and misleadingly touted the Reveal test's benefits for "early-stage" cancer patients through Guardant's study because it was "the only possible source of such comparisons."[312] Further, Natera could challenge any definitions that Guardant's sales teams include in marketing material because their inconsistencies allegedly were deliberate

306. *See supra* Part III.B.1.b.
307. *See supra* Part III.B.1.a.
308. 775 F.3d at 235 (2014).
309. *Id.*
310. 720 F.3d at 497 (2d Cir. 2013).
311. *Eastman*, 775 F.3d at 233.
312. Guardant v. Natera, 580 F. Supp. 3d 691, 707 (N.D. Cal. 2022).

to "confuse patients and physicians into thinking the study's results" relate to their clinical performance.[313]

While Guardant could argue that an injunction is not required if they present new research in the future proving their advertisements are no longer false or misleading, their argument does not immediately nullify the motion. In *Eastman*, the Fifth Circuit noted that if it granted a party to pursue such a course of an action, "companies could make all sorts of unsupported claims and then avoid liability by arguing they might be able to prove the truths" in the future.[314] This would set a dangerous precedent for LDTs (especially liquid biopsy tests) and the healthcare space. Companies like Theranos could hand-wave any misleading claims in advertising that did not match actual scientific data by arguing they would one day achieve their lofty goals.[315] While Silicon Valley stars like Apple can make unsupported claims about their products and then work behind the scenes to actually achieve this claim in a future update,[316] a biotech company cannot mimic this marketing strategy in the healthcare space without potentially jeopardizing patients' lives. If courts agree to scrutinize misleading claims derived from scientific studies on LDTs, then competitors will be able to engage in self-help via the Lanham Act.

Following the Fifth Circuit's decision regarding LDTs is the best short-term solution; it will increase the public's awareness of and concern about these innovative tests while ensuring society's health and safety. Judicial decisions based on LDTs will then provide a backbone for Congress to introduce newer and improved versions of the VALID Act. If most of the healthcare industry eventually agrees to a middle ground based the Fifth Circuit's interpretation, the compromise would further

313. *Id.* at 705; *see also supra* Part II.B.

314. *Eastman*, 775 F.3d at 241 n.2.

315. *See* Elizabeth Lopatto, *How Elizabeth Holmes Sidelined the Real Scientists at Theranos*, THE VERGE, https://perma.cc/P2DA-XBUF (last updated Sept. 24, 2021) (highlighting how Theranos's CEO blatantly ignored concerns from its scientists that the company's marketing claims for its LDTs did not match internal scientific data).

316. *See* Lisa Eadicicco, *Your iPhone's Battery Life Isn't as Long as Apple Says It Is, According to a New Report*, INSIDER (May 4, 2019), https://perma.cc/AF94-W9FJ (pointing out that Apple's recent smartphones have made bold claims about certain iPhone models battery capabilities).

the mission of increasing public access to these novel tests while avoiding potential dangers of misrepresentation and faulty results.[317]

C. *Narrowly Expand FDA Regulatory Power to Liquid-Biopsy Specific Test Claims*

If the first two options are unsuccessful, a narrow administrative solution would at least help guide regulation for liquid biopsy-based tests. Rather than expand the 510(k) process to all LDTs, the FDA instead could initially increase its regulatory reach and claim control over niche liquid biopsy-based LDTs.

Experts currently lack a clear number for the exact number of LDTs companies have launched in the US market. While the healthcare industry runs a total estimate of 3.3 billion IVDs (both FDA-approved and LDTs), the FDA believes about 11,000 LDTs were in use when it issued its 2014 draft guidance.[318] In contrast, researchers studying the market for genetic tests estimated that the industry used 75,000 such IVDs in 2018, with the majority being LDTs.[319] That number has likely grown with the COVID-19 pandemic because of the surge of EUA-based laboratory developed tests.[320]

Further, the FDA has only fully approved four liquid biopsy tests for a narrow range of cancer-based applications.[321] While CMS does not have an exact number for the amount of liquid biopsy tests under its coverage, roughly only fifty companies are developing or have launched liquid biopsy tests in the United

317. *See* Eastman Chemical Co v. Plastipure, Inc., 775 F.3d 230, 236–37 (5th Cir. 2014) (pointing out that most products, including diagnostic tests, reviewed by the Lanham Act "may be tied to public concerns with . . . [public] health and safety" (internal citations omitted)).

318. *Role of Lab-Developed Tests*, *supra* note 48.

319. *Id.*

320. *See In Vitro Diagnostics EUAs—Antigen Diagnostic Tests*, FDA, https://perma.cc/FT49-DBYR (last updated Mar. 3, 2023) (noting that the FDA has approved at least 60 LDTs during the COVID-19 pandemic through the Emergency Use Authorization pathway).

321. *See Liquid Biopsy*, CLEVELAND CLINIC, https://perma.cc/ZG5D-29L8 (noting that out of the four 510(k)-approved tests, three detect ctDNA for various mutations and genetic errors in limited applications).

States so far.[322] By limiting the FDA's purview while forcing all liquid biopsy tests to apply for 510(k)-clearance, the FDA could efficiently review tests that are controversial and at high risk of producing faulty results. If successful, the FDA could choose to scale up and increase the number of LDTs it reviews, selecting different types based on the amount currently available over time. This solution would further bolster legislative support for the VALID Act, which would incorporate data from the FDA's increase in reviewing LDTs across the board.

Admittedly, the option to narrowly review liquid biopsy tests could in the short term stifle commercial growth of liquid biopsy-based research and development. But while the initial out-of-pocket prices of FDA-approved liquid biopsy sequencing tests range from $5,000 to $6,000, partnering with the government may benefit the companies by increasing their access to consumers.[323] The FDA's narrow focus on liquid biopsy tests would drive biotech companies to produce higher-quality tests and increase industry recognition and respect due to their comparability to current forms of testing (e.g. tissue-based tests). Promoting higher quality tests would drive consumer interest because of their advantages over tissue-based tests (e.g., because they are less invasive) at a non-cost prohibitive price. By initially focusing on a small portion of high-risk LDTs, the FDA will be able to reexamine its regulatory methodology every few years and determine if it could efficiently review LDTs on a larger scale, or whether to step back and solely focus on companies actively seeking 510(k)-approval.

CONCLUSION

This Note has demonstrated that while LDTs, especially liquid biopsy tests, can revolutionize the healthcare industry, their potentially misleading claims will place citizens in danger if left unchecked. If the federal government continues to kick the LDT can down the road, biotech companies like Theranos will continue to exploit the regulatory and legal loopholes, placing both private parties' interest and the public's health in jeopardy.

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322. *Liquid Biopsy Employers*, BIOTECH-CAREERS.ORG, https://perma.cc/8AY6-NVQH.

323. *See* Cairns, *supra* note 85 (noting how competitors with FDA-approved liquid biopsy tests have begun price-cutting wars).

To increase widespread access to liquid biopsy tests and other lifesaving, yet high-risks LDTs, the FDA and other federal actors like Congress must act to assure the public that LDTs are properly validated, performed correctly, and produce accurate results.

If Congress eventually does pass a version of the VALID Act, laboratories must then respond by evolving and adapting to the new FDA requirements. While certain industry players fear potential financial and logistical limitations the VALID Act will place on commercial growth, biotech companies that anticipate and successfully navigate the FDA's final guidance will ultimately benefit from the Act's impact. Consumers eager for diagnostic tests that are relatively cheap, reliable, and non-invasively screen for cancer will trust the tools and drive demand for these innovative tools in the future. Thus, companies that capture customer zeal and meet the FDA's requirements for the tests stand to profit.

At the same time, the FDA, frustrated with Congressional failures to the VALID Act, despite fiascos like Theranos, has charged ahead with its own plans to regulate both 510(k)-approved tests and LDTs. While the FDA's short-term efforts may apply an oversized Band-Aid to ameliorate the situation this summer, this Note still advises a long-term recommendation integrating congressional, legal, and regulatory history and opportunities for public health.

Ultimately, the FDA and the federal government must embrace the need for scientific innovation while serving as the stalwarts of medical oversight using a proper framework, whether that is a revised VALID Act, a different bill in response to judicial decisions, an initial regulatory focus on liquid biopsy-based LDTs, or a synthesis of the three viable routes.