Animal-Based Medical Diagnostics: A Regulatory Problem

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ABSTRACT

Fears of global pandemics due to outbreaks of highly virulent diseases like the novel Coronavirus disease of 2019 (COVID-19) have boosted interest in rapid and non-invasive diagnostics. One solution is to use animal-based diagnostics, which have the potential to be more accurate and efficient than conventional diagnostics. For example, researchers have shown that trained detection dogs have been able to identify *C. difficile* infections in patients with 97% accuracy—higher than the 92.7% reported accuracy for real-time PCR diagnostic methods. While these animal-based diagnostics clearly fall within the scope of FDA's regulatory authority, innovations in diagnostic technologies, specifically animal-based diagnostics, have outpaced the Agency's ability to update its requirements for receiving marketing approval. Consequently, researchers in this area face a regulatory regime that does not address the challenges or risks inherent in using animals to detect diseases.

This Article predicts how the Agency will regulate animal-based diagnostics and shows how the current regulatory regime is inadequate. The Article then proposes modifying the current regulatory regime to encourage development of animal-based diagnostics by (1) creating guidelines for demonstrating analytical and clinical validity in animal-based diagnostics and (2) adopting the technology certification pathway provisions of the proposed VALID Act of 2020, a reform bill that would streamline how FDA regulates medical diagnostics.

INTRODUCTION

The *British Medical Journal* published an article in 2012 describing a dog that had been trained to detect *Clostridium difficile* infections in patients with remarkable accuracy.[1] *C. difficile* is a common hospital-borne infection that causes toxin-mediated intestinal disease, with symptoms ranging from mild diarrhea to fatal intestinal

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[1] *See* Marije K. Bomers, Michiel A. van Agtmael, Hotsche Luik, Merck C. van Veen, Christina M. J. E. Vandenbroucke-Grauls & Yvo M. Smulders, *Using a Dog's Superior Olfactory Sensitivity to Identify* Clostridium Difficile *in Stools and Patients: Proof of Principle Study*, BMJ, 22–29 Dec. 2012, at 7, 9, https://www.bmj.com/content/345/bmj.e7396 [https://perma.cc/W2T3-SMFM].

infections.[2] The pervasive nature of the bacteria in hospitals and in patient populations with compromised immune systems or recent exposure to antibiotics makes early detection crucial.[3] The dog, a two-year-old beagle named Cliff, accurately identified 97% of infections in stool samples and 95.3% of infections in patients themselves, which exceeds the performance of FDA-approved diagnostic kits commonly used to detect *C. difficile*.[4] Not only that, Cliff was fast—he could screen an entire ward of patients for *C. difficile* in under ten minutes with no physical contact or need to take stool samples.[5] This first-of-its-kind study suggested that dogs might be a valuable detection aid if given proper training.[6]

The use of dogs to help combat the spread of this bacteria was so promising that, since 2016, a Canadian hospital has employed a team of *C. difficile* detection dogs to identify areas of contamination and has reported lower incidences of *C. difficile* outbreaks in its hospital as a result.[7] Researchers have reported similar findings for many other animal-based diagnostics. For example, in a 2019 study, dogs were able to

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[2] FOOD & DRUG ADMIN, 510(k) PREMARKET NOTIFICATION DECISION SUMMARY PROSPECT® CLOSTRIDIUM DIFFICILE TOXIN A/B MICROPLATE ASSAY, No. K033479 1, 7 (Feb. 26 2004), https://www.accessdata.fda.gov/cdrh_docs/reviews/K033479.pdf [https://perma.cc/7NFH-8AVC].

[3] *Id.*

[4] Bomers et al., *supra* note 1, at 2–3; Pil Hun Song, Jung Hwa Min, You Sun Kim, Soo Yeon Jo, Eun Jin Kim, Kyung Jin Lee, Jeonghun Lee, Hyun Sung, Jeong Seop Moon & Dong Hee Whang, *Rapid and Accurate Diagnosis of* Clostridium Difficile *Infection by Real-Time Polymerase Chain Reaction*, 16 INTESTINAL RES. 109, 111–12 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5797257/pdf/ir-16-109.pdf [https://perma.cc/JA2U-B76M]. This Article reports the data from each study in terms of accuracy, instead of sensitivity or specificity. Sensitivity refers to a test's ability to correctly identify positive (diseased) samples, and specificity refers to a test's ability to correctly identify negative (healthy) samples. Alireza Baratloo, Mostafa Hosseini, Ahmed Negida & Gehad El Ashal, *Part 1: Simple Definition and Calculation of Accuracy, Sensitivity, and Specificity*, 3 EMERGENCY 48, 48 (2015). In contrast, accuracy measures a test's ability to correctly differentiate between positive and negative samples. *Id.* Therefore, the accuracy numbers discussed in this Article are illustrative of the overall performance of each diagnostic test and allow for an easy comparison between conventional and animal-based diagnostics. *Id.* Where a study cited in this Article published sensitivity and specificity data but not accuracy calculations, the Authors calculated accuracy using the raw data from each study, based on the formula provided by Baratloo et al. *See id.* For example, the Bomers et al. study reported that Cliff correctly identified all 50 of the positive stool samples and 47 of the 50 negative stool samples. Bomers et al., *supra* note 1, at 3. Using the formula provided in Baratloo et al., then, the 97% accuracy of stool sample detection was calculated by adding the number of correctly identified positive samples (50) to the number of correctly identified negative samples (47), and then dividing by the total number of samples evaluated (100) and multiplying by 100%. Bomers et al., *supra* note 1, at 3. For the patient samples, Cliff correctly identified 25 of the 30 infected patients and 261 of the 270 healthy patients. In other words, Cliff correctly responded to 286 of the 300 samples, resulting in an accuracy calculation of $\frac{286}{300} x100\% = 95.3\%$. *Id.* In contrast, the conventional FDA-approved methods for identifying *C. difficile* from a stool sample, which can take anywhere from two hours to two days to produce results—real-time PCR, *C. difficile* toxin assay, and cultures—have calculated accuracy rates of 92.8%, 71.0%, and 80.2%, respectively. Song et al*., supra* note 4, at 110. Of the 207 samples tested in the Pil Hung Song et al. study, real-time PCR correctly identified 192 samples ($\frac{192}{207} x100\% = 92.8\%$), *C. difficile* toxin assay correctly identified 147 samples ($\frac{147}{207} x100\% = 71.0\%$), and the culture method correctly identified 166 samples ($\frac{166}{207} x100\% = 80.2\%$). *Id.*; Baratloo et al., *supra*.

[5] Bomers et al., *supra* note 1, at 4.

[6] *Id.*

[7] C. difficile *Canine Scent Detection at Vancouver Coastal Health*, VANCOUVER COASTAL HEALTH, http://www.vch.ca/your-care/your-safety-privacy/infection-control/clostridium-difficile [https://perma.cc/SD3U-KWPL] (last visited Jan. 2, 2020); Vincente Biancardi da Camara, *Meet the Four-Legged Superbug Fighters Who Sniff Out* C. diff *at Vancouver Hospitals*, VANCOUVER COURIER (Aug. 26, 2019, 05:15 PM), https://www.vancourier.com/news/meet-the-four-legged-superbug-fighters-who-sniff-out-c-diff-at-vancouver-hospitals-1.23927908 [https://perma.cc/6D2G-Y4YH].

identify malaria infections in asymptomatic children by smelling their socks.[8] Even more remarkably, multiple studies have confirmed that dogs can be trained to detect the odor of prostate cancer in patient samples at accuracy levels between 90% and 99%, providing a more reliable alternative to conventional diagnostic methods that are only 25% accurate at screening for prostate cancer.[9] Because training dogs to detect human diseases has been such a success, researchers around the world are currently studying whether detection dogs can be trained to detect the novel Coronavirus disease of 2019 (COVID-19) in asymptomatic people.[10] After successful research studies in Finland and the United Arab Emirates, detection dogs are now employed at Helsinki's airport and around Abu Dhabi and Dubai to screen for asymptomatic Coronavirus cases.[11]

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[8] Claire Guest, Margaret Pinder, Mark Doggett, Chelci Squires, Muna Affara, Balla Kandeh, Sarah Dewhirst, Steven V. Morant, Umberto D'Alessandro, James G. Logan & Steve W. Lindsay, *Trained Dogs Identify People with Malaria Parasites by their Odour*, 19 LANCET INFECT. DISEASES 578 (2019), https://www.thelancet.com/action/showPdf?pii=S1473-3099%2819%2930220-8 [https://perma.cc/TGY7-MRAN]. The two dogs in the study achieved 88.0% and 86.9% accuracy in their detection of the malaria-infected children, respectively, more than seventeen months after the socks were collected. *Id.* at 579. The dogs' accuracy was calculated based on the following data: dog L correctly identified 132 of the 145 negative samples and 22 of the 30 positive samples ($\frac{(132+22)}{(145+30)} x100\% = 88.0\%$); dog S correctly identified 131 of the 145 negative samples and 21 of the 30 positive samples ($\frac{(131+21)}{(145+30)} x100\% = 86.9\%$). *Id.*; Baratloo et al., *supra* note 4.

[9] Gian Taverna, Lorenzo Tidu, Fabio Grizzi, Valter Torri, Alberto Mandressi, Paolo Sardella, Giuseppe La Torre, Giampiero Cocciolone, Mauro Seveso, Guido Giusti, Rodolfo Hurle, Armando Santoro & Pierpaolo Graziotti, *Olfactory System of Highly-Trained Dogs Detects Prostate Cancer in Urine Samples*, 193 J. UROLOGY 1382 (2014) (the dogs in this study performed at 99.2% and 98% accuracy, respectively); *see also* Jean-Nicolas Cornu, Géraldine Cancel-Tassin, Valérie Ondet, Caroline Girardet & Olivier Cussenot, *Olfactory Detection of Prostate Cancer by Dogs Sniffing Urine: A Step Forward in Early Diagnosis*, 59 EUR. UROLOGY 197 (2011) (90.9% accuracy); *Prostate-Specific Antigen (PSA) Test*, NAT'L CANCER INST. (Oct. 4, 2017), https://www.cancer.gov/types/prostate/psa-fact-sheet#q1[https://perma.cc/8SNA-L7AL] [hereinafter *PSA TEST*, NAT'L CANCER INST.]. The dogs' accuracy in the Taverna et al. study was calculated based on the following data: Dog 1 correctly identified all 362 positive samples and 533 out of 540 negative samples ($\frac{(362+533)}{(362+540)} x100\% = 99.2\%$) and Dog 2 correctly identified 357 out of 362 positive samples and 527 out of 540 negative samples ($\frac{(357+527)}{(362+540)} x100\% = 98.0\%$) Taverna et al., *supra* note 9; Baratloo et al., *supra* note 4. This study only reported the total number of positive and negative samples tested and the dogs' respective sensitivity (percentage of correct positive samples) and specificity (percentage of correct negative samples), so the actual number of both correct positive and negative samples was calculated using the following equations: $\#\ of\ total\ samples\ x\ \frac{sensitivity\ or\ specificity\ \%}{100} = positive\ samples\ identified$. *See* Baratloo et al., *supra* note 4. The dog's accuracy in the Cornu et al. study was calculated based on the dog correctly identifying 60 out of 66 total samples ($\frac{60}{66} x100\% = 90.9\%$). Cornu et al., *supra* note 9. Notably, the dog in the Cornu et al. study alerted to a negative sample, suggesting a false-positive, but the patient was biopsied again and diagnosed with prostate cancer. *Id.*

[10] Samuel Lovett, *Coronavirus: Sniffer Dogs Could Be Trained to Detect COVID in People*, INDEPENDENT (Apr. 29, 2020, 16:42), https://www.independent.co.uk/news/uk/home-news/coronavirus-uk-sniffer-dogs-lshtm-cases-symptoms-covid-19-a9477981.html [https://perma.cc/3NLT-WHKZ]; *COVID-19 Dogs*, MED. DETECTION DOGS (2020), https://www.medicaldetectiondogs.org.uk/covid-19-dogs/ [https://perma.cc/5VMW-5LHA]; Martin Hackett, *Penn Vet Launches COVID-19 Canine Scent Detection Study*, PENN TODAY (May 1, 2020), https://penntoday.upenn.edu/news/penn-vet-launches-covid-19-canine-scent-detection-study [https://perma.cc/4Q6W-B4ZM]; Richard Connor, *German Sniffer Dogs Show Promise at Detecting Coronavirus*, DW (July 23, 2020), https://www.dw.com/en/german-sniffer-dogs-show-promise-at-detecting-coronavirus/a-54300863 [https://perma.cc/2HFP-3WR9].

[11] Elian Peltier, *The Nose Needed for This Coronavirus Test Isn't Yours. It's a Dog's.*, N.Y. TIMES (Sept. 23, 2020), https://www.nytimes.com/2020/09/23/world/europe/finland-dogs-airport-coronavirus.html [https://perma.cc/B2F5-NE6C]; Ismaeel Naar, *Coronavirus: UAE Uses K9 Sniffer Dogs to Detect COVID-19 Patients*, AL ARABIYA (Jul. 9, 2020), https://english.alarabiya.net/en/coronavirus/2020/07/09/Coronavirus-UAE-uses-K9-sniffer-dogs-to-detect-COVID-19-patients [https://perma.cc/Z82W-WQN3].

Animal-based diagnostics could become novel, non-invasive tools for detecting human diseases, but developers face unknown regulatory challenges. The safety and efficacy of diagnostic kits used to detect illnesses are clearly regulated by the U.S. Food and Drug Administration (FDA). Developers of such kits must follow strict FDA guidelines to get their products to market. But if you replace a diagnostic kit with an animal, how would FDA extend its regulatory authority to regulate the animal's medical use?

Finding the answer to this question has become more urgent as more animal-based diagnostics are developed and have the potential to be commercialized. Furthermore, interest in rapid and non-invasive diagnostics is increasing due to outbreaks of highly virulent diseases like COVID-19, where detection is difficult and transmission between infected patients and healthcare workers is high.[12] However, developers of animal-based diagnostics face unknown regulatory challenges. FDA does not normally regulate animals for medical uses and has never regulated animals for use specifically as diagnostic devices. FDA's current regulatory regime for diagnostic kits does not provide a framework for review and approval of animal-based diagnostics. Moreover, the current regulatory process would likely require developers to provide safety and efficacy data that could be costly and time-consuming to produce on a per-test or per-animal basis.[13] Consequently, potential sponsors may be hesitant to develop

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[12] John Miller, Caroline Copley, Bart H. Meijer, *Countries Turn to Rapid Antigen Tests to Contain Second Wave of COVID-19*, REUTERS (Oct. 14, 2020, 8:32), https://www.reuters.com/article/health-coronavirus-rapid-tests/countries-turn-to-rapid-antigen-tests-to-contain-second-wave-of-covid-19-idUSKBN26Z2C2 [https://perma.cc/7YVT-9GAN]; *see* Friederike Häuser, Seyfullah Gökce, Gesa Werner, Sven Danckwardt, Stefanie Sollfrank, Carolin Neukirch, Vera Beyer, Julia B. Hennermann, Karl J. Lackner, Eugen Mengel & Heidi Rossmann, *A Non-Invasive Diagnostic Assay for Rapid Detection and Characterization of Aberrant mRNA-Splicing by Nonsense Mediated Decay Inhibition*, 130 MOLECULAR GENETICS & METABOLISM 27 (May 2020); *Validation of a Rapid, Non-invasive Point-of-care IVD Test for Diagnosis of SARA-COV-2 (COVID-19) Infection (EasyCov)*, CLINICALTRIALS.GOV, U.S. NAT'L LIB. MED. (last updated Oct. 20, 2020), https://clinicaltrials.gov/ct2/show/NCT04583319 [https://perma.cc/8CXM-DQ9G]; *Non-Invasive Diagnostics to Improve Gynecologic Health (R43.R44 Clinical Trial Optional)*, SBIR-STTR, U.S. DEP'T HEALTH & HUMAN SERVICES (Oct. 16, 2019), https://www.sbir.gov/node/1640977 [https://perma.cc/TVZ5-NP9X]; *NIH Awards Prize to Hemex Health's Non-Invasive Sickle Cell, Malaria, Anemia Rapid Test ("SMART") Diagnostic Technology*, HEMEX HEALTH (Oct. 26, 2020), https://hemexhealth.com/press-releases/2020/10/13/nih-awards-prize-to-hemex-healths-non-invasive-sickle-cell-malaria-anemia-rapid-test-smart-diagnostic-technology [https://perma.cc/9M7X-42BK]. The novel COVID-19 virus has exacerbated existing concerns about the cost and effectiveness of conventional diagnostics due to evolving global understanding of its symptoms and worldwide shortage of testing supplies. CTRS. FOR DISEASE CONTROL & PREVENTION, WHAT YOU SHOULD KNOW ABOUT COVID-19 TO PROTECT YOURSELF AND OTHERS (Mar. 6, 2020), https://www.cdc.gov/coronavirus/2019-ncov/downloads/2019-ncov-factsheet.pdf [https://perma.cc/5MSN-GZ5Y]; Dan Frosch, Ian Lovett & Deanna Paul, *Coronavirus Testing Chaos Across America*, WALL ST. J. (Mar. 19, 2020), https://www.wsj.com/articles/coronavirus-testing-chaos-across-america-11584618703 [https://perma.cc/JU8N-UKRZ] ("As screening sites open and close, supplies run short and criteria for participation change, many can't determine if they have the virus.").

[13] Jonathan S. Kahan, Edward C. Wilson, Jr. & Michael S. Heyl, *Medical Devices*, *in* FOOD AND DRUG LAW AND REGULATION, 554, 569–72 (David G. Adams, Richard M. Cooper, Martin J. Hahn & Jonathan S. Kahan eds., 3d ed. 2015) (detailing the extensive submission requirements for PMA applications). As discussed further below, the predicted inability for animal-based diagnostic developers to utilize the 510(k) premarket notification process and substantial equivalence pathway that is available to Class I and Class II medical devices would require the developers to submit a premarket approval application, which could deter innovation in this field. *Id.* A 2010 survey of FDA regulation of medical devices reported that the average total cost of a single PMA submission was $94 million, compared to $31 million for a 510(k) submission. JOSH MAKOWER, AABED MEER & LYN DENEND, FDA IMPACT ON U.S. MEDICAL TECHNOLOGY INNOVATION: A SURVEY OF OVER 200 MEDICAL TECHNOLOGY COMPANIES 6

animal-based diagnostics because it is not clear how FDA will regulate this new technology or whether it will be worth the investment.

This Article attempts to clarify ambiguities in the current law and predict how FDA will regulate animal-based diagnostics in the future. This Article will show how the current regulatory regime is inadequate for fully addressing the safety and efficacy issues raised by using animals as diagnostics. Part I of this Article provides a brief overview of the science and economics of the use of animals as medical diagnostics and discusses the regulatory challenges that such use faces. Part II reviews FDA regulation of medical devices generally. Part III reviews how FDA currently regulates the use of animals for particular treatments. Part IV then predicts how FDA will apply its regulations to animal-based diagnostics seeking marketing approval. This section will also show how current regulations are inadequate for addressing the challenges of developing animal-based diagnostics and may actually discourage such development. Finally, Part V proposes that FDA could facilitate development of animal-based diagnostics by (1) providing guidance with proposed requirements for the validation and approval of animal-based diagnostics and (2) adopting the technology certification approval pathway proposed by the VALID Act, a reform bill that would streamline how the Agency regulates medical diagnostics, and applying it to animal-based diagnostics.[14]

I. OVERVIEW OF USING ANIMALS AS MEDICAL DIAGNOSTICS

A. The Science of Animal-Based Diagnostics

Animal-based diagnostics have the potential to significantly change the medical diagnostic industry, as researchers are discovering that a variety of animal species can be trained to reliably detect the presence of human disease. For example, in 2015 researchers were able to train pigeons in just fifteen days to distinguish between benign and malignant cancer cells with 85% accuracy.[15] In other studies, researchers have trained mice and fruit flies to signal when they encounter odors related to certain bacteria or viruses.[16] Much of the research pertaining to animal-based diagnostics,

(2010), https://www.advamed.org/sites/default/files/resource/30_10_11_10_2010_Study_CAgenda_makowerreportfinal.pdf [https://perma.cc/R2Q2-49RJ].

[14] It is beyond the scope of this Article to analyze the following issues related to animal-based diagnostics: (1) animal-rights issues related to using animals as diagnostic devices; (2) post-marketing regulatory requirements for animal-based diagnostics; and (3) availability of alternative approval pathways for diagnostics, such as the Emergency Use Authorization, Breakthrough Devices, and Safer Technologies pathways.

[15] Richard M. Levenson, Elizabeth A. Krupinski, Victor M. Navarro & Edward A. Wasserman, *Pigeons* (Columba livia) *as Trainable Observers of Pathology and Radiology Breast Cancer Images*, 10 PLOS ONE (Nov. 18, 2015), https://doi.org/10.1371/journal.pone.0141357 [https://perma.cc/QF79-ELL3] (The pigeons in this study averaged 87% accuracy for familiar tissue samples and 85% accuracy for tissue samples that they had not encountered previously.).

[16] *See* Bruce A. Kimball, Kunio Yamazaki, Dennis Kohler, Richard A. Bowen, Jack P. Muth, Maryanne Opiekun & Gary K. Beauchamp, *Avian Influenza Infection Alters Fecal Odor in Mallards*, 8 PLOS ONE (Oct. 16, 2013), https://doi.org/10.1371/journal.pone.0075411 [https://perma.cc/86T7-JULE] (trained mice accurately discriminated between avian flu infected and non-infected duck feces 80% of the time); *see also* Martin Strauch, Alja Lüdke, Daniel Münch, Thomas Laudes, C. Giovanni Galizia, Eugenio Martinelli, Luca Lavra, Roberto Paolesse, Alessandra Ulivieri, Alexandro Catini, Rosamaria Capuano &

however, is directed toward dogs, which have an unparalleled ability to detect the odor of chemical compounds associated with human disease or other changes in the human body.[17]

Due to their extremely sensitive olfactory receptors, dogs are able to detect odors in parts per trillion, which makes their sense of smell more than 10,000 times stronger than a human's sense of smell.[18] This is because dogs possess an extra olfactory organ in their nose, and the portion of their brain that analyzes scent molecules is forty times larger than ours.[19] These anatomical differences allow dogs to pick out specific scent molecules in the air, even at low concentrations.[20] This level of sensitivity rivals that of the complex analytical instruments conventionally used for medical testing and diagnosis.[21]

Dogs can be trained to perform scent-detection tasks that are inherently difficult for humans and machines to replicate.[22] In fact, dogs are already deployed by law enforcement agencies to detect the odor of firearms, explosives, narcotics, and missing

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Corrado Di Natale, *More Than Apples and Oranges—Detecting Cancer with a Fruit Fly's Antenna*, 4 SCI. REP. 3576 (2015) (describing fruit flies' consistent responses to cancer odors in a controlled environment).

[17] Klaus Hackner & Joachim Pleil, *Canine Olfaction as an Alternative to Analytical Instruments for Disease Diagnosis: Understanding "Dog Personality" to Achieve Reproducible Results*, 11 J. BREATH RES. 1 (Mar. 2017). Over the last two decades, researchers have identified odors emitted from bacterial and cancer cells as gaseous volatile organic compounds (VOCs) that are distinct from those emitted from healthy cells. *Id.* While this Article uses the term "animal-based diagnostics" here to encompass any animals used to diagnose humans with medical conditions, the research literature uses a variety of terms to describe dog-specific applications, including canine olfaction, bio-detection dogs, canine detection, medical detection dogs, scent-detection, and others.

[18] *See* Pascale Quignon, Maud Rimbault, Stéphanie Robin & Francis Galibert, *Genetics of Canine Olfaction and Receptor Diversity*, 23 MAMMALIAN GENOME 132 (2012); Peter Tyson, *Dogs' Dazzling Sense of Smell*, NOVA (Oct. 4, 2012), http://www.pbs.org/wgbh/nova/nature/dogs-sense-of-smell.html [https://perma.cc/D8C7-MS27]; *see also* ALEXANDRA HOROWITZ, INSIDE OF A DOG: WHAT DOGS SEE, SMELL, AND KNOW 72 (Simon & Schuster, Inc., 1st ed. 2010). To put this in perspective, a human may be able to detect a teaspoon of sugar in a cup of water; however, dogs are able to detect a teaspoon of sugar in one million gallons of water—the equivalent of two Olympic-sized pools.

[19] Tyson, *supra* note 18.

[20] Hackner & Pleil, *supra* note 17. According to one study, the lower limit of a dog's olfactory detection of volatile organic compounds is 1.5 parts per trillion (ppt). Astrid R. Concha, Claire M. Guest, Rob Harris, Thomas W. Pike, Alexandre Feugier, Helen Zulch & Daniel S. Mills, *Canine Olfactory Thresholds to Amyl Acetate in a Biomedical Detection Scenario*, FRONTIERS IN VETERINARY SCI. 1 (Jan. 22, 2019).

[21] Hackner & Pleil, *supra* note 17, at 2. While modern analytical instruments and diagnostic tests have been developed to detect the presence of disease-related VOCs in patient samples, they are limited to identifiable compounds that can be isolated and programmed into the system. *Id.* Thus, even the newest scent-detecting analytical instruments are only as good as our ability to profile and program individual scent signatures, and the research in this area is far from complete. *See* Sara Harrison, *The Quest to Make a Bot That Can Smell as Well as a Dog,* WIRED (May 16, 2019), https://www.wired.com/story/quest-to-make-robot-smell-cancer-dog/ [https://perma.cc/5QXP-925N] ("[The] reason we don't have robots that can smell is that olfaction remains a stubborn biological enigma. Scientists are still piecing together the basics of how we sense all those volatile compounds and how our brains classify that information.").

[22] *See generally supra* notes 18–21; *see infra* note 23. For example, the National Pest Management Association encourages the use of certified canine detection teams to detect bed bugs when visual inspections are inadequate. NAT'L PEST MGMT. ASS'N, BEST PRACTICES FOR BED BUGS 10 (2016), https://www.pestworld.org/media/562243/npma-bed-bug-bmps-approved-20160728-1.pdf [https://perma.cc/72L2-EV5G].

persons.[23] Dogs are also widely employed as service animals, assisting patients with post-stroke recovery, seizure mitigation, and the challenges of visual impairment.[24] It's been suggested that dogs may even be able to alert their owners *before* the onset of temporal conditions that currently have no diagnostic tests available, including narcoleptic episodes, migraines, and severe allergic reactions.[25] Therefore, it is no surprise that dogs are being trained to detect certain conditions and diseases that are conventionally detected using FDA-approved diagnostics. To illustrate, Parts I.A.i to I.A.iii, *infra*, will compare the efficacy of FDA-approved diagnostic methods with canine detection studies for *C. difficile*, cancer, and malaria.[26]

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[23] *See FBI Working Dogs*, FED. BUREAU OF INVESTIGATION (Mar. 12, 2019), https://www.fbi.gov/video-repository/newss-fbi-working-dogs/view [https://perma.cc/3JUZ-27FS] (dogs can detect 19,000 different explosive combinations); Stephanie Dazio, *Police Canines Bring Special Skills to Dangerous Job*, NEWSDAY (Sept. 29, 2018, 6:00 AM), https://www.newsday.com/long-island/suffolk/long-island-police-dogs-1.21301029 [https://perma.cc/R97D-2APD].

[24] Henry Hoffman, *The Benefits of Pet Therapy for Stroke Survivors*, SAEBO (July 3, 2017), https://www.saebo.com/benefits-pet-therapy-stroke-survivors/ [https://perma.cc/5GX4-HBVJ]; *Seizure Dogs*, EPILEPSY FOUND. (Aug. 2017), https://www.epilepsy.com/learn/seizure-first-aid-and-safety/seizure-dogs [https://perma.cc/48Z4-3MH9]; *Is a Guide Dog Right for You?*, GUIDE DOGS OF AM. (2020), https://www.guidedogsofamerica.org/admissions/ [https://perma.cc/3U4E-2AME].

[25] L. Dominguez-Ortega, E. Díaz-Gállego, F. Pozo, S. Cabrera García-Armenter, M. Serrano-Comino, E. Domínguez-Sánchez & the Civil Guard's Collaboration, *Narcolepsia y Olor: Resultados Preliminares [Narcolepsy and Odor: Preliminary Report]*, 39 SEMERGEN – MEDICINA DE FAMILIA e41–e46 (2013), https://www.ncbi.nlm.nih.gov/pubmed/23835278 [https//perma.cc/Z5GV-TPF5]; Dawn A. Marcus & Amrita Bhowmick, *Survey of Migraine Sufferers with Dogs to Evaluate for Canine Migraine-Alerting Behaviors*, 19 J. ALT. COMPLEMENTARY MED. 501, 501 (2013), https://www.liebertpub.com/doi/10.1089/acm.2012.0234 [https://perma.cc/QT7P-8LUS]; Stephanie Gibeault, *Peanut Detection Dogs Save Lives*, AM. KENNEL CLUB (Nov. 28, 2017), https://www.akc.org/expert-advice/lifestyle/peanut-detection-dogs-save-lives/ [https://perma.cc/5YH4-3TH6].

[26] There are numerous canine-detection studies for other applications. Much of the research has been focused on cancer types and there are additional studies showing the feasibility of an animal-based diagnostic for breast, colorectal, ovarian, bladder, and skin cancer. *See* Michael McCulloch, Tadeusz Jezierski, Michael Broffman, Allan Hubbard, Kirk Turner & Teresa Janecki, *Diagnostic Accuracy of Canine Scent Detection in Early- and Late-Stage Lung and Breast Cancers*, 5 INTEGRATIVE CANCER THERAPIES 30 (2006); Hideto Sonoda, Shunji Kohnoe, Tetsuro Yamazato, Yuji Satoh, Gouki, Morizono, Kentaro Shikata, Makoto Morita, Akihiro Watanabe, Masaru Morita, Yoshihiro Kakeji, Fumio Inoue & Yoshihiko Maehara, *Colorectal Cancer Screening with Odour Material by Canine Scent Detection*, 60 GUT 814 (2011); Gyorgy Horvath, Gunvor Af, Klinteberg Järverud & Sven Järverud, *Human Ovarian Carcinomas Detected by Specific Odor*, 7 INTEGRATIVE CANCER THERAPIES 76 (2008); Carolyn M. Willis, Susannah M. Church, Claire M. Guest, W. Andrew Cook, Noel McCarthy, Anthea J. Bransbury, Martin R. T. Church & John C. T. Church, *Olfactory Detection of Human Bladder Cancer by Dogs: Proof of Principle Study*, 329 BMJ 1 (Sept. 2004); Duane Pickel, Glenda P. Manucy, Dianne B. Walker, Sandra B. Hall & James C. Walker, *Evidence for Canine Olfactory Detection of Melanoma*, 89 APPLIED ANIMAL BEHAV. SCI. 107 (2004). In addition, the use of animal-based diagnostics for Parkinson's disease, hypoglycemia, and other cancers are widely reported, but there are no published studies validating such uses of animal-based diagnostics at this time. *See* Sarah Knapton, *Dogs Could Sniff Out Parkinson's Disease Years Before Symptoms Appear*, TELEGRAPH (July 9, 2017), https://www.telegraph.co.uk/science/2017/07/09/dogs-could-sniff-parkinsons-disease-years-symptoms-appear/ [https://perma.cc/ET2U-BLKV] (A team at Manchester University is conducting a proof of principle study into whether dogs can be trained to detect the scent of Parkinson's disease in humans.); *Searching for the Odor of Parkinson's Disease*, PADS FOR PARKINSON'S, https://www.padsforparkinsons.org/ [https://perma.cc/DY82-JJJU] ("PADs has trained more than 25 dogs to successfully select Parkinson's samples from healthy human control samples with an accuracy rating of 90% or higher."); *see also* Katharina S. Weber, Michael Roden & Karsten Müssig, *Do Dogs Sense Hypoglycaemia?*, 33 DIABETIC MED. 934 (2016) (a survey-based report of anecdotal evidence from diabetic patients about how their dogs react to hypoglycemic episodes); *see also* Jessica Glenza, *Dog Trained to Detect Thyroid Cancer 'with 88% Accuracy'*, GUARDIAN (Mar. 9, 2015),

i. Clostridium difficile

C. difficile, a highly transmissible bacteria that causes intestinal disease, has the potential to spread quickly throughout hospitals, so its early detection is crucial to containing an outbreak and preventing hospital closures and significant expense.[27] There are a wide array of FDA-approved diagnostic tests for detecting *C. difficile*, but outbreaks are still common because of the delays in diagnosis and the latency period between diagnosis and treatment.[28] There are at least three FDA-approved methods for identifying *C. difficile* from a stool sample, which can take anywhere from two hours to two days to produce results.[29] These methods—real-time PCR, *C. difficile* toxin assays, and cultures—have accuracy rates of 92.7%, 71.0%, and 80.2%, respectively.[30] When compared to these conventional diagnostic methods, the animal-based diagnostic results are promising.

As described in the *British Medical Journal*, a beagle named Cliff was trained to identify the smell of *C. difficile* in both patients and their stool samples.[31] After two months of receiving reward-based training, the beagle was able to correctly characterize 97 out of 100 stool samples and 25 out of 30 patients having *C. difficile* infections.[32] Not only did the dog achieve 97% accuracy in detecting *C. difficile* in stool samples, he was 95.3% accurate in identifying *C. difficile* in patients by simply smelling them (i.e., without the need to collect samples or physically contact the patients).[33] This study was one of the first to demonstrate that a trained dog could serve to "diagnose" a patient in a manner comparable to a conventional diagnostic test.[34] However, as discussed in Part I.B, *infra*, this study and others have noted that there are still challenges to overcome in replicating these results for widespread use.[35]

ii. Cancer

"Cancer-sniffing dogs" have made headlines around the world for their ability to identify cancer in humans, even at early stages.[36] And while some of the claims have

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https://www.theguardian.com/us-news/2015/mar/09/dog-detects-thyroid-cancer-research [https://perma.cc/Z8VB-ZKR2].

[27] Bomers et al., *supra* note 1, at 2.

[28] *See id.*

[29] Song et al., *supra* note 4, at 109. While the *British Medical Journal* study discusses that conventional culture testing takes one to two days, since its publication researchers have developed a real-time PCR assay for *C. difficile* diagnostic testing that takes as little as two hours to produce a result. Bomers et al., *supra* note 1, at 2.

[30] Song et al., *supra* note 4, at 112. This study only calculates and reports sensitivity, so the authors have used the raw data provided in the study to calculate the accuracy for comparison to the animal-based diagnostic studies. *See supra* note 4.

[31] Bomers et al., *supra* note 1, at 1–3.

[32] *Id.* at 3–4.

[33] *Id.* at 3–4. This study only calculates and reports sensitivity and specificity, so the authors have used the raw data provided in the study to calculate the accuracy for comparison to conventional diagnostic tests. *See supra* note 4.

[34] *See* Bomers et al., *supra* note 1.

[35] *Id.* at 4; *see infra*, note 87 and accompanying text (citing to studies that address whether individual dogs have a different level of ability to detect disease, regardless of the training protocol implemented).

[36] Harrison, *supra* note 21 ("It started when researchers realized that canines can smell the early onset of melanoma. Then it turned out they can do the same for breast cancer, lung cancer, colorectal cancer, and

been criticized as dubious, there are numerous studies confirming that canines are able to detect low levels of certain odors associated with cancer from human samples in controlled environments.[37]

For example, studies have demonstrated that dogs are able to detect prostate cancer more reliably than FDA-approved screening methods.[38] Current diagnostic kits for prostate cancer, which are notoriously unreliable, use a blood test for elevated levels of prostate-specific antigen (PSA).[39] High levels of PSA can be an indicator of prostate cancer, but there is no direct correlation between elevated PSA levels and prostate cancer, so there is a significant risk for false-positive and false-negative test results.[40] Thus, a highly invasive prostate biopsy is almost always needed to confirm a suspected diagnosis.[41] However, only 25% of patients who undergo a prostate biopsy due to elevated PSA levels actually have prostate cancer, thus subjecting most patients to unnecessary risks from surgery.[42] But preliminary studies of prostate-cancer-detecting dogs yielded promising results that may help eliminate or mitigate the uncertainty and unnecessary risks surrounding the diagnosis of prostate cancer.[43] In a 2014 study, two dogs were able to detect the odor of prostate cancer in patients' urine samples with a combined accuracy of 98.6%, which provides a more reliable alternative to conventional PSA testing methods that provide high false-positive results.[44]

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ovarian cancer."); *see also* Heather Saul, *Shannen Doherty: Actress' Dog Bowie 'Detected Her Cancer' Before Doctors Diagnosed It*, INDEPENDENT (Aug. 3, 2016, 11:40), https://www.independent.co.uk/news/people/shannen-doherty-actress-dog-bowie-detected-her-cancer-before-doctors-diagnosed-it-a7169696.html [https://perma.cc/W37F-3QJS].

[37] For citations criticizing canine-cancer detection abilities, see *infra*, note 88. For citations supporting canine-cancer detection see *supra* note 26 and *infra* notes 38, 45, 50 and accompanying text.

[38] Taverna et al., *supra* note 9; *see also* Cornu et al., *supra* note 9 (90.9% accuracy). In fact, one study revealed that dogs were able to discern the difference between samples containing biomarkers for prostate cancer and those without biomarkers for prostate cancer with a combined average of 98.6%, simply by detecting the odor in a patient's urine sample. Taverna et al., *supra* note 9. Both the Taverna et al. and Cornu et al. study only calculate and report sensitivity and specificity, so the Authors have used the raw data provided in those studies to calculate the accuracy for comparison to conventional diagnostic tests. *See supra* notes 4 and 9.

[39] *PSA TEST*, NAT'L CANCER INST., *supra* note 9. PSA is a protein which, in high levels, can be indicative of prostate cancer. *Id.* This and other testing methods for prostate cancer cannot be used alone to diagnose prostate cancer. *Id.* Other testing methods include a digital rectal exam (DRE), ultrasound, x-rays, and cystoscopy. *Id.*

[40] *Id.* Elevated PSA can also be indicative of benign conditions that do not cause prostate cancer and DREs can identify small tumors that are not a risk to the patient's life, leading to a false-positive diagnosis. *Id.* Because of the invasiveness of a prostate biopsy and cancer treatment, a false-positive can introduce the patient to many unnecessary risks of surgery and radiation treatment. *Id.*

[41] *Id.* ("During this procedure, multiple samples of prostate tissue are collected by inserting hollow needles into the prostate and then withdrawing them. Most often, the needles are inserted through the wall of the rectum (transrectal biopsy). A pathologist then examines the collected tissue under a microscope.").

[42] *Id.*

[43] Taverna et al., *supra* note 9; *see also* Cornu et al., *supra* note 9.

[44] *See* Taverna et al., *supra* note 9. Because PSA can only be detected in blood samples, it is likely that the dogs in this study were detecting the presence of another compound that is a biomarker for prostate cancer. Natalia Cernei, Zbynek Heger, Jaromir Gumulec, Ondrej Zitka, Michal Masarik, Petr Babula, Tomas Eckschlager, Marie Stiborova, Rene Kizek & Vojtech Adam, *Sarcosine as a Potential Prostate Cancer Biomarker—A Review*, 14 INT'L J. MOLECULAR SCI. 13,893, 13,894–95 (2013). Research suggests that this compound is sarcosine, and its elevated levels can be detected during early stages of prostate cancer when PSA levels are not elevated. *Id.*

As another example, one study showed that dogs were able to detect lung cancer by smelling a patient's breath with nearly the same accuracy as expensive computerized tomography (CT) scans with X-rays.[45] When a patient exhibits lung cancer symptoms, such as a persistent cough, shortness of breath, or chest pain, doctors typically begin their diagnostic testing with CT scans.[46] However, CT scans present substantial risks for false-positive readings, which can lead to invasive follow-up procedures that are unnecessary.[47] Furthermore, because CT scans are done using dozens or even hundreds of X-ray images, the CT scan itself presents a cancer risk by exposing the patient to large doses of radiation (among other potential side effects).[48] In contrast, dogs were able to detect lung cancer with 81.4% accuracy by simply smelling a patient's breath—a novel and non-invasive method that produces promising results as compared to current diagnostic techniques.[49] Dogs have also succeeded in screening patients for lung cancer in blood samples, with similar results.[50]

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[45] Rainer Ehmann, Enole Boedeker, Uwe Friedrich, Jutta Sagert, Jürgen Dippon, Godehard Friedel & Thorsten Walles, *Canine Scent Detection in the Diagnosis of Lung Cancer: Revisiting a Puzzling Phenomenon*, 39 EUR. RESPIRATORY J. 669, 669 (2012) (dogs able to detect lung cancer with 81.4% accuracy); Yanchen Ren, Yiyuan Cao, Weidong Hu, Xiaoxuan Wei & Xiaoyan Shen, *Diagnostic Accuracy of Computed Tomography Imaging for the Detection of Differences Between Peripheral Small Cell Lung Cancer and Peripheral Non-Small Cell Lung Cancer*, 22 INT'L J. CLINICAL ONCOLOGY 865, 868 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5608786/pdf/10147_2017_Article_1131.pdf [https://perma.cc/6A6S-DBAY]. The Ehmann et al. study reported average accuracies among all four dogs for each stage of lung cancer, so the Authors calculated the average accuracy of the dogs' performance in the study by totaling the five reported accuracy percentages (100%, for stage I, 75% for stages IIa and IIb, 94% for stage IIIa, 75% for stage IIIb, and 63% for stage IV), and dividing by five. Ehmann et al., *supra*. Moreover, while the CT scan accuracy study uses the area under the curve (AUC) instead of a pure accuracy calculation to assess the accuracy of CT scans, for our purposes an AUC of 0.834, as reported in the study, is a good indicator of the accuracy of CT scans and is comparable to an accuracy of 83.4%. *Id.* at 672.

[46] *Lung Cancer*, MAYO CLINIC (Aug. 13, 2019), https://www.mayoclinic.org/diseases-conditions/lung-cancer/symptoms-causes/syc-20374620 [https://perma.cc/3E23-V6L6]. CT scans use x-rays to image a patient's chest for irregularities that may indicate the presence of lung cancer. *Glossary of Lung Cancer Terms*, AM. LUNG ASS'N (Dec. 18, 2017), https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/lung-cancer/resource-library/lung-cancer-dictionary.html#ct [https://perma.cc/PT95-YBMJ]; *Who Should Be Screened for Lung Cancer?*, CTRS. FOR DISEASE CONTROL & PREVENTION (Sept. 18, 2019), https://www.cdc.gov/cancer/lung/basic_info/screening.htm [https://perma.cc/H9PC-4ATM].

[47] *Who Should Be Screened for Lung Cancer?*, *supra* note 46. According to one study, there is a 60.4% chance of a false-positive reading for men and a 48.8% chance for women that undergo a CT scan for lung cancer. Jennifer M. Croswell, Barnett S. Kramer, Aimee R. Kreimer, Phil C. Prorok, Jian-Lun Xu, Stuart G. Baker, Richard Fagerstrom, Thomas L. Riley, Jonathan D. Clapp, Christine D. Berg, John K. Gohagan, Gerald L. Andriole, David Chia, Timothy R. Church, David Crawford, Mona N. Fouad, Edward P. Gelmann, Lois Lamerato, Douglas J. Reding & Robert E. Schoen, *Cumulative Incidence of False-Positive Results in Repeated, Multimodal Cancer Screening*, 7 ANNALS FAMILY MED. 212, 216 (2009), http://www.annfammed.org/content/7/3/212.full.pdf+html [https://perma.cc/B7GH-T596].

[48] *What are the Radiation Risks from CT?*, U.S. FOOD & DRUG ADMIN. (Dec. 5, 2017), https://www.fda.gov/radiation-emitting-products/medical-x-ray-imaging/what-are-radiation-risks-ct [https://perma.cc/QTX5-Y3C9].

[49] Ehmann et al., *supra* note 45, *passim*. Notably, this study used four family dogs that had no specific detection training prior to their involvement in this study, suggesting that higher accuracy rates could be achieved using dogs that are bred for or highly trained at scent detection tasks. *Id.*

[50] Heather Junqueira, Thomas A. Quinn, Roger Biringer, Mohamed Hussein, Courtney Smeriglio, Luisa Barrueto, Jordan Finizio, Xi Ying & "Michelle" Huang, *Accuracy of Canine Scent Detection of Bib-Small Lung Cancer in Blood Serum*, 119 J. AM. OSTEOPATHIC ASS'N 413, 413 (2019). This study, published as an abstract, does not provide enough data to calculate the accuracy of the test. *See id.* The study did disclose, however, that the dogs correctly identified the cancerous samples 96.7% of the time (sensitivity) and the non-cancerous samples 97.5% of the time (specificity), suggesting a high accuracy rate. *Id.*

iii. Malaria

Malaria is a mosquito-borne illness that affects hundreds of millions of people worldwide each year.[51] When left untreated, malaria can cause serious health complications or death.[52] The keys to preventing malaria outbreaks are rapid, accurate detection and early treatment of those infected with the parasite.[53] Inaccurate diagnoses can lead to higher mortality rates (for under-treated populations) and/or antimalarial drug resistance (for over-treated populations).[54] Moreover, it is difficult to suppress a malaria outbreak with conventional blood testing methods because infected patients can be asymptomatic.[55] Thus, detecting the presence of malaria in asymptomatic patients with animal-based diagnostics could be a promising alternative to conventional diagnostic testing.

Notably, the World Health Organization (WHO) recommends that anyone with malaria symptoms confirm their diagnosis with microscopy or a rapid diagnostic test (RDT), but the WHO does not have a recommendation to confirm the presence of malaria in asymptomatic patients.[56] To combat malaria transmission from asymptomatic hosts, the WHO recommends agencies administer anti-malarial drugs

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[51] *Malaria*, CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/parasites/malaria/index.html [https://perma.cc/ZK46-EUFM] (last updated Aug. 20, 2020); *Global Health Observatory Data: Malaria*, WORLD HEALTH ORG., https://www.who.int/gho/malaria/en/ [https://perma.cc/QC8G-XPX4] (last visited Jan. 2, 2020) ("According to the World Malaria Report 2018, there were 219 million cases of malaria globally in 2017 (uncertainty range 203–262 million) and 435,000 malaria deaths.").

[52] *Malaria, supra* note 51. Malaria symptoms include high fever, chills, nausea, and other flu-like symptoms. *Id.*

[53] Pedro Berzosa, Aida de Lucio, María Romay Barja, Zaida Herrador, Vicenta González, Luz García, Amalia Fernández Martínez, Maria Santana-Morales, Policarpo Ncogo, Basilio Valladares, Matilde Riloha & Agustín Benito, *Comparison of Three Diagnostic Methods (Microscopy, RDT, and PCR) for the Detection of Malaria Parasites in Representative Samples from Equatorial Guinea*, 17 MALARIA J., 2 (Sept. 2018).

[54] *Id.*

[55] Nicola Davis, *Dogs Can Detect Malaria by Sniffing Peoples' Socks*, GUARDIAN (Oct. 29, 2018), https://www.theguardian.com/world/2018/oct/29/dogs-noses-powerful-weapon-malaria-symptoms [https://perma.cc/5BUX-S3S3] (Steven Lindsay, a public health entomologist at Durham University, explains, "if you have one in 1,000 people with a malaria parasite, you can't finger-prick and take blood from 1,000 people to identity that one – you need a non-invasive [approach] . . . .").

[56] *Malaria*, WORLD HEALTH ORG. (Jan. 14, 2020), https://www.who.int/news-room/fact-sheets/detail/malaria [https://perma.cc/26ZE-5FQT]; WORLD HEALTH ORG., GUIDELINES FOR THE TREATMENT OF MALARIA 28 (3rd ed. 2015), https://apps.who.int/iris/bitstream/handle/10665/162441/9789241549127_eng.pdf;jsessionid=EACD11BFAC2280862C7BC087467BFF73?sequence=1 [https://perma.cc/J6WR-BVUP]. Of the available malaria diagnostic tests, the least expensive and most widely used tests are microscopy and rapid diagnostic tests (RDTs), which require patient blood samples and have false-negative rates of 19.4% and 13.3%, respectively. Berzosa et al., *supra* note 53, at 5. One study by Berzosa et al. reported that microscopy accurately detected the presence of malaria only 66.6% of the time, while RDTs were 86.7% accurate at detecting the disease. *Id.* Where RDTs are not yet available, health care facilities rely on microscopy or predictive diagnosis for malaria detection. *Id.* The main risk factors for inaccurate diagnosis are the lack of skilled health care workers and inadequate quality control in microscopy and the low reliability of RDTs generally. *Id.* The Berzosa et al. study provided the following raw data, which the Authors used to calculate the accuracy rates provided: microscopy identified 734 out of 937 negative samples and 415 out of 787 positive samples ($\frac{(734+415)}{(937+787)} x100\% = 66.6\%$) and RDT identified 835 out of 937 negative samples and 659 out of 787 positive samples ($\frac{(835+659)}{(937+787)} x100\% = 86.7\%$), as compared to SnM-PCR. *Id.* at 5–6; Baratloo et al., *supra* note 4.

to as many people as possible.[57] However, mass administration is expensive, wasteful, and can contribute to the prevalence of antimalarial drug resistance.[58] Thus, there is a need to target administration of antimalarial drugs more narrowly to those who are actually infected with malaria.

A preliminary study shows that dogs can be trained to detect the presence of asymptomatic malaria infections with similar accuracy to that of conventional diagnostic tests used on symptomatic patients.[59] The two dogs in this study achieved 88.0% and 86.9% accuracy in their respective detection of the parasite.[60] Not only is the reported accuracy in the animal study higher than the reported accuracy of RDTs (86.7%), the malaria-sniffing dogs do not require a blood sample, making the animal-based technique a less invasive alternative for detecting the presence of malaria.[61]

B. The Economics of Animal-Based Diagnostics

While the animal-based diagnostic applications discussed in Part I.A, *supra*, are promising, questions remain about the feasibility of commercializing animal-based diagnostics because of development costs, reproducibility issues, and FDA regulatory uncertainty. However, conventional medical devices, particularly single-use devices (SUDs), also have downsides. There is limited data on the total costs of animal-based and conventional diagnostic test kits, but the information available suggests that animal-based diagnostics could become a cost-effective, sustainable alternative to conventional diagnostic tests.

i. Costs of Conventional Diagnostic Testing

Many diagnostic kits are SUDs, which are generally inexpensive to purchase in bulk, but health care facilities absorb the hidden costs associated with SUD use, maintenance, and waste disposal.[62] Moreover, SUDs are known to be inaccurate and generate significant waste.[63] Over two billion lateral flow assays (a subset of single-use rapid diagnostic tests) are manufactured every year, including approximately 400

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[57] *See* WORLD HEALTH ORG., GUIDELINES FOR THE TREATMENT OF MALARIA, *supra* note 56, at 96.

[58] Thomas P. Eisele, *Mass Drug Administration Can be a Valuable Addition to the Malaria Elimination Toolbox*, 18 MALARIA J., 1, 2 (Aug. 22, 2019) ("Poor adherence and monotherapy may have contributed to drug resistance.").

[59] Guest et al., *supra* note 8, at 4. This study only calculates and reports sensitivity and specificity, so the authors have used the raw data provided in the study to calculate the accuracy for comparison to conventional diagnostic tests. *See supra* notes 4 and 8.

[60] Guest et al., *supra* note 8, at 4. This study only calculates and reports sensitivity and specificity, so the authors have used the raw data provided in the study to calculate the accuracy for comparison to conventional diagnostic tests. *See supra* notes 4 and 8.

[61] Berzosa et al., *supra* note 53, at 6. Moreover, the researchers in the animal study preserved the malaria samples for seventeen months before performing the study, suggesting the possibility of higher accuracy rates if applied to more recently collected samples. Guest et al., *supra* note 8, at 579.

[62] *Rethinking Health Care Supply Chain Costs: The Total Cost of Ownership Project*, PRACTICE GREENHEALTH (Apr. 27, 2016), https://practicegreenhealth.org/sites/default/files/upload-files/tco_flyer_draft_04.27.2016.pdf [https://perma.cc/64PL-66TG].

[63] *See supra* Parts I.A.i–I.A.iii and accompanying footnotes; *see also* Wendy Glauser, Jeremy Petch & Sachin Pendharkar, *Are Disposable Hospital Supplies Trashing the Environment?*, HEALTHY DEBATE (Aug. 18, 2016), https://healthydebate.ca/2016/08/topic/hospital-medical-waste [https://perma.cc/3KAJ-2H5L]. SUD waste in operating rooms has become a focus for waste quantification and elimination, but the environmental impact of single-use diagnostic tests remains largely unreported. *Id.*

million for malaria diagnosis alone.[64] In additional to waste generated by the device itself, SUDs often require excessive packaging to preserve sterility, generating further waste.[65] And like other medical waste, used SUDs are subject to hazardous waste regulations, typically requiring expensive processing in order to be safely disposed of.[66] Indeed, the cost of medical waste containment, transportation, and treatment can be up to 2,000% higher than the cost of regular waste disposal.[67] In 2012, health care facilities in the United States spent an estimated $2.5 billion on total medical waste disposal.[68] Moreover, SUD waste imposes negative externalities on the public health and the environment through water pollution and disease transmission.[69] And while eliminating waste through SUD reprocessing has become a priority, reprocessed SUDs have their own shortcomings, including high energy consumption during sterilization, contamination risks from bacterial resistance, consumable component waste, and the inevitable end-of-life disposal costs for devices that can no longer be reprocessed.[70] In

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[64] Darren Rowles, *Why the Diagnostic Industry Has a Responsibility to Tackle Plastic Pollution*, DIAGNOSTIC WORLD (May 3, 2019), https://www.diagnosticsworldnews.com/news/2019/05/03/why-the-diagnostics-industry-has-a-responsibility-to-tackle-plastic-pollution [https://perma.cc/P9Z5-ZVGT]. Lateral flow assays (LFAs) are disposable rapid diagnostic tests that can be operated without the need for expensive equipment or laboratory analysis. Katarzyna M. Koczula & Andrea Gallotta, *Lateral Flow Assays*, 60 ESSAYS BIOCHEMISTRY 111, 111 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4986465/ [https://perma.cc/REL5-LG77]. LFAs are commonly used to detect analytes associated with many common diseases, including cancer biomarkers, malaria antigens, and *C. difficile* toxins. *Id.*; Bryony Hayes, Caroline Murphy, Aoife Crawley & Richard O'Kennedy, *Developments in Point-of-Care Diagnostic Technology for Cancer Detection*, DIAGNOSTICS 1, 5 (June 2, 2018), https://www.mdpi.com/2075-4418/8/2/39?type=check_update&version=1 [https://perma.cc/W833-FDVL]; Susan E. Sharp, Lila O. Ruden, Julie C. Pohl, Patricia A. Hatcher, Linda M. Jayne & W. Michael Ivie, *Evaluation of the C. Diff Quik Chek Complete Assay, a New Glutamate Dehydrogenase and A/B Toxin Combination Lateral Flow Assay for Use in Rapid, Simple Diagnosis of* Clostridium difficile *Disease*, 48 J. CLINICAL MICROBIOLOGY 2082, 2082 (2010), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2884466/ [https://perma.cc/P3PV-LLPS]; Jinsu Kim, Xiangkun Elvis Cao, Julia L. Finkelstein, Washington B. Cárdenas, David Erickson & Saurabh Metha, *A Two-Colour Multiplexed Lateral Flow Immunoassay System to Differentially Detect Human Malaria Species on a Single Test Line*, MALARIA J. 1, 2 (Sept. 18, 2019), https://malariajournal.biomedcentral.com/articles/10.1186/s12936-019-2957-x [https://perma.cc/E3FG-EEDZ].

[65] Glauser et al., *supra* note 63.

[66] *Id.* Because disposable diagnostic tests use human bodily fluid samples (e.g., blood, urine, or saliva) to confirm a diagnosis, the waste generated must be treated and disposed of as medical waste. Sarah Overstreet, *Infographic: 10 Things to Know About Medical Waste Compliance,* SHARPS COMPLIANCE, INC. (Jan. 8, 2018), https://blog.sharpsinc.com/10-things-to-know-about-medical-waste-compliance [https://perma.cc/5B6U-8ZY7].

[67] Overstreet, *supra* note 66.

[68] Intan Airlina, *Medical Waste Disposal – The Definitive Guide 2020*, BIOMEDICAL WASTE SOLUTIONS https://www.biomedicalwastesolutions.com/medical-waste-disposal/ [https://perma.cc/XJ3F-R3XD] (last updated June 2020). It is unclear how much of that 2.5 billion dollars was spent on diagnostic testing waste. *See id.*

[69] PRACTICE GREENHEALTH, *supra* note 62. For commentary on the environmental impacts of medical waste, see *Healthcare Solid Waste*, WORLD HEALTH ORG., https://www.who.int/sustainable-development/health-sector/health-risks/solid-waste/en/ [https://perma.cc/7PKT-DHHE]; *see also* Nicole Pavlick, *A Toxic Relationship: Hospital Waste and Environmental Health*, CLEAN WATER ACTION (April 19, 2018), https://www.cleanwateraction.org/2018/04/19/toxic-relationship-hospital-waste-and-environmental-health [https://perma.cc/LZV9-F2K9]. For discussion of the human health risks presented by medical waste, see *Health-Care Waste*, WORLD HEALTH ORG. (Feb. 8, 2018), https://www.who.int/en/news-room/fact-sheets/detail/health-care-waste [https://perma.cc/X4PF-S9ET].

[70] Laura Landro, *Hospitals Reuse Medical Devices to Lower Costs*, WALL STREET J. (March 19, 2008), https://www.wsj.com/articles/SB120588469924246975 [https://perma.cc/4XC2-A5Q6]; Philip Jacobs & Ilke Akpinar, *Single-use Medical Devices: Economic Issues*, 10 HEART ASIA (Nov. 9, 2018),

addition to cost and waste, SUDs can be subject to shortages due to supply chain disruption, as recently seen with the COVID-19 pandemic.[71]

Another major concern regarding currently available SUDs is the economic and public health cost associated with inaccurate diagnoses. In 2016, a study reported that diagnostic errors can cause up to 80,000 deaths per year and contribute to the approximately $750 billion dollars annually wasted in the U.S. health care system.[72] Furthermore, there is a lack of efficiency associated with the expensive and invasive need to collect samples or perform confirmation tests, especially in the case of invasive biopsies typically needed to confirm a cancer diagnosis.[73] All of the cost and waste associated with SUDs creates a unique opportunity for animal-based diagnostic developers to provide a solution.

ii. Costs of Animal-Based Diagnostic Testing

Considering the cost of diagnostic equipment, medical waste disposal, inaccuracies, and laboratory testing, animal-based diagnostics may be more cost-effective in the long run. Using animals instead of SUDs would cut down the amount of medical waste associated with testing, especially given that many animal-based diagnostics do not require the collection of samples.[74] Moreover, even where samples are collected for training and testing animals, the total amount of equipment used and waste generated is still likely to be lower than conventional diagnostics, particularly considering that one animal-based diagnostic can be reused repeatedly. In contrast, SUDs and associated consumable testing equipment must be disposed of after each use.

As discussed in the Introduction, *supra*, one Canadian healthcare team used dogs trained to detect *C. difficile* and reported a reduction in the number of outbreaks and overall cost of identifying and containing *C. difficile* since implementing the detection dogs.[75] Maintaining the dog detection system costs the facility roughly $230,000 USD

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6267293/ [https://perma.cc/MS4C-SEBB]; Sam Brusco, *Deliberate Disposal: Single-use & Disposal*, MED. PROD. OUTSOURCING (April 3, 2018), https://www.mpo-mag.com/issues/2018-04-01/view_features/deliberate-disposal-single-use-disposables-technologies/ [https://perma.cc/D3A3-YG5Z]; Chloe Kent, *Making Sustainable Medical Devices: Five Top Tips*, VERDICT MED. DEVICES, https://www.medicaldevice-network.com/features/sustainable-medical-devices/ [https://perma.cc/BV63-AXBF] (last updated July 11, 2019).

[71] Chris Canipe & Travis Hartman, *The COVID-19 Testing Challenge*, REUTERS GRAPHICS (May 13, 2020), https://graphics.reuters.com/HEALTH-CORONAVIRUS/TESTING/azgvomklmvd/ [https://perma.cc/JPT4-9B37]; Joel Rose, *Coronavirus Testing Machines Are Latest Bottleneck in Troubled Supply Chain*, NPR (May 28, 2020, 5:02 AM), https://www.npr.org/2020/05/28/863558750/coronavirus-testing-machines-are-latest-bottleneck-in-troubled-supply-chain [https://perma.cc/FRP8-FAQJ]; ASS'N FOR MOLECULAR PATHOLOGY, SARS-COV-2 MOLECULAR TESTING: SUMMARY OF RECENT; SARS-COV-2 MOLECULAR TESTING SURVEY 5, https://www.amp.org/AMP/assets/AMP_SARS-CoV-2_Survey_Report_FINAL.pdf?pass=98 [https://perma.cc/GV8K-NY28] (last visited July 2, 2020).

[72] PINNACLE CARE, WHITE PAPER: THE HUMAN COST AND FINANCIAL IMPACT OF MISDIAGNOSIS (2016), https://www.pinnaclecare.com/forms/download/Human-Cost-Financial-Impact-Whitepaper.pdf [https://perma.cc/QVU8-NH7Z].

[73] *Id.*

[74] *See supra*, notes 2, 31–35, 45, 49, 59–61 and accompanying text. While both the malaria study and the lung cancer breath study did collect samples, the results suggest that it would be feasible to train a dog to smell a human's feet or breath, respectively, to test for the presence of odors associated with the relevant diseases tested in those studies. Guest et al., *supra,* note 8; Ehmann et al., *supra* note 45.

[75] *See* Biancardi da Camara, *supra* note 7. The dogs at the Vancouver Coastal Health facility were trained and validated using best practices from the Scientific Working Group on Dog & Orthogonal Detector

per year—an amount less than the facility's previous expenditures on conventional *C. difficile* detection and laboratory testing.[76] As another example, United Kingdom-based non-profit Medical Detection Dogs reports that its so-called bio-detection dogs, trained to identify the presence of disease from certain odors in human urine, stool, and skin samples, cost approximately $15,000 through initial training.[77] After initial training, the research projects conducted to establish the clinical feasibility for the bio-detection dogs can cost up to $200,000 per project.[78]

Because of the variability in dog detection abilities reported so far, it is unclear how employing animals as diagnostics would affect the costs of misdiagnosis.[79] The studies discussed in Part I.A, *supra*, all had higher accuracy rates relative to the respective conventional diagnostics, suggesting that their use may decrease incidence of misdiagnosis and lower associated costs.[80] However, there are also multiple studies suggesting that dogs' ability to detect disease can vary based on a dog's breed, age, and level of distraction.[81] These factors could create reproducibility issues and lead to more false-positive or false-negative diagnoses than conventional diagnostics, resulting in higher rates of unnecessary medical procedures or delays in treatment. Until a standardized procedure for developing animal-based diagnostic tests exists and is properly validated, there are no guarantees that animal-based diagnostics will increase patient outcomes related to misdiagnosis.

Guidelines and the U.S. Department of Agriculture's National Detector Dog Manual. The dogs' detection abilities are validated by an independent agency yearly. VANCOUVER COASTAL HEALTH, *supra* note 7. *Id.*

[76] *See* Biancardi da Camara, *supra* note 7 ("All in all, the project costs VGH $300,000 [Canadian dollar] a year, which is less than the traditional costs of identifying and testing for the bug through a lab."). Allison Muniak, Vancouver Coastal Health's Executive Director of Quality and Patient Safety and Infection Control, also reported increased patient well-being and reduced hospital wait times. *Id.*

[77] Pete Wedderburn, *Medical Detection Dogs – The Science Behind the Sniff*, TELEGRAPH (Aug. 21, 2018, 3:31 PM), https://www.telegraph.co.uk/pets/news-features/medical-detection-dogs-science-behind-sniff/ [https://perma.cc/C56Z-8A3W]. Medical Detection Dogs also offers Medical Alert Assistance Dogs that are "trained to detect minute changes in an individual's personal odour triggered by their disease and alert them to an impending medical event" and used for patients suffering from Type 1 Diabetes, severe nut allergy, Addison's disease, and postural orthostatic tachycardia syndrome. *About Medical Detection Dogs*, MED. DETECTION DOGS (2020), https://www.medicaldetectiondogs.org.uk/about-us/ [https://perma.cc/88YC-BM4P]. Medical Alert Assistance Dogs cost just over $38,000 to train with ongoing support costs of approximately $1,300 per year after placement. Wedderburn, *supra*.

[78] *See* MED. DETECTION DOGS, *supra* note 77. Medical Detection Dogs has been involved in studies on bio-detection dogs' ability to detect cancer, Parkinson's disease, malaria, and various bacterial infections. *Id.*

[79] *See* Maureen T. Taylor, Janine McCready, George Broukhasnski, Sakshi Kiepalaney, Haydon Lutz & Jeff Powis, *Using Dog Scent Detection as a Point-of-Care Tool to Identify Toxigenic* Clostridium difficile *in Stool*, 5 OPEN FORUM INFECTIOUS DISEASES 1, 1 (Aug. 22, 2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6105104/ [https://perma.cc/Q6G3-NMB3]; *see also infra* note 88 for citations to other studies demonstrating the variation in dog detection abilities.

[80] See *supra* Parts I.A.i–I.A.iii for a discussion of the animal-based diagnostics and their accuracy rates.

[81] *See infra* note 88 and accompanying text; Taylor et al., *supra* note 79, at 3 ("The reason for variability in diagnostic accuracy is uncertain and may be due to either the individual dog's ability to learn a new task, distractibility of the specific animal, or the sensitivity of different breeds' olfactory systems."). In a 2019 lung cancer detection study, one of the four dogs did not perform as well as the other three during the study, and researchers described that dog as "unmotivated" on test day. Junqueira et al., *supra* note 50, at 414.

It could be that the most effective way to use animal-based diagnostics is in combination with other devices.[82] Notably, at least two studies reported that a trained dog correctly detected disease from a patient sample after conventional diagnostics failed to detect disease in the same patient.[83] While using both animal-based and conventional diagnostics would add to the total cost of testing, combining these techniques has the potential to reduce overall medical costs by reducing the costs associated with misdiagnosis.

However, the cost of bringing an animal-based diagnostic to market is not clear. The regulatory pathway for getting FDA approval to sell an animal-based diagnostic is untested, and this unpredictability will certainly increase the time and cost needed to get such approval. Furthermore, the variability and potential inaccuracies of animal-based methods create challenges in using current regulatory methods to evaluate these animal-based diagnostics for safety and effectiveness. But utilizing animal-based diagnostics, either alone or in combination with conventional diagnostics, could greatly reduce costs for medical facilities and patients, and more importantly, also save human lives.

C. The Challenges of Bringing Animal-Based Diagnostics to Consumers

Animal-based diagnostics could significantly enhance the way in which certain diseases are detected and mitigated.[84] These diagnostics have the potential to supplement or replace current screening methods, which are typically more invasive, expensive, and wasteful. However, because FDA's regulatory purview covers the manufacture and use of diagnostic devices, animals that perform analogous diagnostic functions should also fall within the scope of FDA's regulatory authority.[85]

Development and commercialization of animal-based diagnostics is likely to be stymied by the uncertainty over how the current regulatory regime for diagnostic tests will be applied to animals.[86] As discussed in Part IV.B, *infra*, FDA's current risk-based

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[82] György Horvath, Håkan Andersson & Szilárd Nemes, *Cancer Odor in the Blood of Ovarian Cancer Patients: A Retrospective Study of Detection by Dogs During Treatment, 3 and 6 Months Afterward*, 13 BMC CANCER 396 (2013).

[83] Pickel et al., *supra* note 26, at 107 ("In a sixth patient, this dog 'reported' melanoma at a skin location for which initial pathological examination was negative, despite clinical suspicion. More thorough histopathological examination in this individual then confirmed melanoma in a fraction of the cells."); Cornu et al., *supra* note 9, at 199 (The dog in this study alerted to a negative sample, suggesting a false positive, but the patient was biopsied again and diagnosed with prostate cancer.).

[84] Since the early 2000s, there have been attempts to develop artificial olfactory (AO) devices for use in diagnosing disease, but none have been able to perfectly emulate the ability of dog noses. Harrison, *supra* note 21 ("Paul Waggoner, a scientist who studies canine olfaction at Auburn University, estimates we are 'decades away' from creating machines that could successfully compete with natural olfactory abilities."). Allowing properly trained animals to conduct diagnostic tests in the interim could provide AO researchers with crucial data and be a stopgap for alleviating the single-use waste and invasiveness concerns of current diagnostic technologies.

[85] Federal Food, Drug, and Cosmetic Act (FDCA) § 201(h), 21 U.S.C. § 321(h) (2016) (defining "devices" as including items "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals"). This Article assumes that an animal-based diagnostic falls within the definition of a "device" as defined under Section 321(h).

[86] Taylor et al., *supra* note 79, at 3 ("The reason for variability in diagnostic accuracy is uncertain and may be due to either the individual dog's ability to learn a new task, distractibility of the specific animal, or the sensitivity of different breeds' olfactory systems."). As discussed in *infra* Part IV, the inherent unknowns

classification system could potentially be applied to animal-based diagnostics. However, such regulations have traditionally only been applied to conventional diagnostics, which are typically electrochemical devices, and may not be adequate to deal with the predicted variabilities present in animal-based diagnostic methods. As such, it is not clear how FDA would regulate an animal-based diagnostic or what testing would be required to get marketing clearance from the Agency.

Because of this lack of clarity, sponsors of animal-based diagnostics likely would need to develop novel protocols to generate the safety and efficacy data required to obtain FDA premarket approval, which would likely require sponsors to conduct clinical studies.[87] However, unlike conventional diagnostics, animal-based diagnostics present unique challenges that would require alterations to the way clinical studies are currently performed. For instance, some animals, such as dogs, are prone to distractions; require intensive, repetitive training; present issues of cross-contamination; and may have inconsistent detection abilities depending on the dog's breed or age.[88] In addition to being less predictable than conventional diagnostics, animal-based diagnostics are also less understood—it is still unclear if the animals are detecting the same analyte as the equivalent diagnostic kits or something else.[89] And while studies have shown that dogs are remarkably able to detect different diseases from various different sample types, the wide range of potential applications for animal-based diagnostics introduces further complications with designing a uniform

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in the diagnostic accuracy of animal-based diagnostics will likely impede their path to premarket approval and use.

[87] Kahan et al., *supra* note 13, at 569 ("In evaluating the safety and effectiveness of a device, [the] FDA is permitted to consider only valid scientific evidence . . . . [I]n most cases [the] FDA requires studies on Class III medical devices that are designed like new drug trials (e.g., prospective, randomized controls)."). As discussed, *supra* note 13, this Article predicts that an animal-based diagnostic will be required to submit a premarket approval application as a Class III device, based on the lack of a predicate device to animal-based diagnostics, discussed in further detail *infra*, Part IV.

[88] Taylor et al., *supra* note 79, at 3; Concha et al., *supra* note 20, at 1, 9; Fay Porritt, Martin Shapiro, Paul Waggoner, Edward Mitchell, Terry Thomson, Steve Nicklin & Alex Kacelnik, *Performance Decline by Search Dogs in Repetitive Tasks, and Mitigation Strategies*, 166 APPLIED ANIMAL BEHAV. SCI. 112 (2015); Nathan E. Stone, Lindsay C. Sidak-Loftis, Jason W. Sahl, Adam J. Vazquez, Kristin B. Wiggins, John D. Gillece, Nathan D. Hicks, James M. Schupp, Joseph D. Busch, Paul Keim & David M. Wagner, *More than 50% of* Clostridium difficile *Isolates from Pet Dogs in Flagstaff, USA, Carry Toxigenic Genotypes*, 11 PLOS ONE (2016), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0164504 [https://perma.cc/Z2VW-55VB]; Robert T. Gordon, Carole Beck Schatz, Lawrence J. Myers, Michael Kosty, Constance Gonczy, Joan Kroener, Michael Tran, Pamela Kurtzhals, Susan Heath, James A. Koziol, Nan Arthur, Madeline Gabriel, Judy Hemping, Gordon Hemping, Sally Nesbitt, Lydia Tucker-Clark & Jennifer Zaayer, *The Use of Canines in the Detection of Human Cancers*, 14 J. ALTERNATIVE & CONTEMPORARY MED. 61, 65 (2008), https://www.liebertpub.com/doi/abs/10.1089/acm.2006.6408 [https://perma.cc/KQ6P-XB4Q]. Multiple studies have concluded that there is considerable variation in scent detection ability among dog breeds and individual dogs of the same breed, even when all dogs are subject to the same training protocols. Taylor et al., *supra* note 79, at 3; Concha et al., *supra* note 20, at 1, 9; Fay Porritt et al*., supra*. Moreover, a single dog's ability to detect disease under the same training conditions can vary depending on distractions, such as hunger or boredom. Concha et al., *supra* note 20, at 1, 9. Interestingly, a recent study found that 10% of studied dogs were carriers of toxigenic *C. difficile* strains that have the potential to cause *C. difficile* infections in humans, suggesting possible cross-contamination issues. Stone et al., *supra* note 88.

[89] *See* Cernei et al., *supra* note 44 and accompanying text (discussing dogs' ability to detect the presence of prostate cancer in urine samples where conventional prostate cancer diagnostic tests rely on the presence of PSA, a biomarker only found in the blood stream).

training and testing protocol.[90] These variations in training protocols and reproducibility may require multiple rounds of studies to ensure the accuracy of animal-based diagnostics, leading to high costs of training and implementing the animals.[91] The relatively large variability from animal-to-animal and disease-to-disease will likely make it difficult for FDA to use its current regulations in a manner that provides both assurance of patient safety and a clear regulatory framework for sponsors of animal-based diagnostics. Nevertheless, the current regulatory regime for diagnostic tests, discussed below, may provide a starting point for predicting how FDA will regulate their animal-based equivalents.

II. FDA REGULATION OF CONVENTIONAL DIAGNOSTIC TESTS

FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating medical devices, ensuring that devices manufactured and sold for medical use in the United States meet certain standards for safety and effectiveness.[92] Because of the breadth of the definition of "device" under the Federal Food, Drug, and Cosmetic Act (FDCA), FDA has asserted its authority to regulate a majority of diagnostic tests as medical devices, and animal-based diagnostics are unlikely to be exempted.[93] There are two subsets of conventional diagnostic tests—in vitro diagnostic (IVD) assays and laboratory-developed tests (LDTs)—and FDA has historically only elected to regulate IVDs as medical devices.[94] The practical difference between the two categories is that "if [the tests] are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them," the tests cannot be LDTs.[95] The distinction between IVDs and LDTs is

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[90] Carola Fischer-Tenhagen, Dorothea Johnen, Wolfgang Heuwieser, Roland Becker, Kristin Schallschmidt & Irene Nehls, *Odor Perception by Dogs: Evaluating Two Training Approaches for Odor Learning of Sniffer Dogs*, 42 CHEMICAL SENSES 435 (2017).

[91] *Id.* For example, dogs that can detect *C. difficile* in patients would require specific training and close monitoring to ensure replicability and accuracy of clinical studies—training that might be different from that for other animals trained to detect different illnesses. *See supra* note 1, and Parts I.A.i–I.A.iii for a discussion of different applications of animal-based diagnostics.

[92] *Center for Devices and Radiological Health*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/office-medical-products-and-tobacco/center-devices-and-radiological-health [https://perma.cc/XX6P-CF7J] (last updated July 12, 2019).

[93] Federal Food, Drug, and Cosmetic Act (FDCA), *supra* note 85. As relevant here, a "device" is defined within the FDCA as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals." *Id.*

[94] U.S. DEP'T OF HEALTH & HUMAN SERVICES, SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH & SOC'Y, REALIZING THE POTENTIAL OF PHARMACOGENOMICS: OPPORTUNITIES AND CHALLENGES 53–54 (2008) [hereinafter SACGHS PHARMACOGENOMICS REPORT]. Notably, FDA has proclaimed its authority to regulate all diagnostic tests under the FDCA as medical devices but has historically elected not to exercise that authority for LDTs. *Id.*

[95] *Laboratory Developed Tests*, U.S. FOOD & DRUG ADMIN, https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests [https://perma.cc/XSH4-FJ9Q] (last updated Sept. 27, 2018).

important here because, under the current regime, IVDs and LDTs are regulated differently.[96]

This Article assumes that animals that perform diagnostic functions analogous to conventional tests would also be subject to FDA's regulatory purview. However, because technological innovations in diagnostic testing have outpaced the promulgation of regulations, it is uncertain how FDA would specifically regulate animals that perform diagnostic functions.[97] It is possible that an animal-based diagnostic will be performed by clinical laboratory services as an LDT, where developers can control the environment and testing conditions to ensure accurate performance. However, it is equally possible that the animal-based diagnostic could be individually marketed as an IVD test kit.[98] The regulation of both types of diagnostics will be discussed in more detail below.

A. Regulation of In Vitro Diagnostic Assays

IVDs are assays that allow examination of patient samples to provide information for disease screening, diagnosis, and treatment.[99] FDA regulates IVDs as medical devices.[100] First, depending on the safety risks posed by a device, FDA classifies devices as Class I, II, or III, with increasing levels of regulatory control for each class.[101] For IVDs, safety is measured by the impact that the assay has on patient management (e.g., potential harm from false-positive or false-negative results).[102]

Class I devices present minimal safety risks and are generally exempt from premarket review and subject only to "general controls" that require the manufacturer to register the device with FDA, manufacture it in accordance with Good

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[96] *Id.* There is, however, proposed legislation to reform the diagnostic test regulatory process that would recharacterize IVDs and LDTs such that IVDs and LDTs would be subject to the same approval requirements. *See infra*, Part II.B.

[97] The proposed legislation to reform the regulatory process for the approval of IVDs and LDTs adds to the uncertainty of the regulation of animal-based diagnostics. *See infra*, Part II.B.

[98] For example, after an animal has been trained to detect *C. difficile*, it can be sold to a hospital that will perform the tests on-site without supervision from the developer. *See supra*, Part I.B.ii; *see also supra* notes 8, 75–78 and accompanying text.

[99] *Laboratory and In vitro Diagnostics*, WORLD HEALTH ORG. (2020), https://www.who.int/in-vitro-diagnostic/en/ [https://perma.cc/NE9E-XSB8]; 21 C.F.R. § 809.3(a) (2019) ("In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act.").

[100] *See* SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 51.

[101] *See* 21 U.S.C. § 360c(a)(1) (2018).

[102] SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 52. Safety is evaluated by demonstrating analytical validity, while effectiveness is evaluated by a showing of clinical validity. Julia T. Lathrop, *Analytical Validation and Points for Discussion*, U.S. FOOD & DRUG ADMIN. 3, 7, https://www.fda.gov/media/88823/download [https://perma.cc/E98R-UQX6]. Effectiveness, discussed *infra*, is measured by the usefulness of the IVD in determining clinical outcomes (e.g., patient diagnosis) for its intended use. *Id.* An adequate showing of both safety and effectiveness is required for device approval. *Id.*; *PMA Clinical Studies*, U.S. FOOD & DRUG ADMIN. (May 22, 2020), https://www.fda.gov/medical-devices/premarket-approval-pma/pma-clinical-studies [https://perma.cc/36ZR-BQWN]; SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 34.

Manufacturing Practices, and provide proper labeling for the device.[103] General controls do not require the sponsor to submit any clinical data related to the safety and effectiveness of the device.[104]

Class II devices present moderate risk and typically require submission of a so-called "510(k) premarket notification," which requires the sponsor to show that the device is "substantially equivalent" to an approved predicate device.[105] A predicate device is typically any device that has already been approved by FDA.[106] In addition to general controls, FDA can subject Class II devices to "special controls," which may include special labeling requirements, mandatory performance standards, and post-market surveillance.[107]

Class III devices are those that may present serious safety risks to the patient.[108] In addition to complying with general and special controls, sponsors of Class III devices

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[103] *See* 21 U.S.C. §§ 351, 352, 360, 360f, 360h, 360i, 360j (2018); *Classify Your Medical Device*, U.S. FOOD & DRUG ADMIN. (Aug. 31, 2018), https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device [https://perma.cc/X4H6-M2A7]; *see also* 21 C.F.R. §§ 801, 809, 820 (2019). As an example of labeling requirements, if an IVD assay is intended for use with a specific branded drug, FDA requires that the drug and IVD have mutually conforming labels. U.S. FOOD & DRUG ADMIN., INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH (CDER) AND THE CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH), at VII.A.1(a)ii., VII.B (2018), https://www.fda.gov/combination-products/classification-and-jurisdictional-information/intercenter-agreement-between-center-drug-evaluation-and-research-and-center-devices-and [https://perma.cc/RV93-L9UQ].

[104] *See* 21 U.S.C. § 360c(a)(1)(A) (2018).

[105] *Premarket Notification 510(k)*, U.S. FOOD & DRUG ADMIN. (Sept. 27, 2018), https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k [https://perma.cc/ACM3-3LQ8]. Note that general controls require submission of a 510(k) premarket notification for both Class I and II devices. *See* 21 U.S.C. §§ 360(k), 360c(i) (2017). However, by regulation, almost all Class I and many Class II devices are exempt from the 510(k) submission requirement. *See* 21 C.F.R. §§ 862–892 (2019); *Class I/II Exemptions*, U.S. FOOD & DRUG ADMIN. (July 1, 2019), https://www.fda.gov/medical-devices/classify-your-medical-device/class-i-ii-exemptions [https://perma.cc/4L6Y-FKTK]. FDA has established a voluntary Breakthrough Devices program available for devices subject to 510(k), PMA, or *de novo* submission requirements that allows a sponsor access to a shortened, prioritized application review period. Sponsors can apply for this program at any time before submitting the appropriate device application if the device "treat[s] or diagnos[es] a life-threatening or irreversibly debilitating condition." *See How to Study and Market Your Device*, U.S. FOOD & DRUG ADMIN. (Dec. 13, 2019), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/how-study-and-market-your-device [https://perma.cc/FL8Z-MNLA]. FDA has also issued a draft guidance for a similar voluntary Safer Technologies program that would provide the same shortened, prioritized review period for devices that do not meet the Breakthrough Devices program criteria and are subject to application submission requirements. *See* U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF, AND CLINICAL LABORATORIES ON SAFER TECHNOLOGIES PROGRAM FOR MEDICAL DEVICES (2019), https://www.fda.gov/media/130815/download [https://perma.cc/VF3T-YAXZ] (last visited Jan. 31, 2020).

[106] *See* SACGHS Pharmacogenomics Report, *supra* note 94, at 52; *Premarket Notification 510(k)*, *supra* note 105.

[107] *See* 21 U.S.C. § 360c(a)(1)(B) (2018).

[108] *How to Study and Market Your Device*, *supra* note 105. Class III devices are defined as those that "sustain or support life, are implanted, or present potential unreasonable risk of illness or injury." *Id.*; *See* 21 U.S.C. § 360c(a)(1)(C)(ii) (2017); SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 52. Note that devices with no equivalent predicate are classified as Class III devices by default, regardless of their safety. Consequently, sponsors of these devices can request a down-classification to either a Class I or II device if they can show the device presents only a low or moderate risk. SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 52; *See* 21 U.S.C. § 360c(f)(3) (2017). If FDA approves the down-classification (a so-called "*de novo* classification"), the device can be marketed without obtaining a PMA, subject to any general or special controls required by FDA. *See* U.S. FOOD & DRUG ADMIN., CENTER FOR DEVICES & RADIOLOGICAL HEALTH, DE NOVO CLASSIFICATION PROCESS (EVALUATION OF AUTOMATIC CLASS III

must submit a premarket approval (PMA) application that includes "valid scientific evidence" and sufficient data analysis providing a reasonable assurance that the device is safe and effective for its intended use.[109]

FDA determines that a device is safe, or meets analytical validation standards, when a sponsor demonstrates that the probable benefits of the device, "when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks."[110] In other words, FDA looks at the overall performance of the IVD (i.e., accuracy, precision, and reproducibility of the test), considering the risks of test administration and the detrimental effects of an incorrect test result on patient care.[111] As for effectiveness, or clinical validation, of the device, FDA evaluates how relevant an IVD and its results are for the medical condition the IVD is intending to diagnose.[112] The goal of clinical validation is to evaluate any sources of variation in test results based on individual test administration and develop a range of values that indicate positive and negative results.[113] FDA looks to well-controlled investigations to evidence device effectiveness.[114] If an IVD is clinically valid, the result of the test will have some bearing on a patient's diagnosis or management of patient care.[115]

While noting that the amount and type of evidence required varies depending on the device and its intended use, in general, FDA defines valid scientific evidence as

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DESIGNATION), GUIDANCE FOR INDUSTRY AND FDA STAFF (2017), https://www.fda.gov/media/72674/download [https://perma.cc/9QWU-NEUN].

[109] *PMA Clinical Studies*, *supra* note 102; *see* 21 U.S.C. § 360c(a)(1)(C) (2017); SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 52. 21 C.F.R. § 860.7(b) (2018) lists the following factors as relevant to FDA's determination of device safety and effectiveness:

(1) The persons for whose use the device is represented or intended; (2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) The reliability of the device.

Id.

[110] *PMA Clinical Studies*, *supra* note 102; *see also* Lathrop, *supra* note 102.

[111] *See PMA Clinical Studies*, *supra* note 102; *see also* Lathrop, *supra* note 102. For example, FDA considers the importance of the test in the patient management lifecycle. *See PMA Clinical Studies*, *supra* note 102; *see also* Lathrop, *supra* note 102. A test that is the sole evaluation before treatment determinations must meet stricter analytical validity standards than a test that is used in combination with other signs and symptoms to aid in patient diagnosis. *See PMA Clinical Studies*, *supra* note 102; *see also* Lathrop, *supra* note 102.

[112] Lathrop, *supra* note 102.

[113] Lawrence Jennings, Vivianna M. Van Deerlin & Margaret L. Gulley, *Recommended Principles and Practices for Validating Clinical Molecular Pathology Tests*, 133 ARCHIVES PATHOLOGY & LAB. MED. 743, 747 (2009).

[114] *PMA Clinical Studies*, *supra* note 102. A well-controlled investigation is one that includes a detailed study protocol and report addressing the study's objectives, explanation of methods used, comparison of testing results with a valid control, and a summary of the data analysis and statistics used. *Id.* See the criteria and factors listed under "Well-Controlled Clinical Investigation" heading for an enumerated list. *Id.*

[115] Jennings et al., *supra* note 113, at 750. A test could be analytically valid at detecting a specific analyte in a patient sample but would have no clinical validity if the detected analyte did not predict or identify any patient outcomes or potential diagnosis. *Id.* For example, a 2008 study reported results that only two of six dogs in the study were able to detect the cancerous samples at levels higher than chance. Gordon et al., *supra* note 88, at 64. While this study appears to have flaws in its application, assuming that it was analytically valid, it did not demonstrate clinical validity because the results were not sufficient to determine the presence of cancer in the samples. *Id.*

"evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device."[116] These investigations may include animal model studies, studies involving human subjects, and nonclinical investigations, or bench laboratory tests.[117] During the PMA process, FDA reviews the submitted data for adequate evidence demonstrating both analytical and clinical validity, and approves applications that demonstrate "the absence of unreasonable risk of illness or injury" and "clinically significant results" in the target population associated with the use of the device for its intended uses and conditions of use.[118]

The PMA application must be approved by FDA before the sponsor can commercially market the device.[119]

B. Regulation of Laboratory-Developed Tests

Diagnostic tests manufactured and used internally by a laboratory service are classified as "laboratory-developed tests" (LDTs).[120] The regulation of LDTs has received significant attention over the last ten years, and this section discusses some of the reform proposals because they highlight potential approaches for regulating animal-based diagnostics as LDTs.

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[116] 21 C.F.R. § 860.7(c)(2) (2018). The amount and type of evidence required varies according to device characteristics, device use conditions, whether adequate warnings and use restrictions exist for the device, and the amount of experience with the device. *Id.* Valid scientific evidence explicitly does not include "isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions." *Id.* While FDA has not enumerated specific evidence required for PMA applications, FDA generally looks for nonclinical laboratory studies conducted in compliance with 21 C.F.R. § 58 (2019) and clinical study data that includes, *inter alia*, sound study protocols, adverse reactions and complications, device failures and replacements, patient complaints, and results of statistical analyses. *PMA Clinical Studies*, *supra* note 102; *Premarket Approval (PMA)*, U.S. FOOD & DRUG ADMIN. (May 16, 2019), https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma [https://perma.cc/9PNR-XBEF].

[117] 21 C.F.R. § 860.7(d)(2) (2018). It should be noted that human clinical trials of unapproved devices require approval by either FDA or the Institutional Review Board (IRB) prior to institution of the clinical trial, depending on the risk level of the device. *Overview of Regulatory Requirements: Medical Devices*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/training-and-continuing-education/cdrh-learn/overview-regulatory-requirements-medical-devices-transcript [https://perma.cc/R5FT-2ZNJ] (transcript of Nov. 2011 presentation). Those sponsors seeking clinical trial approval do not submit a PMA application, but instead must apply for an Investigational Device Exemption for significant risk devices (i.e., high-risk Class III, life-supporting, or life-sustaining devices) or seek IRB approval for non-significant risk devices. *Id.*; *PMA Clinical Studies*, *supra* note 102.

[118] *PMA Clinical Studies*, *supra* note 102. Safety is evaluated by demonstrating analytical validity, while effectiveness is evaluated by a showing of clinical validity. *See* Lathrop, *supra* note 102.

[119] 21 U.S.C. § 360e (2017). FDA encourages applicants to consult relevant FDA guidance documents, industry and voluntary consensus standards, and schedule pre-submission meetings with FDA officials to request feedback on their application prior to submission. *Premarket Approval (PMA)*, *supra* note 116; *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program*, U.S. FOOD & DRUG ADMIN. (May 6, 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program [https://perma.cc/4PX9-23K9]; *How to Study and Market Your Device*, *supra* note 104. FDA has also set up a "Device Advice" page with recorded presentations on various medical device application approval topics. *Device Advice: Comprehensive Regulatory Assistance*, U.S. FOOD & DRUG ADMIN. (Sept. 14, 2018), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance [https://perma.cc/S6D8-LDFP].

[120] SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 51.

Under current law, FDA has authority to regulate LDTs.[121] However, FDA has historically elected not to exercise this authority.[122] Instead, LDTs have been regulated by the Center for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988.[123] Under these Amendments, CMS requires the laboratory service to demonstrate analytical validity for the LDT.[124] However, no showing of clinical utility or validity is required.[125]

Due to modern technological advancements and rapidly evolving business models, LDTs have become more complex and more common throughout the industry, and they now present higher risks than pre-amendment LDTs.[126] This has prompted a series of proposed reforms to ensure their safety and efficacy.[127]

In 2010, FDA announced its intent to actively enforce regulations to ensure that the clinical validity of moderate- to high-risk LDTs is consistent with the FDCA.[128] After several years of anticipation, FDA finally released a draft guidance document in 2014, which outlined FDA's risk-based, phased-in approach to enforcing premarket review

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[121] *See* Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (May 28, 1976) (codified as amended in scattered sections of 21 U.S.C.); Safe Medical Devices Act of 1990 § 16, 21 U.S.C. § 353(g) (2018).

[122] SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 53–54. However, FDA has issued warning letters in the past to companies marketing LDTs for uses that have significant public safety risks and lack clinical validation. *See, e.g.*, U.S. FOOD & DRUG ADMIN., CENTER FOR DEVICES & RADIOLOGICAL HEALTH, WARNING LETTER: INOVA GENOMICS LABORATORY (2019), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/inova-genomics-laboratory-577422-04042019 [https://perma.cc/ER7F-A98C] ("[T]he Agency always retains discretion to take action when appropriate, such as when it is appropriate to address significant public health concerns") [hereinafter FDA WARNING LETTER].

[123] *See* Clinical Laboratory Improvements Amendments of 1988, Pub. L. No. 100-578, 102 Stat. 2903 (codified at 42 U.S.C. § 263a (2012)); Randy Prebula, *The Ever-Evolving Role of "Companion Diagnostics,"* FDLI UPDATE, Sept./Oct. 2008, at 14, 16.

[124] *See* Aaron Bouchie, *MDx: A Murky Brew*, BIOCENTURY A1, A2 (Jan. 26, 2009). "Analytical validity is a measure of how accurately and consistently the test detects the presence of a specific genotype." SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 32; Marta Gwinn & Muin J. Khoury, *Epidemiologic Approach to Genetic Tests: Population-Based Data for Preventive Medicine*, *in* HUMAN GENOME EPIDEMIOLOGY (Muin J. Khoury & J. Little eds., 2003).

[125] *See* Bouchie, *supra* note 124, at A2. Clinical utility refers to the device's ability to inform clinical decision making and predict clinical outcomes. S.D. Grosse & Muin J. Khoury, *What is the Clinical Utility of Genetic Testing?*, 8 GENETIC MED. 448 (2006). Clinical validity means how well the test predicts a given phenotype (i.e., clinical disorder or outcome). SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 32; Gwinn & Khoury, supra note 124, at 196.

[126] *Laboratory Developed Tests*, *supra* note 95.

[127] *Id.* ("The FDA has identified problems with several high-risk LDTs including: claims that are not adequately supported with evidence; lack of appropriate controls yielding erroneous results; and falsification of data.").

[128] U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY, FDA STAFF, AND CLINICAL LABORATORIES ON FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY DEVELOPED TESTS (LDTS) 4–5, 11–14 (2014), https://www.fda.gov/media/89316/download [https://perma.cc/H37U-4XB5] (last visited Jan. 3, 2020) [hereinafter 2014 DRAFT GUIDANCE ON LDTS]; Kahan et al., *supra* note 13, at 588–89 ("[The] FDA commented that it was taking this step in part because it does not feel that the Clinical Laboratory Improvement Amendments (CLIA), which also contain regulatory requirements applicable to laboratories, are sufficient to 'ensure that LDTs are properly designed, consistently manufactured, and are safe and effective for patients.'").

requirements for moderate- to high-risk LDTs.[129] Under the draft guidance, FDA would require device sponsors to demonstrate *both* analytical validity and clinical validity.[130] The draft guidance also indicated that FDA would implement the same risk-based classification system as other devices (such as Class I, II, or III IVDs) and the requisite premarket review process—510(k), PMA, or *de novo*—for each LDT classification.[131]

Before FDA finalized its 2014 draft guidance, however, the House Appropriations Committee responded by ordering FDA "to suspend further efforts to finalize the [draft] Guidance" because it "put[] forth a proposed regulatory framework that is a significant shift in the way LDTs are regulated" and "circumvents the normal rulemaking process."[132]

In response to Congress's express limitation on issuing further guidance, FDA published a discussion paper in 2017 that outlined suggestions for reform that scaled back most of the proposals in the 2014 draft guidance.[133] The discussion paper retained the risk-based, phased-in approach to enforcement, but would have exempted conventional LDTs and those already on the market from registration and approval requirements.[134] Moreover, the 2017 discussion paper proposed a complementary oversight system that would pair CMS's more lenient analytical validity requirements with FDA's clinical validity requirements.[135]

C. The VALID Act of 2020: Proposed Reform of Diagnostic Test Regulation

In response to FDA Commissioner Scott Gottlieb's call for comprehensive legislation in this area, a bipartisan group of Senators and Representatives drafted the

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[129] *See* 2014 DRAFT GUIDANCE ON LDTS, *supra* note 128. However, opponents of FDA's Draft Guidance suggested that expanding CLIA would be more appropriate and efficient to "ensure that they meet the changing needs of the healthcare community." Kimberly Scott, *Future of LDT Oversight Still Uncertain*, AM. ASS'N CLINICAL CHEMISTRY (Apr. 1, 2016), https://www.aacc.org/publications/cln/articles/2016/april/future-of-ldt-oversight-still-uncertain [https://perma.cc/4R4U-T69E].

[130] 2014 DRAFT GUIDANCE ON LDTS, *supra* note 128, at 7, 9–10. FDA's standard of analytical validity is more stringent and comprehensive than the CMS regulatory scheme because it is primarily focused on the LDT's safety and effectiveness. *See id.* Furthermore, in addition to analytical validity, FDA would assess an LDT's clinical validity (i.e., "the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient"). *Id.* at 6.

[131] 2014 DRAFT GUIDANCE ON LDTS, *supra* note 128, at 10–14. The *de novo* classification process is used when a sponsor of a device without an equivalent predicate requests a down classification from the default Class III to either a Class I or II device. *See supra* note 108.

[132] HOUSE APPROPRIATIONS COMM., SIGNIFICANT ITEMS, H.R. REP. NO. 114-531, at 261–62 (2016), https://www.fda.gov/media/106426/download [https://perma.cc/3V3M-QK5L] (last visited Jan. 3, 2020) (The House Report further stated that the public should provide their input regarding the proposed changes, and that Congress is speaking with various constituents and stakeholders to pass legislation that addresses the optimal regulatory method for modern LDTs.).

[133] U.S. FOOD & DRUG ADMIN., DISCUSSION PAPER ON LABORATORY DEVELOPED TESTS (LDTS) (January 13, 2017), https://www.fda.gov/media/102367/download [https://perma.cc/J96Q-YD5X] [hereinafter 2017 LDT DISCUSSION PAPER]; *see also* Hira Ahmed, *FDA 2017 Discussion Paper on Laboratory Developed Tests*, DUKE SCIPOL (May 23, 2017), http://scipol.duke.edu/content/fda-2017-discussion-paper-laboratory-developed-tests [https://perma.cc/WR2F-9TUG] (summarizing the discussion paper).

[134] 2017 LDT DISCUSSION PAPER, *supra* note 133, at 2.

[135] *Id.*

Verifying, Accurate, Leading-edge IVCT Development (VALID) Act of 2020.[136] The VALID Act proposes a complete overhaul of diagnostic test regulation, creating a new class of medical devices called in vitro clinical tests (IVCTs) that would encompass both conventional IVDs and LDTs.[137] This new class of tests would likely still be regulated by CDRH.[138]

Under the proposed law, an IVCT would be defined as a "test intended . . . to be used in the collection, preparation, analysis, or in vitro clinical examination of specimens taken or derived from the human body."[139] The IVCTs would be further classified into high-risk and low-risk IVCTs, with high-risk IVCTs subject to premarket approval unless exempt under another provision of the Act.[140] Low-risk IVCTs would be exempt from the premarket approval process but would be subject to

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[136] Verifying Accurate Leading-edge IVCT Development Act of 2020, H.R. ____, 116th Cong. (2020), https://degette.house.gov/sites/degette.house.gov/files/VALID%20Bill%20Text.pdf [https://perma.cc/8LMY-BC2A] [hereinafter VALID Act of 2020]; *Lawmakers Introduce Legislation to Expand Nation's Diagnostic Testing Capabilities*, CONGRESSWOMAN DIANA DEGETTE (Mar. 5, 2020), https://degette.house.gov/media-center/press-releases/lawmakers-introduce-legislation-to-expand-nation-s-diagnostic-testing [https://perma.cc/9ZEH-LK6A]. An earlier iteration of this bill was released as the VALID Act of 2018 on December 6, 2018. Verifying Accurate Leading-edge IVCT Development Act of 2018, H.R. ____, 115th Cong. (2018), https://degette.house.gov/sites/degette.house.gov/files/valid_act_discussion_draft_12.6.18.pdf [https://perma.cc/D6YM-6F2Q] [hereinafter VALID Act of 2018]; *Senators Bennet, Hatch & Reps. Bucshon, DeGette Release Draft Legislation to Modernize FDA Regulation of Diagnostic Tests*, MICHAEL BENNET: U.S. SENATOR FOR COLORADO (Dec. 6, 2018), https://www.bennet.senate.gov/public/index.cfm/2018/12/senators-bennet-hatch-reps-bucshon-degette-release-draft-legislation-to-modernize-fda-regulation-of-diagnostic-tests [https://perma.cc/9W79-57UA]. Before the VALID Act of 2018 was circulated, the Diagnostic Accuracy and Innovation Act (DAIA) was introduced in the U.S. House of Representatives. Allyson B. Mullen & Jeffery N. Gibbs, *The Proposed VALID Act: A Possible Next Step in FDA's Goal of Regulating LDTs*, REGULATORY FOCUS (Feb. 2019), https://hpm.com/wp-content/uploads/2019/06/The-Proposed-VALID-Act.pdf [https://perma.cc/F4AD-ZNEG]. DAIA also proposed a new statutory framework to regulate LDTs, but did not gain much traction in Congress. Thus, the VALID Act of 2018 was not the first attempt at legislation on this subject, and of course was modified as it passed through the House and Senate, with input from FDA. *Id.* The VALID Act of 2020 is the latest draft to advance these reform efforts. *See* CONGRESSWOMAN DIANA DEGETTE, *supra*.

[137] *See* VALID Act of 2020, *supra* note 136, § 2(a)(1).

[138] Blake E. Wilson, *IVDs and LDTs: Evolving Visions of FDA Oversight Under the VALID Act*, MED. DEVICE ONLINE (July 29, 2019), https://www.meddeviceonline.com/doc/ivds-and-ldts-evolving-visions-of-fda-oversight-under-the-valid-act-0001 [https://perma.cc/V77E-4HQ4] ("[The new law] does not require the creation of a new center within [the] FDA dedicated to regulating IVCTs, and it is possible that oversight could fall to the Center for Devices and Radiological Health (CDRH).").

[139] VALID Act of 2020, *supra* note 136, § 2(a)(1). An IVCT is further defined as a test, as described, for the purpose of (i) identifying, diagnosing, screening, measuring, detecting, predicting, prognosing, analyzing, or monitoring a disease or condition, including by making a determination of an individual's state of health; or (ii) selecting, monitoring, or informing therapy or treatment for a disease or condition. VALID Act of 2020, *supra* note 136, § 2(a)(1). The definition also explicitly includes any testing protocols, test instruments, "an article for taking or deriving specimens from the human body," software, and any related parts, including reagents, calibrators, and controls. VALID Act of 2020, *supra* note 136, § 2(a)(1)(ss)(1)(B)(i-iv).

[140] VALID Act of 2020, *supra* note 136, §§ 587(9), 587(14), 587A. Notably, an IVCT would not be considered high-risk under the act "if mitigating measures are established and applied to sufficiently mitigate the risk of inaccurate results." *Id.* §§ 587(9), 587(15), 587E. Among the many exemptions to premarket approval under the draft VALID Act, a subset of IVCTs called "manual tests" are exempt from premarket approval. *Id.* § 587A(f). Manual tests are those that result from "direct, manual observation, without the use of automated instrumentation or software for intermediate or final interpretation, by a qualified laboratory professional" and are "designed, manufactured, and used within a single laboratory" and meet requirements of Section 353 under the Public Health Service Act. *Id.*

registration and some post-market regulations.[141] IVCTs are defined as high-risk if an "undetected inaccurate result . . . presents potential unreasonable risk for serious or irreversible harm or death to a patient or patients, or would otherwise cause serious harm to the public health."[142] The classification system allows an otherwise high-risk IVCT to be regulated as a low-risk IVCT if mitigating measures exist that would reduce the inherent risks of a misdiagnosis.[143]

In addition to the new approval pathways that would become available for IVCT sponsors under the VALID Act, a full-fledged PMA process will remain in place.[144] However, in a December 2018 press release, FDA has stated that the VALID Act would likely exempt 90% of IVCTs from premarket review.[145]

In lieu of submitting a PMA application, sponsors of eligible IVCTs would be able to utilize a novel technology certification program.[146] Under this program, sponsors are issued a technology certification order that encompasses a single technology or test method.[147] The issued order would exempt all IVCTs within its scope from premarket review for up to four years, with the potential to renew the order for another four years if there are no substantial changes to the underlying application information.[148]

To take advantage of the technology certification pathway under the VALID Act, the sponsor must identify the highest complexity representative test among those

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[141] VALID Act of 2020, *supra* note 136, § 587A(e); Wilson, *supra* note 138.

[142] *Id.* § 587(9). Low-risk IVCTs are classified as those that would not cause serious or life-threatening injuries to patients or significant harm to public health if they produce inaccurate results when used as intended. *Id.* § 587(14).

[143] *Id.* §§ 587(9), 587(15), 587E.

[144] *Id.* § 587B. A PMA application for IVCTs would need to include the same evidence demonstrating analytical and clinical validity, but the VALID Act of 2020 would also require sponsors to include mitigation techniques and the methods, controls, and facilities used in test development. *Id.* § 587E; Wilson, *supra* note 138.

[145] Wilson, *supra* note 138. In the press release, FDA noted that a novel technology certification process, discussed *infra*, would ideally cover between 40–50% of new IVCTs, 10% (high-risk IVCTs) would be subject to premarket review, and the rest of the IVCTs would be exempt from the approval process as low-risk IVCTs. Scott Gottlieb, Jeff Schuren & Lauren Silvis, *FDA Proposes New Steps to Advance Clinical Testing to Deliver New Cures*, U.S. FOOD & DRUG ADMIN. (Dec. 6, 2018), https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fda-proposes-new-steps-advance-clinical-testing-deliver-new-cures [https://perma.cc/BP7T-FJ4W]. The precertification process discussed in the 2018 FDA press release has been retitled as "technology certification" under the 2020 draft, but the main requirements of the precertification process are the same. *Id.*; VALID Act of 2020, *supra* note 136, § 587D; Wilson, *supra* note 138.

[146] *See* VALID Act of 2020, *supra* note 136, § 587D; Wilson, *supra* note 138.

[147] *See* VALID Act of 2020, *supra* note 136, §§ 587D(a)(2)(B), 587D(e)(2)(A); Wilson, *supra* note 138.

[148] VALID Act of 2020, *supra* note 136, §§ 587A(k), 587D(a)(2), 587D(a)(2)(B), 587D(g)(2), 587D(g)(3)(B); Wilson, *supra* note 138. The technology certification order can be transferred or sold to a transferee or purchaser if that transferee or purchaser is eligible under Section 587D(b)(1) and "maintains, upon such transfer or sale, the site, test design and quality requirements, processes and procedures under the scope of the technology certification, and scope of the technology certification identified in the applicable technology certification order." VALID Act of 2020, *supra* note 136, § 587A(n)(3)(A). Developers are eligible for technology certification under Section 587D(b)(1) as long as they are in good standing with the Secretary of Health and Human Services and do not have any outstanding violations of any provisions of the Public Health Service Act. *Id.* § 587D(b)(1). Premarket approvals can also be sold or transferred. *See* VALID Act of 2020, *supra* note 136, § 587A(n)(2).

subject to the proposed scope of the technology certification order.[149] The sponsor must also explain how the representative test is an adequate representation of the procedures included in the technology certification application.[150] For this representative test, the sponsor must provide much of the same information required for the PMA process, so a PMA application can serve as the representative test for a technology certification order.[151] However, in addition to providing specific evidence demonstrating analytical and clinical validity for the representative test, the sponsor must also provide procedures for assuring analytical and clinical validity of all IVCTs within the proposed scope of the technology certification order.[152] If the technology certification order is granted and the sponsor complies with the validation procedures therein, all IVCTs within the scope of the order are exempt from premarket review, allowing sponsors to market these tests without submitting additional data to FDA.[153]

The technology certification pathway also lists a category of tests that are ineligible to take advantage of this expedited form of review.[154] One of the ineligible categories is for "first-of-a-kind" IVCTs.[155] Essentially, any diagnostic that differs from a previously approved diagnostic may fall in this category under FDA's discretion.[156] If excluded from the technology certification pathway, sponsors would likely be required to submit a PMA application for each diagnostic.[157] However, the VALID Act also has a special premarket approval pathway for eligible IVCTs, including first-of-a-kind

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[149] VALID Act of 2020, *supra* note 136, §§ 587D(b)(2), 587D(e)(2)(G). The following IVCTs are not eligible for the technology certification pathway under the VALID Act: high risk IVCTs; first-of-a-kind IVCTs; test kits for home use; direct-to-consumer; cross-referenced IVCTs; components or parts of IVCTs; test instruments; software; reagents used to collect, manufacture or use blood or human tissues from donors; and specimen receptacles. *Id.* In addition, the test sponsor itself must be an eligible person under § 587D(b)(1). *Id.* The application must also include a statement of scope that encompasses only a single technology or test method. VALID Act of 2020, *supra* note 136, § 587D(e)(2)(A). Interestingly, in the VALID Act of 2018 draft, the scope of the certification order was narrower and required sponsors to identify a single test method as applied to a specific intended disease or condition. VALID Act of 2018, *supra* note 136, § 587D(c)(2)(A). The removal of the intended use language and the insertion of the broad definition of "technology" seems to suggest that the scope of the technology order can be broader than a single use. *See infra* note 245 (reciting the definition of "technology" under the VALID Act); VALID Act of 2020, *supra* note 136, § 587(17)(A).

[150] VALID Act of 2020, *supra* note 136, § 587D(e)(2)(G).

[151] *Id.* §§ 587B(c)(2), 587D(e)(2)(G), 587J, 587B(b)(2)(A). There are, however, FDA inspection rights, so sponsors should still have documentation that each device subject to the technology certification order meets the same requirements as the representative test. *Id.* § 587I(a)(3).

[152] *Id.* § 587D(e)(2)(C)–(E).

[153] *Id.* § 587D(e)(2); Wilson, *supra* note 138.

[154] VALID Act of 2020, *supra* note 136, § 587D(b)(2).

[155] *Id.* § 587D(b)(2)(B). "First-of-a-kind" means a test that differs from any test legally available in the U.S. based on a list of criteria, including substance measured, test method, test purpose, intended diseases or conditions of use, and context of use (e.g., over-the-counter, clinical laboratories, point-of-care). *Id.* at § 587(8), (10); *see also supra* notes 81, 88 and accompanying text for a discussion about the variability and reproducibility issues present in animal-based diagnostic studies.

[156] VALID Act of 2020, *supra* note 136, § 587D(b)(2)(B).

[157] *Id.* § 587A(4). The VALID Act provisions are in sync with existing medical device regulatory requirements, including the use of premarket review as the highest level of review required for IVCT sponsors that do not meet any exemptions from premarket review as outlined in the VALID Act. Aaron L. Josephson, *The VALID Act, Aiming to Reform the Regulation of Diagnostic Products, Is Finally Introduced in Congress*, NAT'L L. REV. (March 12, 2020), https://www.natlawreview.com/article/valid-act-aiming-to-reform-regulation-diagnostic-products-finally-introduced [https://perma.cc/443N-V7AA].

devices, under which sponsors are not required to submit raw data demonstrating analytical validity or quality requirement information, similar to exempt IVCTs under a technology certification order.[158] Additionally, the VALID Act provides for a petition process that allows sponsors to argue that new information is available relating to the IVCT's risks and mitigating measures, and thus the IVCT should be eligible for technology certification or otherwise exempt from premarket review.[159]

If the VALID Act becomes law as written, this new regulatory pathway could save diagnostic test sponsors time and money that would ordinarily be expended on gathering data for FDA approval of each new device.[160] And the VALID Act appears to encompass the regulation and approval of animal-based diagnostics based on its expansive definition of IVCTs.[161] The question remains, however, how its implementation would affect approval of animal-based diagnostic methods.

III. FDA REGULATION OF MAGGOTS AND LEECHES

While FDA has never approved animals for use as medical devices in diagnostic contexts, FDA has approved animals for use in therapeutic contexts. For centuries, maggots and leeches have been used in medicine—maggots are used to debride necrotic flesh in wounds, while leeches are used to restore venous blood circulation.[162] While maggots and leeches do not perform diagnostic functions like the *C. difficile*-sniffing dogs discussed in the Introduction, *supra*, FDA's approach to regulating these animals as therapeutic devices may be useful for predicting how FDA will regulate animals in the diagnostics context.

A "device" is defined within the FDCA as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article" intended for use in the diagnosis, cure, treatment, or prevention of a disease.[163] Although this definition does not explicitly include animals, FDA approved both maggots and leeches as medical devices in 2004, establishing the first-ever animals as safe and effective medical devices through 510(k) premarket review.[164] In response to the 510(k) submissions, FDA determined that maggots and leeches were substantially equivalent to pre-amendment predicate devices (i.e., medicinal maggots and medicinal

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[158] VALID Act of 2020, *supra* note 136, § 587B(d)(1)(D). The following first-of-a-kind IVCTs are not exempt, however: high-risk, direct-to-consumer, or cross-referenced tests that do not have mitigating measures under Section 587E of the VALID Act. *Id.* at §§ 587B(d)(1)(D), 587(d)(2)(A)(i)–(ii).

[159] *Id.* §§ 587E, 587F.

[160] Wilson, *supra* note 138.

[161] VALID Act of 2020, *supra* note 136, § 2(a)(1); *see supra* note 137 and accompanying text.

[162] Michael Smith, *Maggots and Leeches Creep onto FDA Radar,* MEDPAGE TODAY (Aug. 29, 2005), http://www.medpagetoday.com/ProductAlert/DevicesandVaccines/1618 [https://perma.cc/NHV4-N9B3]. Maggots have proven to be quite useful in cases where human skin refuses to heal properly after injury or surgery, and leeches have the ability to restore blood circulation to an area after surgery. *Id.*; FDA, 510(k) SUMMARY, MEDICINAL LEECHES, No. K040187, at 2 (2004), https://www.accessdata.fda.gov/cdrh_docs/pdf4/K040187.pdf [https://perma.cc/VT3L-C3PJ] [Hereinafter MEDICINAL LEECHES 510(k)].

[163] Federal Food, Drug, and Cosmetic Act (FDCA) § 201(h), 21 U.S.C. §321(h) (2016).

[164] Smith, *supra* note 162; U.S. FOOD & DRUG ADMIN., 510(k) SUMMARY, MEDICAL MAGGOTS, No. K072438, at 4 (2007), https://www.accessdata.fda.gov/cdrh_docs/pdf7/K072438.pdf [https://perma.cc/J7H3-87Z3] [hereinafter MEDICAL MAGGOTS 510(K)]; MEDICINAL LEECHES 510(K), *supra* note 162, at 3.

leeches) that had yet to be classified.[165] As such, maggots and leeches are both currently regulated as unclassified medical devices subject to general controls.[166] However, because maggots and leaches were cleared using the 510(k) process, the sponsors were not required to produce any clinical trial data demonstrating safety or efficacy.[167] Instead, the sponsors only had to show that the device under review was not significantly changed or modified compared to its pre-amendment predicate device.[168] FDA approved maggots and leeches as medical devices because they both perform the same mechanical processes as their pre-amendment predicate devices (i.e., chewing dead flesh and eating blood, respectively) and they have a long history of providing medicinal benefits.[169]

It should be noted that, although maggots and leeches are currently unclassified, FDA has considered recommendations that they both be designated as Class II medical devices subject to special controls.[170] In 2005, one of FDA's advisory committees—the General & Plastic Surgery Review Panel—provided recommendations to FDA to develop special controls for maggots and leeches.[171] The special controls considered by the advisory committee would require sponsors to submit a 510(k) application containing information on the device description, risks to health, biocompatibility, sterility and disinfection, device manufacturing facilities, any available clinical data, and labeling.[172] The advisory committee did not recommend requiring clinical trials

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[165] MEDICAL MAGGOTS 510(K), *supra* note 164; MEDICINAL LEECHES 510(K), *supra* note 162, at 3. Pre-amendment predicate devices are those devices that were legally marketed before the enactment of the Medical Device Amendments of 1976 (MDA). Such pre-amendment predicate devices were exempted from the 510(k) requirements of the MDA and can be used as predicate devices if the new devices have the same intended use as the predicate device and have not been "significantly changed or modified." *How to Effectively Find and Use Predicate Devices*, U.S. FOOD & DRUG ADMIN. (Sept. 4, 2018), https://www.fda.gov/medical-devices/premarket-notification-510k/how-find-and-effectively-use-predicate-devices#link_3 [https://perma.cc/5GRR-U64Q].

[166] *510(k) Product Classification Database*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/PCDSimpleSearch.cfm [https://perma.cc/SY5B-ZZ69] (search for "maggots"; search for "leeches"; review device class data).

[167] MEDICAL MAGGOTS 510(K), *supra* note 164; MEDICINAL LEECHES 510(K), *supra* note 162, at 3.

[168] *Class I/II Exemptions*, *supra* note 105.

[169] Smith, *supra* note 162.

[170] Cathy T. Hess, *FDA Panel Seeks to Classify 2 Wound Therapies*, 18 ADVANCES SKIN & WOUND CARE 400 (2005), https://journals.lww.com/aswcjournal/Fulltext/2005/10000/THE_CUTTING_EDGE.1.aspx [https://perma.cc/P4JX-P89G]; *CDRH Advisory Meeting Materials Archive*, U.S. FOOD & DRUG ADMIN. (Aug 25 & 26, 2005), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=552 [https://perma.cc/QR3E-TRE2].

[171] *See generally General and Plastic Surgery Review Panel*, U.S. FOOD & DRUG ADMIN. (Mar. 29, 2018), https://www.fda.gov/advisory-committees/medical-devices-advisory-committee/general-and-plastic-surgery-devices-panel [https://perma.cc/5XV2-3E6Q] ("The General and Plastic Surgery Devices Panel (GPSDP) reviews and evaluates data concerning the safety and effectiveness of marketed and investigational general and plastic surgery devices and makes appropriate recommendations to the Commissioner of Food and Drugs."); *Medical Devices Advisory Committee on the General and Plastic Surgery Devices Panel*, U.S. FOOD & DRUG ADMIN. (Aug. 25, 2005), http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4168t1.htm [https://perma.cc/QB2R-AX54] (panel deliberation discussions on medical maggots and medicinal leeches) [hereinafter FDA Panel on Medical Maggots and Leeches].

[172] FDA Panel on Medical Maggots and Leeches, *supra* note 171 (presentation on medical maggots by Dr. Charles N. Durfor, Office of Device Evaluation); *id.* (presentation on medicinal leeches by Dr. Charles N. Durfor, Office of Device Evaluation).

to demonstrate safety and efficacy.[173] Instead, the advisory committee's recommendation indicated that these special controls, as described in an FDA guidance document, should be sufficient to provide FDA with the necessary clinical information to evaluate the safety and efficacy of medicinal maggots and leeches.[174] However, to date, maggots and leeches remain unclassified.[175] Thus, they are only subject to general controls to ensure their safety and efficacy.[176] Nevertheless, by considering whether to classify maggots and leeches as Class II medical devices, FDA has clearly demonstrated it is willing to regulate animals that perform tasks that fall within the broad definition of "device" under the FDCA.[177] As such, developers of animal-based diagnostics should be on notice that FDA could begin actively enforcing its regulations over their animals at any time.

IV. FDA REGULATION OF ANIMALS AS DIAGNOSTIC DEVICES

As discussed previously, animal-based diagnostics clearly fall within the scope of FDA's regulatory authority. The definition of a device under the FDCA is broad and meant to cover all in vitro diagnostic tests.[178] FDA has also demonstrated its willingness to regulate animals as medical devices through its approval of maggots and leeches as therapeutic devices.[179] Therefore, understanding the requirements of both conventional diagnostics (e.g., diagnostic kits) and animal-based therapeutics (e.g., maggots and leeches) can enable sponsors of animal-based diagnostics to determine the best premarket application strategy and to prepare for what may be unfamiliar and unexpected regulations.

At the time of this writing, we know of no animal-based diagnostics products that have received marketing approval from FDA or have even sought such approval.[180] Thus, it is unknown how FDA will regulate animal-based diagnostics. But it is possible to predict the Agency's approach based on the current regulatory scheme. This analysis assumes that an animal-based diagnostic will be regulated similarly to conventional diagnostics, but that various features unique to animals will necessarily alter the pathway to marketing approval. Among the unique features of animal-based diagnostics is the inherent variation in diagnostic accuracy from animal to animal, and

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[173] FDA Panel on Medical Maggots and Leeches, *supra* note 171 (panel deliberation discussions on medical maggots and medicinal leeches).

[174] *See generally* FDA Panel on Medical Maggots and Leeches, *supra* note 171.

[175] *510(k) Product Classification Database*, *supra* note 166.

[176] MEDICAL MAGGOTS 510(K), *supra* note 164; MEDICINAL LEECHES 510(K), *supra* note 162, at 3.

[177] FDA Panel on Medical Maggots and Leeches, *supra* note 171 (presentation on medical maggots by Dr. Charles N. Durfor, Office of Device Evaluation); *id.* (presentation on medicinal leeches by Dr. Charles N. Durfor, Office of Device Evaluation); MEDICINAL LEECHES 510(K), *supra* note 162, at 3.

[178] Federal Food, Drug, and Cosmetic Act (FDCA) § 201(h), 21 U.S.C. § 321(h) (2016); *see also supra* note 93 and accompanying text. Even if animal-based diagnostic tests are considered LDTs, FDA still has discretionary authority to regulate them under its interpretation of FDCA. *See supra* notes 121–23 and accompanying text.

[179] MEDICAL MAGGOTS 510(K), *supra* note 164; MEDICINAL LEECHES 510(K), *supra* note 162, at 3.

[180] However, because marketing applications are confidential, it is possible that an application may have been filed and not yet made public.

even between testing rounds using the same animal.[181] This animal-related variance could contribute to reproducibility issues that would make it challenging for animal-based diagnostics developers to prove analytical and clinical validity, as required by the FDCA.[182]

A. The Regulation of Animal-Based Diagnostics Compared to Maggots/Leeches

Because medicinal maggots and leeches gained FDA approval through the 510(k) pathway based on their pre-amendment device predicates, which were never formally approved by the Agency, the approval process for animal-based diagnostics will not be completely analogous. Animal-based diagnostics do not yet have FDA-approved predicate devices, so the 510(k) pathway is not available, and developers will likely be required to submit a PMA application.[183] Additionally, because animal-based diagnostics do not have a long history of medical use, sponsors will need to collect and submit their own clinical information as evidence of the safety and efficacy of the technology.

In some respects, there are similarities between animal-based therapeutics and animal-based diagnostics. Both types of devices introduce new risks and require special safety considerations that would likely be different from using a manufactured, mechanical device.[184] For example, two of the most significant risks associated with medicinal maggots, medicinal leeches, and animal-based diagnostics are the unpredictability of using live animals and user error.[185] To mitigate these risks, sponsors of medicinal maggots created a special wound dressing that secures the maggots on the wound, which prevents their escape and helps health care professionals ensure the therapy is working correctly.[186] There are also special protocols for

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[181] See *supra* notes 81, 88 and accompanying text for a discussion about the variability and reproducibility issues present in animal-based diagnostic studies.

[182] 21 U.S.C. § 360c(a)(3) (2017); 21 C.F.R. § 860.7(b) (2018).

[183] To date, the Authors are not aware of any animals other than maggots and leeches under FDA regulation as devices. Service animals employed in healthcare-related roles are not subject to any uniform laws regarding their certification. *See* U.S. DEP'T OF JUSTICE, FREQUENTLY ASKED QUESTIONS ABOUT SERVICE ANIMALS AND THE ADA (2015), https://www.ada.gov/regs2010/service_animal_qa.pdf [https://perma.cc/DLB5-Z869] (Questions 5, 8, and 17 discuss the lack of requirements for training, certification, and identification of service animals); Jan Reisen, *Service Dogs, Working Dogs, Therapy Dogs, Emotional Support Dogs: What's the Difference?*, AM. KENNEL CLUB (Jul. 31, 2019), https://www.akc.org/expert-advice/lifestyle/service-working-therapy-emotional-support-dogs/ [https://perma.cc/7CKN-NDX9] ("[t]here are no uniform state or national rules that regulate and certify therapy dogs, and different organizations have different guidelines").

[184] Jalal Arabloo, Serajaddin Grey, Mohammadreza Mobinizadeh, Alireza Olyaeemanesh, Pejman Hamouzadeh & Kiumars Khamisabadi, *Safety, Effectiveness and Economic Aspects of Maggot Debridement Therapy for Wound Healing*, 30 MED. J. ISLAM. REPUB. IRAN 4 (2016).

[185] *Id.*; Agata Litwinowicz & Joanna Blaszkowska, *Preventing Infective Complications Following Leech Therapy: Elimination of Symbiotic* Aeromonas spp. *From the Intestine of* Hirudo verbana *Using Antibiotic Feeding*, 15 SURGICAL INFECTIONS 757, 758 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4268569/ [https://perma.cc/8Q9X-ZMJY] (discussing the prevalence of infectious diseases in leeches used for human wound treatment); Brian Krans & Kathryn Wilson, *What is Leech Therapy?*, HEATHLINE (April 21, 2017), https://www.healthline.com/health/what-is-leech-therapy#side-effects [https://perma.cc/R222-7JYU].

[186] MEDICAL MAGGOTS 510(K), *supra* note 164, at 2 (medicinal maggots approved for use with a special "cage dressing" to keep maggots in place).

manufacturing both medicinal maggots and leeches to prevent contaminations, infections, and negative side effects of the therapies, including strict standards for "germ-free" breeding and storage in sanitized, refrigerated clean rooms.[187]

However, there are also significant differences between the risks presented by animal-based therapeutics and animal-based diagnostics. For example, medicinal maggots and leeches present the risk of directly harming patients if the therapeutic is contaminated or misused. In contrast, animal-based diagnostics present the risk of indirectly harming patients if the diagnostic delivers a false-positive or -negative result. An inaccurate test result from an animal-based diagnostic may cause a patient to receive unnecessary treatments, or worse, not receive needed treatments. The risk from a false-positive result should be mitigated because, like many other diagnostic tests, animal-based tests will likely be used by a healthcare professional in combination with other signs, symptoms, and testing to determine a diagnosis. The false-positive result would likely be identified before a patient treatment plan is established.[188] The greater risk is the possibility of providing false-negative test results—risks that are likely to cause harm to patients if the diagnostic fails to identify harmful conditions. The risk-mitigating factors identified above for medicinal maggots and leeches are probably not applicable to animal-based diagnostics because it is not clear that breeding "germ-free" dogs specifically for diagnostic applications would mitigate the risks of diagnostic accuracy variation present in the most-current research studies.[189] As such, sponsors would need to develop new techniques to mitigate the risks for animal-based diagnostics, such as standardized training protocols for both the animals and the test administrators.

Because animal-based diagnostics will be unable to follow the same regulatory pathway as medicinal maggots and leeches, sponsors will be subject to FDA regulations depending on the level of risk of the animal-based diagnostic test's intended use. Some animal-based diagnostic tests may create higher risks than others for patients, depending upon the severity of the disease they are diagnosing and possible patient outcomes for that disease. Moreover, this variation in risk level is compounded by the inherent variation in diagnostic accuracy of animal-based diagnostics, which will likely make it challenging for animal-based diagnostic sponsors to get approval under the FDCA, as discussed in Part IV.B.ii, *infra*.

B. The Regulation of Animal-Based Diagnostics Compared to IVDs and LDTs

Animal-based diagnostics would most likely be categorized as either Class II or Class III devices because the inherent risks of defective or inaccurate animal-based diagnostics could cause moderate or severe safety risks to patients. Sponsors that can identify predicate devices will be able to seek approval using the simpler 510(k) process. It is also possible that animal-based diagnostics will be performed as a clinical

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[187] Bob Carlson, *Crawling Through the Millenia: Maggots and Leeches Come Full Circle*, 3 BIOTECHNOLOGY HEALTHCARE 14, 17 (2006), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3571037/ [https://perma.cc/2STE-DSVA].

[188] NAT'L ACADEMY OF SCIENCES, ENGINEERING, & MEDICINE, *The Diagnostic Process*, *in* IMPROVING DIAGNOSIS IN HEALTH CARE (Erin P. Balogh, Bryan T. Miller & John R. Ball eds., 2015), https://www.ncbi.nlm.nih.gov/books/NBK338593/ [https://perma.cc/ZA9Q-HRR2].

[189] *See supra* notes 81, 88 (discussing that the highest risk from animal-based diagnostics as compared to conventional diagnostic tests is the reported variations in diagnostic accuracy).

laboratory service and be subject to the relaxed regulation requirements as an LDT. However, the more likely scenario, at least for the initial sponsors of animal-based diagnostics, is that no such predicate will be identified, and the Agency will require the sponsors to conduct clinical trials to demonstrate safety and efficacy for a PMA submission. Understanding the PMA process and the limits of animal-based diagnostics, then, is crucial to the widespread implementation of animal-based diagnostics in clinical settings. These scenarios are discussed in detail below.

i. The LDT Approval Pathway for Animal-Based Diagnostics Manufactured and Used Internally by the Same Laboratory

If animal-based diagnostics developers manufacture, offer, and perform the tests in their own laboratories, those tests would fall outside of the IVD category and would be treated as an LDT.[190] As discussed in Part II.B, *supra*, FDA has always maintained its authority to regulate LDTs as medical devices, but has historically reserved that authority and allowed CMS to regulate laboratories that produce LDTs.[191] Regulation as an LDT rather than an IVD will likely be a less arduous process for animal-based diagnostic developers because CMS only requires evidence that LDTs are analytically valid—no showing of clinical utility or validity is required.[192]

But demonstrating analytical validity of an animal-based diagnostic will likely be difficult, particularly in view of research demonstrating significant variation in some of the current animal-based diagnostic applications.[193] However, because LDTs are, by definition, only used in the developers' own labs, developers can control the environment and testing conditions of their animal-based lab-administered tests in order to limit factors that might contribute to such variation. Thus, they should be able to ensure that the correct training and testing protocols are followed to get the most accurate results and modify the testing procedures as needed. For example, the Clinical Laboratory Improvement Amendments (CLIA) require that analytical validation be demonstrated through the development of verified performance characteristics on a range of metrics including accuracy, precision, range, analytical sensitivity and

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[190] SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 51, 53–54; *Laboratory Developed Tests*, *supra* note 95.

[191] *Id.* FDA has proclaimed its authority to regulate all diagnostic tests under the FDCA as medical devices but has historically elected not to exercise that authority for LDTs. *Id.*; *see* Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (May 28, 1976) (codified as amended in scattered sections of 21 U.S.C.); Safe Medical Devices Act of 1990, Pub. L. No. 101-629, § 16, 104 Stat. 4511 (codified at 21 U.S.C. § 353(g) (2016)); *see* Clinical Laboratory Improvements Amendments of 1988, Pub. L. No. 100-578, 102 Stat. 2903 (codified at 42 U.S.C. § 263a (2012)).

[192] *See* Bouchie, *supra* note 124, at A1, A2. Analytical validity is a measure of how accurately and consistently the test detects the presence of a specific genotype. SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 32; Gwinn & Khoury, *supra* note 124. Clinical utility refers to the device's ability to inform clinical decision making and predict clinical outcomes. Grosse & Khoury, *supra* note 125. Clinical validity means how well the test predicts a given phenotype (i.e., clinical disorder or outcome). SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 32; Gwinn & Khoury, *supra* note 124.

[193] See *supra* notes 81 and 88 for a discussion of the reproducibility issues with animal-based diagnostic studies. FDA is particularly concerned with diagnostic test developers using the LDT regulatory pathway to evade oversight and has identified high-risk LDTs that "are not adequately supported with evidence [and] lack [] appropriate controls yielding erroneous results." *Laboratory Developed Tests*, *supra* note 95.

specificity, and reference intervals.[194] After a developer establishes the required performance criteria under CLIA, the testing procedures are only relevant to the specific conditions, testing equipment, laboratory staff, and patients of a laboratory.[195] So, these performance criteria need to be repeated and maintained for each separate test application and updated if there are changes to the laboratory environment.[196] If an animal-based diagnostic developer is able to address the analytical validity of its test, the LDT pathway provides a shorter, less expensive route to market because it will not be required to conduct clinical studies to demonstrate clinical validity or the animal-based diagnostic's accuracy of diagnosing patients.

Because of the recent proposed reforms to LDT regulation in the VALID Act of 2020 and FDA's express intention to regain authority over LDT regulation, any benefit from animal-based diagnostic developers' self-selection into regulation as an LDT is likely to be short-lived.[197] Moreover, the *C. difficile* detection dog team at Vancouver Coastal Health, discussed in Part I, *supra*, illustrates the likely reality that at least some of these animal-based diagnostics will be subject to FDA regulation as IVDs because the testing will be conducted outside of the facility that trains and validates the animals as diagnostics.[198]

ii. The 510(k) Approval Pathway for Animal-Based Diagnostics with Substantially Equivalent Predicates

To seek approval using the 510(k) process, a sponsor must show that its animal-based diagnostic is substantially equivalent to a predicate device—i.e., a conventional IVD or LDT.[199] Critically, substantial equivalence requires the sponsor either to show the device has the same technological characteristics as the predicate or, if there are different technological characteristics, to show that the differences do not diminish safety or efficacy of the device.[200] Since animal-based diagnostics would have entirely different technological characteristics from current diagnostics, sponsors must be able

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[194] CLIA OVERVIEW, CTR. MEDICARE & MEDICAID SERVICES 1 (Oct. 22, 2013), https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf [https://perma.cc/7Y92-FTAQ]; 42 C.F.R. § 493.1253(b)(2) (2003) (establishment of performance specifications).

[195] CLIA OVERVIEW, *supra* note 194.

[196] *Id.*

[197] See Part II.B, *supra*, for a discussion of the latest draft of the VALID Act legislation. FDA has issued warning letters in the past to companies marketing LDTs for uses that have significant public safety risks and lack clinical validation. *See* FDA WARNING LETTER, *supra* note 122 ("[T]he Agency always retains discretion to take action when appropriate, such as when it is appropriate to address significant public health concerns.").

[198] *See* Biancardi da Camara, *supra* note 8. See also Part I.B.ii, *supra*, for a discussion of Vancouver Coastal Health's use of detection dogs to identify *C. difficile* in its hospital. An animal-based diagnostic must be "designed, manufactured and used within a single laboratory" to qualify for regulation as an LDT. *Laboratory Developed Tests*, *supra* note 95. Otherwise, the animal-based diagnostic will be regulated as an IVD. *Id.*

[199] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, FDA STAFF ON THE 510(K) PROGRAM: EVALUATING SUBSTANTIAL EQUIVALENCE IN PREMARKET NOTIFICATION [510(K)] 24 (2014), https://www.fda.gov/media/82395/download [https://perma.cc/DC6F-JF94] (last visited Jan. 6, 2020) [hereinafter 2014 SUBSTANTIAL EQUIVALENCE GUIDANCE].

[200] *Id.*

to show these differences do not present different questions of safety or efficacy.[201] Specifically, the sponsor must show that the analytical and clinical validity of the animal-based diagnostic is substantially equivalent to a conventional diagnostic predicate.[202] As mentioned previously, this will likely be the biggest hurdle to FDA clearance for sponsors of animal-based diagnostics under either a 510(k) substantial equivalence or a PMA analysis.

Animal-based tests that rely on an animal's sense of smell clearly have different technological characteristics than conventional tests that use some form of electrochemical assay. And the studies published to date indicate that animal-based detection methods lack consistency. As such, sponsors will have a difficult time proving that the safety and effectiveness of the animal-based diagnostics is not diminished compared to conventional diagnostics. FDA has suggested that modifying a device's function from mechanical (in the predicate) to electrical (in the new device) would raise different questions of safety and effectiveness that were not initially addressed when assessing the predicate.[203] Similarly, for animal-based diagnostics, changing the process from a conventional electrochemical test to an animal-based test would certainly raise new questions that were not raised when the predicate was approved as a diagnostic. For instance, dogs that can detect the presence of *C. difficile* rely on their olfactory receptors, whereas current Class II predicates that detect *C. difficile* rely on a gene amplification assay.[204] Moreover, it is not fully known which analyte is being detected by the detection dog in the *C. difficile* study.[205] While the animal-based diagnostic could be detecting one of the same *C. difficile* biomarkers that are detected with conventional assays, toxin A/B or glutamate dehydrogenase (GDH), there is not yet enough research to know whether the scent detected by dogs on patients with *C. difficile* is linked to these analytes.[206] Although both conventional and animal-based diagnostics have the same intended use (e.g., detecting the presence of *C. difficile* in patients), there are inherent differences that raise different issues of safety and efficacy, which may prevent animal-based diagnostics from being considered substantially equivalent to current Class II devices.

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[201] *Id.* at 20. A "different question of safety or effectiveness" is a "question raised by technological characteristics of the new device that was not applicable to the predicate device, and poses a significant safety or effectiveness concern for the new device." *Id.*

[202] *Id.* at 18–20.

[203] *Id.* at 20–21. Suppose the predicate is a mechanical device used for embryo dissection, and the new device is an electronic device used for embryo dissection. Although both have the same intended use, changing the process from mechanical to electrical (e.g., using a laser) "changes the way the device operates and raises different safety concerns regarding how the heating aspect of the electrical mechanism affects the embryo." *Id.*

[204] Bomers et al., *supra* note 1, at 2; Song et al., *supra* note 4, at 112; *510(k) Product Classification Database*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/PCDSimpleSearch.cfm [https://perma.cc/SA8C-DXCQ] (search for "C. difficile"; review device class data).

[205] *See* Cernei et al., *supra* note 44 and accompanying text.

[206] For example, a study discussed in Part I.A.ii, *supra*, explains that dogs that were trained to detect prostate cancer from urine samples were not detecting the presence of PSA because PSA is only found in blood. PSA is the measured biomarker in most conventional prostate cancer diagnostic tests, demonstrating that at least in the prostate cancer urine test, the animal-based diagnostic is not using the same diagnostic testing method as conventional devices. *See* Cernei et al., *supra* note 44 and accompanying text.

However, sponsors of animal-based diagnostics may argue that their disease-sniffing animals do not present new questions of safety and effectiveness or diminish the analytical or clinical validity of the test because the animal-based diagnostics can outperform conventional devices. For example, in terms of safety, the cancer-sniffing dogs discussed in Part I.A.ii, *supra*, are safer than conventional tests because an invasive biopsy is not required.[207] In terms of efficacy, the dog in the *C. difficile* study discussed in Part I.A.i, *supra*, outperformed conventional diagnostic tests in terms of accuracy.[208] However, studies that have tested multiple dogs show that there can be a variation in accuracy levels from animal to animal or even within an individual animal's repeat performances that create reproducibility issues theoretically not present in conventional devices that can all be manufactured to the same specifications.[209] This variation translates to significant differences in the analytical validity of animal-based diagnostics that FDA can point to as affecting safety and effectiveness with respect to the predicate device. Further, if the test results cannot be reproduced with different animals, or even the same animal over time, under the same testing conditions, the clinical validity of the test would be questionable. But the reproducibility of animal-based diagnostics has not been fully researched, so more studies need to be conducted to allow a better comparison between animal-based and conventional diagnostics.

Consequently, early sponsors of animal-based diagnostics will unlikely be able to use the 510(k) approval pathway due to the differing technological characteristics and the questions affecting safety and efficacy with respect to the predicate. Because these questions of safety and efficacy arise from animal-to-animal variations, they are likely to make demonstrating analytical and clinical validity challenging under any scenario, regardless of whether the 510(k) or PMA pathway is used.[210]

iii. The PMA Pathway for Animal-Based Diagnostics as Novel Devices

If an animal-based diagnostic is not considered substantially equivalent to any predicate device, then it would likely be categorized as a Class III device subject to premarket review.[211] As discussed in Part II.A, *supra*, a PMA application will require animal-based diagnostic sponsors to provide "valid scientific evidence" to demonstrate analytical and clinical validity of the diagnostic.[212] To generate such

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[207] *See* Bomers et al., *supra* note 1, at 4; *See supra* Part I.A.ii. For example, a CT scan would present higher safety risks to the patient based on how the test is performed. However, the BMJ *C. difficile* study also determined that dogs can be trained to detect *C. difficile* without the need for fecal samples, so the use of animal-based diagnostics in this manner may raise additional validity concerns. *See* Bomers et al., *supra* note 1, at 3–4; *see supra* Part I.A.i.

[208] Bomers et al., *supra* note 1, at 3–4; Song et al., *supra* note 4, at 112. The dog that was able to detect *C. difficile* did so with 97% accuracy, which is comparable to the most accurate predicate devices. Bomers et al., *supra* note 1, at 3–4. PCR is the most accurate assay currently on the market for detecting *C. difficile*, performing at 87.2% accuracy. Song et al., *supra* note 4, at 112.

[209] *See supra* notes 81, 83, 90 and accompanying text.

[210] For example, if the sponsors cannot show that the range of accuracy for each animal-based diagnostic over its lifetime of use is above a reasonable threshold, the sponsor would be unable to demonstrate the clinical validity required to meet FDA approval standards.

[211] FDA will approve a PMA application if there is a reasonable assurance of safety and effectiveness. Federal Food, Drug, and Cosmetic Act (FDCA) § 513(a)(1)(C), 21 U.S.C. § 360c(a)(1)(C) (2017).

[212] *See supra* notes 87, 109 and accompanying text.

evidence, sponsors will likely need to conduct clinical studies to demonstrate the safety and effectiveness of the animal-based test for a PMA submission.[213]

For new devices, clinical studies are generally divided into three stages: early feasibility studies to show proof of concept, pivotal studies to demonstrate the safety and effectiveness of the device, and post-approval studies to monitor the safety of the device.[214] Sponsors of animal-based diagnostics should consider factors such as device novelty, intended use, design stability, and test data available before deciding which type of clinical study to conduct.[215] Because animal-based diagnostics are novel and there is a limited amount of data available about their analytical and clinical validity, an early feasibility study should be performed to determine preliminary clinical safety.[216] Moreover, sponsors of animal-based diagnostics should have a robust exploratory stage so the selection of a pivotal study design will be easier and to reduce the likelihood that the pivotal study would need to be altered to account for unexpected results or variations in data.[217] Accordingly, early feasibility studies of animal-based diagnostics should aim to provide initial insights into several key aspects of safety and efficacy that will help direct the clinical study plan going forward.[218] Among the factors to evaluate during an early feasibility study, sponsors should plan the study to address the challenges associated with the animal performing diagnostic functions and its failure rate.[219]

For example, if sponsors were interested in performing an early feasibility study of the *C. difficile*-detecting dogs, sponsors could attempt to model their study after the original study in the *British Medical Journal*, which already generated data to make a

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[213] *Premarket Approval (PMA)*, *supra* note 116. FDA does accept foreign clinical studies, so sponsors could potentially supplement their application with the data from foreign clinical studies being conducted in the UK, assuming the results of those tests are favorable for animal-based diagnostics. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF, FDA ACCEPTANCE OF FOREIGN CLINICAL STUDIES NOT CONDUCTED UNDER AN IND: FREQUENTLY ASKED QUESTIONS (2012), https://www.fda.gov/media/83209/download [https://perma.cc/YK3P-Y444] (last visited Feb. 21, 2020).

[214] U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, FDA STAFF ON INVESTIGATIONAL DEVICE EXEMPTIONS (IDES) FOR EARLY FEASIBILITY MEDICAL DEVICE CLINICAL STUDIES, INCLUDING CERTAIN FIRST IN HUMAN (FIH) STUDIES 6 (2013), https://www.fda.gov/media/81784/download (last visited Jan. 6, 2020) [https://perma.cc/6QQK-QYD6] [hereinafter 2013 EARLY FEASIBILITY STUDIES GUIDANCE]. Before clinical studies can be performed on a device that has not been cleared for marketing, the new device must have an approved Investigational Device Exemption (IDE). This exemption permits a new device to be used in clinical studies even though it has not been cleared for marketing. Once FDA approves an animal-based diagnostic as an IDE, clinical studies can be performed to demonstrate its safety and effectiveness. *See* 21 U.S.C. § 360j(g) (2017); *see also* U.S. FOOD & DRUG ADMIN., *IDE Approval Process* (May 16, 2019), https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-approval-process [https://perma.cc/4SDN-FLYD]. Post-approval study issues are beyond the scope of this article. *See supra* note 14.

[215] 2013 EARLY FEASIBILITY STUDIES GUIDANCE, *supra* note 214, at 7.

[216] *Id.* at 4. Early feasibility studies are appropriate in early device development "when clinical experience is necessary because nonclinical testing methods are not available or adequate to . . . advance the development process." *Id.*

[217] *Id.*

[218] *See id.* at 6. The factors that should be addressed by an early feasibility study include: clinical safety, whether the animal performs for its intended purpose, the human variables that affect comprehending procedural steps, the success rate of the animal, the challenges associated with the animal performing diagnostic functions, and failure rate. *Id.* Evaluating these factors increases the efficiency of the device development process. *Id.*

[219] *See id.* at 6.

preliminary demonstration of safety and efficacy to support a PMA application.[220] In the *C. difficile* study discussed in Part I.A.i, *supra*, however, only one dog was used, so the study did not test or address reproducibility issues associated with multiple dogs that undergo the same training, variation in the scent detection abilities among multiple dogs, or consistency issues as the dogs age. Other studies have confirmed that dogs' ability to correctly identify infected patient samples varies among the dogs participating in the study.[221] Notably, researchers do not know what factors affect the variation and lack of precision among test results, so developing strategies to increase the reliability and accuracy of animal-based diagnostics and mitigate any variation between animals or testing sessions is even more difficult for sponsors.[222] However, using early feasibility studies to assess the testing protocols and develop ways to create consistency across animals engaged in diagnostic work will be instrumental to FDA approval of animal-based diagnostic testing.

Finally, sponsors will need to conduct large-scale pivotal clinical studies to collect enough data to demonstrate analytical and clinical validity of their animal-based diagnostics. Because clinical studies are so lengthy and expensive, and FDA's requirements for animal-based diagnostics are uncertain, sponsors should engage the Agency early in the process and seek consultation for clinical study planning and PMA requirements.[223] FDA often holds informal meetings with device sponsors to discuss its predicted requirements for approving the device, but sponsors can also submit requests for the Agency to issue written decisions specifying the requirements for demonstrating safety and efficacy for specific devices.[224] In addition, FDA has published guidelines on the approval process for diagnostics generally, so device sponsors should review any relevant guidelines when preparing an application.[225] To provide FDA with a reasonable assurance that an animal-based diagnostic is safe and effective for its intended use, sponsors will need to present valid scientific evidence that it is safe and effective.[226] Such evidence will likely need to be in the form of a well-controlled investigation into how the animal conducting the diagnostic test

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[220] *See* Bomers et al., *supra* note 1, at 2 (describing training methods).

[221] Taylor et al., *supra* note 79.

[222] *Id.* at 3 ("[t]he reason for variability in diagnostic accuracy is uncertain and may be due to either the individual dog's ability to learn a new task, distractibility of the specific animal, or the sensitivity of different breeds' olfactory systems").

[223] *PMA Guidance Documents*, U.S. FOOD & DRUG ADMIN. (May 3, 2018), https://www.fda.gov/medical-devices/premarket-approval-pma/pma-guidance-documents [https://perma.cc/4WG7-55LT].

[224] *Id.*

[225] *Search for FDA Guidance Documents*, U.S. FOOD & DRUG ADMIN. (March 6, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents [https://perma.cc/EV7T-YRB6]. For example, FDA has published a guidance document addressing how to appropriately report results from diagnostic test evaluation studies. U.S. FOOD & DRUG ADMIN., FDA GUIDANCE FOR INDUSTRY AND FDA STAFF—STATISTICAL GUIDANCE ON REPORTING RESULTS FROM STUDIES EVALUATING DIAGNOSTIC TESTS (2007), https://www.fda.gov/media/71147/download [https://perma.cc/TX9L-XA5D] (last visited Feb. 21, 2020).

[226] *See* 21 U.S.C. § 360c(a)(1)(C) (2017); SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 52; *PMA Clinical Studies*, *supra* note 102. 21 C.F.R. § 860.7(b) (2018) lists the following factors as relevant to FDA's determination of device safety and effectiveness: (1) The persons for whose use the device is represented or intended; (2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) The reliability of the device. *Id.*

responds under a variety of clinical conditions. [227] Because early studies of animal-based diagnostics have highlighted the potential inconsistency in an animal's performance based on a variety of individual characteristics and external factors, developers should attempt to demonstrate the animal's diagnostic accuracy under various different conditions, such as when the animal performing the test is prone to distraction in the presence of food or under stressful conditions. While the amount and type of evidence required will vary depending on its intended use, for any animal-based diagnostic, FDA will likely want to evaluate the training and testing protocols used in the study and a statistical analysis of the diagnostic accuracy of the animal under various testing conditions.[228] The Agency will require sponsors to provide evidence sufficient to show that the animals are not merely producing isolated or random results.[229] However, because it is unclear how these existing requirements actually apply to animal-based diagnostics, sponsors and FDA staff could benefit from the adoption of some of the reform measures discussed in Part V, *infra*.

V. SUGGESTIONS FOR REGULATING ANIMAL-BASED DIAGNOSTICS

Unclear regulations and inconsistencies in training and results are among the biggest challenges for the sponsors of animal-based diagnostics seeking FDA marketing approval. Unfortunately, the Agency's regulatory regime is poorly suited to this unconventional technology. As a result, developers of animal-based diagnostics will face challenges and setbacks as they attempt to get their products approved under the current regulations. Furthermore, FDA's uncertain regulatory approach to animal-based diagnostics would likely result in unnecessary delays and expenses for sponsors. To solve these problems, we propose the following solutions.

A. FDA Guidance on Animal-Based Diagnostic Validation

In order to facilitate market entry for animal-based diagnostics, FDA should issue a guidance document to clarify the requirements for sponsors to receive regulatory approval. As previously discussed, animal-related variance—i.e., the variations from animal to animal and variations in an individual animal's performance over time—is

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[227] 21 C.F.R. § 860.7(c)(2) (2018). A well-controlled investigation is one that includes a detailed study protocol and report addressing the study's objectives, explanation of methods used, comparison of testing results with a valid control, and a summary of the data analysis and statistics used. *PMA Clinical Studies*, *supra* note 102.

[228] 21 C.F.R. § 860.7(c)(2) (2018); 21 C.F.R. § 860.7(d)(2) (2018). The amount and type of evidence required varies according to device characteristics, device use conditions, whether adequate warnings and use restrictions exist for the device, and the amount of experience with the device. 21 C.F.R. § 860.7(c)(2) (2018). Valid scientific evidence explicitly does not include "isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions." *Id.* While FDA has not enumerated specific evidence required for premarket approval, FDA generally looks for nonclinical laboratory studies conducted in compliance with 21 C.F.R. § 58 (2019) and clinical study data that includes, *inter alia*, sound study protocols, adverse reactions and complications, device failures and replacements, patient complaints, and results of statistical analyses. *PMA Clinical Studies*, *supra* note 102; *Premarket Approval (PMA)*, *supra* note 116. See *supra* note 117 for approval requirements for human clinical trials of unapproved devices.

[229] *PMA Clinical Studies*, *supra* note 102.

likely to be the biggest hurdle to FDA approval for animal-based diagnostics.[230] Therefore, such a guidance document would need to address what are likely to be the most challenging aspects of the PMA process for sponsors—demonstrating analytical and clinical validity in view of animal-related variance. The FDA must specify what evidence a sponsor would need to provide to show its diagnostic is safe and effective in view of any animal-related variance. To create a standardized review process, FDA needs to be sure that the animal-based diagnostics are "manufactured" in a way that ensures their accuracy and reproducibility, similar to the Agency's regulations on current Good Manufacturing Practices for conventional medical devices.[231] For example, FDA currently recognizes third-party quality assurance and manufacturing standards for conventional medical devices, including standards published by organizations such as the Clinical and Laboratory Standards Institute (CLSI) and the American Society for Testing and Materials (now known as ASTM International).[232] A sponsor's compliance with those third-party metrics, like CLSI's Verification and Validation of Multiplex Nucleic Acid Assays, can be used to demonstrate that a diagnostic based on a nucleic acid assay is safe and effective.[233] FDA could help sponsors of animal-based diagnostics by endorsing similar standards specific to training and testing animals for diagnostic use.

First, FDA should evaluate the training methods to ensure that animals performing diagnostic functions produce accurate results. Indeed, some animals may provide more accurate results than current diagnostic devices; however, animals are not completely error-free—false-positive and false-negative results are inevitable.[234] Accordingly, FDA should implement training standards that essentially calibrate the animals' diagnostic functions such that they can be relied upon to diagnose patients accurately. A few organizations have published guidelines for training dogs in other vital contexts, such as detection of drugs, explosives, missing persons, pests, and agricultural substances, which FDA could adopt directly or use as the basis for developing its own guidelines for training animals in the medical diagnostics context.[235] FDA guidelines

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[230] Helen Branswell, *The Dogs Were Supposed to be Experts at Sniffing Out* C. Diff. *Then They Smelled Breakfast*, STAT NEWS (Aug. 22, 2018), https://www.statnews.com/2018/08/22/dogs-c-diff-hospitals/ [https://perma.cc/XZ4Z-DH5J]. Marije Bomers, the consultant who published the original *C. difficile* dog detection study cited in note 2, *supra*, commented on another *C. difficile* dog detection study that produced less accurate data, stating, "the capability of one dog cannot simply be extrapolated to other dogs, complicating practical implementation of *C. diff* sniffer dogs on a larger scale." *Id.*

[231] 21 C.F.R. Part 820 outlines the Quality System Regulation of Medical Devices. *See* 21 C.F.R. § 820.75 (2019).

[232] *See Recognized Consensus Standards Database*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm (last visited Dec. 23, 2019) [https://perma.cc/4YB5-FZXQ]; *Standards Development*, CLINICAL LABORATORY STANDARDS INSTITUTE, https://clsi.org/standards-development/ (last visited July 2, 2020); *Standards and Publications*, ASTM INTERNATIONAL, https://www.astm.org/Standard/standards-and-publications.html [https://perma.cc/JHN7-L4L9] (last visited July 2, 2020).

[233] CLINICAL LABORATORY STANDARDS INSTITUTE, VALIDATION AND VERIFICATION OF MULTIPLEX NUCLEIC ACID ASSAYS (2d ed. May 21, 2018), https://clsi.org/standards/products/molecular-diagnostics/documents/mm17/ [https://perma.cc/N4PG-SDKE].

[234] See Part I, *supra*, for a discussion about the capabilities and limitations of animal-based diagnostics.

[235] *See* U.S. DEP'T AGRIC., NATIONAL DETECTOR DOG MANUAL (2012), https://www.aphis.usda.gov/import_export/plants/manuals/ports/downloads/detector_dog.pdf [https://perma.cc/G8NW-WMT5]; *Scientific Working Group on Dog and Orthogonal Detector Guidelines*, INT'L FORENSIC RES. INST., https://swgdog.fiu.edu/approved-guidelines/ [https://perma.cc/4RFW-UUED] (last visited Feb. 21,

should also include strategies to mitigate the risk of false-positive and false-negative results and help researchers maintain consistent performance across all animals conducting the diagnostic test.[236]

Next, FDA should borrow some of the quality assurance and process validation requirements that are currently used in drug manufacturing and medical device reprocessing.[237] Manufacturers of both drugs and reprocessed medical devices are required to revalidate the quality and consistency of their processes over time to ensure safety and effectiveness standards are continuing to be met.[238] A similar type of revalidation likely would be needed for animal-based diagnostics based on current research that suggests that these animals require continuous retraining to maintain their detection abilities.[239] The Agency should provide guidance on how to implement quality control checks in the animal-based diagnostic context, particularly with respect to standards for retraining procedures for revalidating the accuracy of detecting disease markers, to ensure that the animals continue to meet FDA safety and effectiveness standards over time.[240]

Finally, FDA's guidance should clarify how sponsors could utilize the 510(k) approval pathway. In particular, the guidance would need to clarify how sponsors could demonstrate that their animal-based diagnostic is substantially equivalent to a predicate device. As discussed in Part IV.B.ii, given the different technological characteristics between animals and conventional diagnostics and the challenges with showing analytical and clinical validity, early sponsors of animal-based diagnostics

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2020); John Pearce, L. Paul Waggoner, Jeanne S. Brock, Timothy Baird, David A. Baffa, Daniel McAfee, Robert E. Leonard, Jr., DYNAMIC CANINE TRACKING METHOD FOR HAZARDOUS AND ILLICIT SUBSTANCES, USPTO US10123509B2 (Nov. 13, 2018). None of these training methods are specific to animals that detect diseases. Instead, they are directed to training methods for scent detection dogs in various law enforcement applications that do not need FDA approval, including firearms, narcotics, agriculture inspections, and missing persons. Thus, significant testing may need to be conducted on these training methods to determine which of them, if any, mitigates the risk associated with variations in animal-based diagnostic test results. However, researchers are already beginning to evaluate the differences in training protocols, and FDA can utilize some of those research findings to bolster its own analysis. Fischer-Tenhagen et al., *supra* note 90.

[236] Porritt et al*., supra* note 88.

[237] 21 C.F.R. Parts 210 and 211 address the process validation requirements for drugs and 21 C.F.R. Part 820 outlines the Quality System Regulation of Medical Devices. *See* 21 C.F.R. §§ 210, 211, 820.75 (2019). "[P]rocess validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product." U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY, PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES (2011), https://www.fda.gov/media/71021/download [https://perma.cc/E8EL-6QXW] (last visited Feb. 26, 2020) [hereinafter FDA PROCESS VALIDATION GUIDANCE].

[238]FDA PROCESS VALIDATION GUIDANCE, *supra* note 237; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF, REPROCESSING MEDICAL DEVICES IN HEALTH CARE SETTINGS: VALIDATION METHODS AND LABELING (2015), https://www.fda.gov/media/80265/download [https://perma.cc/GQQ9-3BGK] (last visited Feb. 26, 2020); *Reprocessing of Reusable Medical Devices*, U.S. FOOD & DRUG ADMIN. (2018), https://www.fda.gov/medical-devices/products-and-medical-procedures/reprocessing-reusable-medical-devices/ [https://perma.cc/QHD5-ZNVN] ("[W]e review premarket and postmarket information from all manufacturers and reprocessed device types, to communicate clear regulatory requirements, to promote good manufacturing requirements, and to work with manufacturers to address public health concerns that arise after a device has entered the market.").

[239] Porritt et al., *supra* note 88.

[240] Analytical validity is a measure of how accurately and consistently the test detects the presence of a specific genotype. SACGHS PHARMACOGENOMICS REPORT, *supra* note 94, at 32; Gwinn & Khoury, *supra* note 124.

likely will be unable to utilize the 510(k) approval pathway. However, after the first animal-based diagnostic has been approved (presumably via a PMA process), later sponsors should be able to use the 510(k) pathway if the proposed predicate diagnostic is for the same intended use, assuming that animal-related variance is accounted for in the application data.[241] For example, FDA should clarify whether later sponsors need to use the same animal breed in order to meet the "same technological characteristics" requirement for demonstrating substantial equivalence for the 510(k) application.[242] Similarly, FDA should clarify whether using different training methods than the predicate animal would raise "different questions of safety and effectiveness" for purposes of substantial equivalence.[243] Assuming FDA provides guidance on animal selection, training, and testing protocols, later sponsors seeking 510(k) clearance should be able to simply follow these protocols, and not necessarily require sponsors to use identical training methods as the sponsor of the predicate diagnostic.[244] Thus, a PMA application should not be required for animal-based diagnostics for the same intended use as previously-approved animals where sponsors can demonstrate conformity with the approved methodology.

In theory, applying the 510(k) pathway to animal-based diagnostics might operate similarly to the proposed technology certification pathway from the VALID Act, discussed in Part V.B, *infra*, and could drastically decrease the regulatory burden on animal-based diagnostic developers. Under the current regime, FDA may be hesitant to allow approval of an animal-based diagnostic without specific evidence of analytical and clinical validity, though, because there would be limited data available to evaluate the safety and effectiveness of each animal-based diagnostic.

B. Adopt the Technology Certification Pathway from the Draft VALID Act

Given the potential for animal-based diagnostics to revolutionize disease detection, Congress should act to explicitly bring regulation of this technology into the framework of the FDCA. This could be done most directly by passing the VALID Act, discussed in Part II.C, *supra*. The technology certification pathway created by the VALID Act could ease the regulatory burden that sponsors of animal-based diagnostics face under the FDCA by allowing them to utilize the same underlying test method within the scope of an issued technology certification order to be exempt from the PMA process.[245]

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[241] If the animal-based diagnostic is for a different disease than the predicate, then the 510(k) pathway is likely not available since the diagnostic would not have the "same intended use as the predicate." *Premarket Notification 510(k)*, *supra* note 105. For example, a sponsor of a prostate cancer detection dog likely cannot use a previously approved breast cancer detection dog as a predicate since these are different intended uses, even if both dogs are the same breed and trained using the same training methods.

[242] 2014 SUBSTANTIAL EQUIVALENCE GUIDANCE, *supra* note 199, at 20, 24.

[243] *Id.*

[244] After a draft guidance issues and the public comment period begins, there are likely to be many suggestions from researchers and other working groups that could help ensure the analytical and clinical validity of animal-based diagnostics that FDA could include in its final guidance document.

[245] *See supra* Part II.C for a discussion of the proposed VALID Act legislation and the technology certification pathway. The VALID Act broadly defines "technology" as "a developer's grouping of [IVCTs] that do not significantly differ in control mechanisms, energy sources, or operating principles and for which design, development, and manufacturing, including analytical and clinical validation, as applicable, of the

For example, the sponsor of a *C. difficile* animal-based diagnostic could apply for a technology certification order to cover the use of scent-detection dogs to diagnose *C. difficile* in human stool samples. Assuming the test sponsor could come up with procedures of analytical and clinical validation to help address the reproducibility issues and variation risks of current animal-based diagnostics, FDA could review and approve a class of these *C. difficile*-detecting dogs without the need to submit clinical data for each dog after the representative dog identified in the application.[246] Furthermore, a technology certification order for *C. difficile*-detecting dogs may also allow a sponsor to use different animal breeds, training methods, and testing protocols without the need to seek additional approval from FDA, assuming the sponsor follows the procedures for assuring analytical and clinical validity provided in the technology certification order. Even assuming that sponsors could use the 510(k) pathway for animal-based diagnostics after the first one gets approved, as discussed in Part V.A, *supra*, the proposed technology certification pathway appears to be broader than the 510(k) predicate device pathway because multiple IVCTs can be exempt under a single technology certification application, unlike a 510(k) submission, which only provides clearance for a single, specific diagnostic.

Ultimately, whether the technology certification pathway under the VALID Act will be applied to animal-based diagnostics depends on whether the Act is passed and how it is later interpreted and applied by FDA. However, if Congress fails to pass the VALID Act, FDA could still issue a regulation pursuant to its authority under the FDCA and the Administrative Procedure Act to achieve a similar effect and ease the regulatory pathway for animal-based diagnostic developers.[247] For example, FDA could propose a regulation that allows sponsors of animal-based diagnostics to forgo the PMA process and instead use the abbreviated 510(k) notification process, much like the VALID Act allows.[248] To accomplish this, FDA could formally adopt a rule to allow early sponsors to down-classify an animal-based diagnostic to Class II using the *de novo* pathway by demonstrating the safety and effectiveness of the device through compliance with established analytical and clinical validation procedures.[249]

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tests would be addressed in a similar manner or through similar procedures." VALID Act of 2020, *supra* note 136, § 587(17)(A).

[246] The animal-based diagnostic sponsors here would also benefit from specific FDA guidance as to the analytical and clinical validation of animal-based diagnostics, discussed in Part V.A.

[247] FDA has statutory authority to promulgate regulations under various sections of the FDCA, including a general "authority to promulgate regulations for the efficient enforcement" of the FDCA. Federal Food, Drug, and Cosmetic Act (FDCA) § 701, 21 U.S.C. § 371(a) (2016); *see also* 21 U.S.C. §§ 351, 352, 353, 360, 360c–360n-1, 360bbb–360bbb-8d (2016) (codifying FDA authority to regulate medical devices under the FDCA). In addition, or alternatively, FDA could issue new guidance documents interpreting how the relevant sections of the FDCA apply to animal-based diagnostics, as discussed in Part V.A, *supra*, but issued guidance documents are less desirable because they are not binding on the agency or sponsors. U.S. FOOD & DRUG ADMIN., FDA LAWS, REGULATIONS, AND GUIDANCE DOCUMENTS 13, https://www.fda.gov/media/133830/download [https://perma.cc/ZN72-S2MJ] (last visited July 3, 2020). In issuing guidance documents, FDA must follow the procedures laid out in 21 C.F.R. § 10.115. *Id.*

[248] *See supra* notes 136–61 and accompanying text.

[249] Under *de novo* review, a sponsor of a device without a substantially equivalent predicate may request a down-classification from the default Class III to either a Class I or II device so the sponsor can take advantage of the 510(k) notification process. *See supra* note 108. Effectively, the *de novo* pathway serves to exempt devices from the PMA process if general and special controls alone provide a reasonable assurance of safety and effectiveness for a given device. *De Novo Classification Request*, *infra* note 252. "A De Novo request includes administrative information, regulatory history, device description, classification summary information, benefits and risks of device use, and performance data to demonstrate

Comparable to the VALID Act, the rule proposed here could require animal-based diagnostic sponsors to provide procedures for assuring the analytical and clinical validity of animal-based diagnostics for a specific intended use and/or for a specific species/breed of animal.[250] If the *de novo* request from an animal-based diagnostic is approved and future animal-based diagnostic sponsors demonstrate compliance with the appropriate validation procedures, then FDA could allow all of these subsequent sponsors to take advantage of the 510(k) notification pathway.[251]

This new rule could operate similarly to a rule proposed by FDA in 2018 that sought to clarify the *de novo* classification process and its requirements.[252] The proposed rule demonstrates the Agency's desire to reduce costs by allowing device sponsors to rely on a down-classified *de novo* device as a predicate for future 510(k) submissions, allowing eligible devices to avoid the cumbersome PMA process.[253] Here too, FDA could issue a new rule specifically to exempt eligible animal-based diagnostics from needing to submit a PMA application through a *de novo* down-classification, saving valuable FDA resources while maintaining safety and efficacy standards.[254] In lieu of congressional action, our proposal for a new regulation allowing *de novo* down-classification for animal-based diagnostics, in combination with the proposed FDA guidance discussed in Part V.A, *supra*, would provide the most benefit to sponsors.

CONCLUSION

Animal-based diagnostics have the potential to revolutionize medical diagnostics by providing faster and more effective diagnostics, which may be particularly useful for combatting highly virulent diseases like COVID-19. These animal-based technologies may provide a new method to detect odors of diseases that currently do not have a reliable diagnostic method. Animal-based diagnostics may also be more accurate, less wasteful, and potentially less expensive than their conventional electrochemical device counterparts. The promise of animal-based diagnostics is countered, however, by the reported reproducibility issues that could have detrimental effects on their diagnostic accuracy.

For example, critics of detection dogs have concerns that the varied attention span and olfactory capabilities among dog breeds and within a single dog's lifetime mean

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reasonable assurance of safety and effectiveness." Medical Device De Novo Classification Process, *infra* note 252, at I(B).

[250] *See* VALID Act of 2020, *supra* note 136, § 587D(e)(2)(C)–(E).

[251] *See id.* § 587D(e)(2). To illustrate, the sponsor of the *C. difficile* animal-based diagnostic could submit a *de novo* classification request instead of a PMA application, and upon approval and designation as a Class II device, later sponsors of *C. difficile* animal-based diagnostics would be able to use the less arduous 510(k) notification process.

[252] Medical Device De Novo Classification Process, 83 Fed. Reg. 63,127 (proposed Dec. 7, 2018). This proposed rule on the *de novo* classification process has not yet been finalized. *See De Novo Classification Request*, U.S. FOOD & DRUG ADMIN. (Nov. 20, 2019), https://www.fda.gov/medical-devices/premarket-submissions/de-novo-classification-request [https://perma.cc/XF7X-VN4S].

[253] Medical Device De Novo Classification Process, *supra* note 252, at I(A).

[254] *Id.* at Summary ("These requirements are intended to ensure the most appropriate classification of devices consistent with the protection of the public health and the statutory scheme for device regulation, as well as to limit the unnecessary expenditure of FDA and industry resources that may occur if devices for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness are subject to premarket approval.").

that detection dogs will never be a viable substitute for current diagnostic technologies. However, these concerns have not stopped sponsors of these animal-based diagnostics from adjusting training protocols and conducting further research studies to identify and mitigate any risks involved with using animals as detection devices. Because the animals are being used "in the diagnosis of disease or other conditions," as detailed in the FDCA's definition of medical device, FDA authority to regulate the animals is not in question.[255] What is up for debate, though, is how FDA will exercise its authority and apply the FDCA regulation of medical devices to their approval process.

The Authors urge FDA to take action to clarify the requirements for sponsors to receive regulatory approval and facilitate market entry for animal-based diagnostics. A review of the current regulatory regime for medical devices makes clear that the current FDCA is not a one-size-fits-all solution for regulation of animal-based diagnostics. Regulating animal-based diagnostics under the FDCA with the presently available FDA guidance can result in unnecessary delay and expense to developers that may ultimately discourage development of animal-based diagnostic solutions. An FDA guidance document outlining a guide to the analytical and clinical validation for animal-based diagnostics that accounts for the unique challenges of animal-related variance would provide much needed clarity on how to seek FDA approval of animal-based devices. The Authors also urge Congress to pass the VALID Act of 2020, which would allow sponsors to utilize the Act's technology certification pathway to bring animal-based diagnostics to market. The VALID Act could ease the regulatory burden that animal-based diagnostic developers currently face and incentivize innovation in this burgeoning field of diagnostic technology.

[255]Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 201(h), 321(h) (2016).