COMMENT

AMBIGUOUS REGULATION AND QUESTIONABLE PATENTABILITY: A TOXIC FUTURE FOR IN VITRO COMPANION DIAGNOSTIC DEVICES AND PERSONALIZED MEDICINE?

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Adverse drug reactions are the fourth leading cause of death in the United States. Personalized medicine, specifically in vitro companion diagnostic devices, has the potential to drastically improve patients' reactions to treatment by providing information that is essential for the safe and effective use of a corresponding therapeutic product. Despite the great promise of these devices, pharmaceutical and diagnostics manufacturers are reluctant to invest the millions of dollars necessary to create and develop these products because a guarantee of reimbursement on investment does not exist. After the FDA approves a diagnostic device, manufacturers do not enjoy market exclusivity that would bar others from piggybacking off of their inventions. For this reason, investors depend on patents to gain market exclusivity.

Meanwhile, a recent United States Supreme Court decision threatens to eliminate the promise of patents on diagnostic devices, thereby eliminating the requisite incentive to invest in research and development. A change in the regulations surrounding diagnostic devices that would grant market exclusivity to inventors of diagnostic devices could solve the problem; however, the industry does not anticipate such changes anytime soon. To save the future of the personalized medicine industry, the judicial branch must interpret the recent Supreme Court decision so as not to invalidate future diagnostic device patents.

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INTRODUCTION

The future of patient treatment lies in personalized medicine. Personalized medicine is a medical model that proposes customizing health care to each individual patient's needs.[1] Because no two human beings have the same genetic makeup, both diseases and treatments for those diseases affect people differently.[2]

Because the way in which diseases affect people differs from person to person, tailoring dosing regimens to individual responses to drug therapies is crucial.[3] Health-care providers can tailor treatments by using devices that identify the presence or absence of biomarkers[4] in patients to match an appropriate drug product.[5] These devices are commonly referred to as diagnostic devices.[6]

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1. PERSONALIZED MED. COAL., PERSONALIZED MEDICINE: AN INTRODUCTION, http://www.personalizedmedicinecoalition.org/sites/default/files/personalmed_backgrounder.pdf (last visited Apr. 1, 2013).

2. *See generally* Laviero Mancinelli et al., *Pharmacogenomics: The Promise of Personalized Medicine*, 2 AAPS PHARMSCI 1 (2000), *available at* http://link.springer.com/article/10.1208%2Fps020104 (describing pharmacogenomics as a discipline critical in gauging the genetic basis of drug response and toxicity in targeted patient populations).

3. *Id.* at 1.

4. A biological marker (biomarker) is a measurable molecular, biological, or physical attribute—such as a gene, a protein circulating in the blood, or a metabolite—whose presence is indicative of clinically relevant conditions such as disease, disease susceptibility, or a person's potential to benefit from or be harmed by a particular treatment. C. Wilson et al., *Biomarker Development, Commercialization, and Regulation: Individualization of Medicine Lost in Translation*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 153, 153 (2007).

5. *Companion Diagnostic Devices: In Vitro and Imaging Tools*, FDA, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/

Currently, patients appropriately respond to prescription medication 50 to 75 percent of the time; however, treatments for severely debilitating and life-threatening diseases such as Alzheimer's disease and various cancers fall far below that response range.[7] Additionally, adverse drug reactions have been reported to be as high as the fourth leading cause of death in the United States.[8] Scientists look to personalized medicine, and specifically in vitro companion diagnostic devices,[9] to solve these problems by identifying genotype-response associations[10] to maximize treatment efficacy.[11]

Unfortunately, the current regulation of diagnostic devices is convoluted and inefficient. The health care industry does not know how or when the complex regulatory puzzle in the pathway towards personalized medicine will be solved. If we continue down the path of complex regulation and uncertain patentability, the future of personalized medicine does not look promising.

Given the vast support for personalized medicine, one would think that the diagnostics and pharmaceutical industries would be producing in vitro companion diagnostic devices at an alarming rate. But that is not

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ucm301431.htm (last updated Aug. 26, 2013) [hereinafter *Companion Diagnostic Devices*].

6. *Id.*

7. Brian B. Spear et al., *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR MED. 201, 201–03 (2001) (advocating for an increased use of pharmacogenetic methods to optimize patient response to drug therapies).

8. Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients*, 279 J. AM. MED. ASSOC. 1200, 1204 (1998).

9. An in vitro companion diagnostic device is an in vitro diagnostic device "that provides information that is essential for the safe and effective use of a corresponding therapeutic product." *Companion Diagnostic Devices*, *supra* note 5. An in vitro companion diagnostic device could help to: identify patients who are most likely to benefit from a particular therapeutic product, identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product, and/or monitor response to treatment for the purpose of adjusting treatment (for example, schedule, dose, discontinuation) to improve the safety or effectiveness of a therapeutic product. *See id.* An example of an in vitro companion diagnostic device is the FerriScan: "The FerriScan R2-MRI Analysis System is intended to measure liver iron concentration to aid in the identification and monitoring of non-transfusion dependent thalassemia patients receiving therapy with deferasirox." *Id.*

10. Genotype-response associations concern the genetic differences in metabolic pathways that affect an individual's response to drugs. *See generally* Sabrina Angelini et al., *Association between Imatinib Transporters and Metabolizing Enzymes Genotype and Response in Newly Diagnosed Chronic Myeloid Leukemia Patients Receiving Imatinib Therapy*, 98 HAEMATOLOGICA 193 (2013). For a description of a pharmacogenetic study, see Amber L Beitelshees & Howard L. McLeod, *Clopidogrel Pharmacogenetics: Promising Steps towards Patient Care?*, 26 ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY 1681, 1681 (2006).

11. Matthew Avery, *Personalized Medicine and Rescuing "Unsafe" Drugs with Pharmacogenomics: A Regulatory Perspective*, 65 FOOD & DRUG L.J. 37, 41 (2010).

the case.[12] Companies are hesitant to invest money in the research and development of diagnostic devices if they cannot secure market exclusivity and industry protection to ensure high rates of reimbursement.[13]

One reason for the lack of production lies in the convoluted Food and Drug Administration (FDA) regulatory scheme. The FDA regulates in vitro companion diagnostic devices as medical devices.[14] To introduce a new prescription drug or medical device into the market, companies must first gain regulatory approval from the FDA.[15] To complicate matters, drugs and medical devices are regulated in completely different ways, with varying degrees of regulation, subject to standards applied by two different offices of the FDA.[16] Importantly, upon FDA approval, drug manufacturers enjoy market exclusivity for a period of years,[17] but device manufacturers do not.

In addition to cumbersome regulatory barriers, obtaining a patent for diagnostic devices involves a great deal of uncertainty. Over three decades ago the United States Supreme Court held that "laws of nature, natural phenomena, and abstract ideas" are unpatentable.[18] The Supreme Court's most recent decision addressing the patentability of diagnostic devices is *Mayo Collaborative Services v. Prometheus Laboratories, Inc*.[19] In *Prometheus*, the Court held that a diagnostic device invented by Prometheus used to treat autoimmune diseases was ineligible for patent protection.[20]

The Prometheus inventors sought to patent a method of optimizing the dosage of thiopurine drugs for the treatment of immune-mediated gastrointestinal disorders.[21] Puzzlingly, the Court determined this patent to impermissibly claim laws of nature with an obvious process to apply

12. As of August, 26, 2013, the FDA had approved only nineteen in vitro companion diagnostic devices. *See Companion Diagnostic Devices*, *supra* note 5.

13. Michael M. Hopkins & Stuart Hogarth, *Biomarker Patents for Diagnostics: Problem or Solution?*, 30 NATURE BIOTECHNOLOGY 498, 499 (2012).

14. *See Companion Diagnostic Devices*, *supra* note 5.

15. *E.g.*, 21 U.S.C. § 355(a) (2006) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.").

16. *See* Avery, *supra* note 11, at 45–49.

17. *See* 21 C.F.R. § 314.108 (2013).

18. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981) (holding that a process of curing rubber articles through the combination of measuring mold temperature, recalculating the necessary cure time, and opening the press if the necessary cure time had elapsed satisfied the patentability requirements under 35 U.S.C § 101 (2006)).

19. 132 S. Ct. 1289 (2012).

20. *Id.* at 1294.

21. *Id.* at 1295.

it.[22] As the industry currently stands, the future of personalized medicine depends upon patent protection for diagnostic devices, yet the Court's arguably invalid application of the patentability standard in *Prometheus* threatens to preclude this protection.

Absent clear regulation and patent protection, manufacturers have little incentive to invest in the necessary research to develop diagnostic devices. On July 14, 2011, in an attempt to improve the regulatory pathway for diagnostics, the FDA issued *Draft Guidance* for in vitro companion diagnostic devices.[23] The *Draft Guidance* posited a new approach in which pharmaceutical companies that seek FDA approval based on the concomitant use of a diagnostic would be limited to approved diagnostics.[24] Further, the *Draft Guidance* would require sponsors to seek approval for the drug and diagnostic contemporaneously.[25]

Congress could alter the regulation of diagnostic devices, but despite several attempts, so far it has not passed any new legislation.[26] Senator Orrin Hatch's proposed legislation, The Better Evaluation and Treatment through Essential Regulatory Reform for Patient Care Act of 2011, seeks to create a new regulatory category.[27] That category, in vitro diagnostic products (IVDP), would free diagnostics from the "medical device" regulatory scheme.[28]

If the scheme regulating companion diagnostic devices does not change, and the recent *Prometheus* decision is read broadly to invalidate all diagnostic devices and method patents that help to determine the relationship of drug dosage to toxicity, personalized medicine will not have a future. Part I of this Comment briefly summarizes cases evaluating the patentability of companion diagnostic devices, along with the current FDA regulatory scheme. Part II argues that because

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22. *Id.* at 1296–98.

23. U.S. DEP'T OF HEALTH & HUMAN SERVS., DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: IN VITRO COMPANION DIAGNOSTIC DEVICES (2011), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf [hereinafter DRAFT GUIDANCE].

24. *Id.* at 5.

25. *Id.* at 4.

26. *See* Jonathan Stroud, *A Thousand Tiny Pieces: The Federal Circuit's Fractured* Myriad *Ruling, Lessons to Be Learned, and the Way Forward*, 2 IP THEORY 71, 77 (2012), *available at* http://www.repository.law.indiana.edu/ipt/vol2/iss2/.

27. Scott Gottlieb, *Will Regulation Thwart the Personalization of Medicine?*, 3 HEALTH POL'Y OUTLOOK 1, 7 (2010), *available at* http://www.aei.org/files/2010/10/22/2010-10-No-3-g.pdf.

28. Steve Usdin, *Regulation: New Diagnostics Pathway*, BIOCENTURY (Dec. 6, 2010), http://www.biocentury.com/promotions/hatch/details-emerge-of-sen-hatch-plan-for-new-regulatory-pathway-for-diagnostics.htm.

manufacturers cannot currently gain market exclusivity through FDA approval alone, the future of the diagnostics industry depends on the ability of manufacturers to secure patents on diagnostic devices. The analysis highlights the inadequacies of the FDA's proposed diagnostic device regulations from the *Draft Guidance* and of recent draft legislation. This Comment concludes that absent a drastic regulatory change or new legislation from Congress that explicitly affords diagnostic devices market exclusivity, the future of personalized medicine depends upon a narrow interpretation of *Prometheus* to allow diagnostic manufacturers to obtain patents on their technologies.

I. CURRENT REGULATION AND MARKET PROTECTION OF DIAGNOSTIC DEVICES

Before a pharmaceutical company or manufacturer can advertise and sell a drug or medical device, the FDA must approve the product.[29] The FDA regulates drugs and medical devices in two completely different ways, which arguably hinders the progression of personalized medicine. Unlike drugs, after the FDA approves a diagnostic device for marketing, the FDA does not set a period of years in which other manufacturers cannot market an identical product.[30] As a result, diagnostics manufacturers must seek protection from industry copycats in the form of patents, which both grant the inventor exclusive rights for a period of years and require him to publicly release details regarding the creation of the invention.[31] The patentable scope of diagnostic devices, however, remains unsettled in the courts.[32]

A. Current FDA Regulations

Risk accompanies all drugs and medical devices.[33] The FDA is in charge of weighing the risks and benefits of drugs and medical devices and ultimately deciding whether the product will be used in patient

29. *See* 21 U.S.C. § 355(a) (2006) ("No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.").

30. *See* 21 C.F.R. § 314.108 (2013).

31. *See generally* Hopkins & Hogarth, *supra* note 13, at 498–500.

32. *See id.* at 498.

33. Burgunda V. Sweet et al., *Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products*, 17 J. MANAGED CARE PHARMACY 40, 42 (2011).

care.[34] The FDA review and approval process used for drugs and medical devices differs greatly.[35] Although both manufacturers of drugs and medical devices can only market their products for their approved uses once cleared by the FDA, drug manufacturers enjoy market protection upon approval, whereas device manufacturers do not.[36]

1. REGULATION OF DRUGS

The FDA must approve each drug as safe, effective, and accurately labeled before pharmaceutical companies can market the drug.[37] Within the FDA, the Center for Drug Evaluation and Research (CDER) "regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs."[38] Under the regulations, pharmaceutical companies must conduct extensive studies on drugs showing the

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34. Larry Kessler & Kimber Richter, *Technology Assessment of Medical Devices at the Center for Devices and Radiological Health*, 4 AM. J. MANAGED CARE 129, 129 (1998).

35. *Id.*

36. *See* 21 C.F.R. § 314.108 (2013).

37. *See* 21 U.S.C. § 355(d) (2006). This Section sets forth six specific requirements that must be met before a new drug application is approved:

> If the Secretary finds . . . that (1) the . . . reports . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application.

Id.

38. *About the Center for Drug Evaluation and Research*, FDA, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm (last updated Oct. 21, 2013).

pharmacological and toxicological effects.[39] They must also provide information relating to drug safety and efficacy.[40]

Before conducting human clinical testing, the pharmaceutical company (or sponsor) must perform laboratory and animal tests.[41] Following animal testing, applicants submit an Investigational New Drug Application (IND).[42] Next, the sponsor begins human clinical studies.

Clinical studies are comprised of three phases.[43] Phase I clinical studies, generally conducted in healthy volunteers, aim to identify pharmacokinetic and pharmacological effects of the drug.[44] Phase II studies are conducted in several hundred people with the disease and aim to collect preliminary data on the efficacy of the drug.[45] If the preliminary data from the Phase II study suggests that the drug is effective, sponsors may proceed to Phase III.[46] Phase III studies, which can include up to several thousand subjects, look to determine large-scale efficacy by studying different populations and different dosages.[47]

After human clinical trials, the sponsor and the FDA meet to agree on post-market requirements and commitment studies "to gather additional information about a product's safety, efficacy, or optimal use."[48] The process culminates with the sponsor submitting a New Drug Application (NDA), which includes detailed reports from the animal and human studies.[49] With the submission of the NDA, the drug sponsor formally requests approval to market a new drug in the United States.[50]

But pharmaceutical companies and drug sponsors are not done yet. All drugs must be properly labeled, which requires directions for use, safe dosing regimens, contraindications, and adequate warnings about

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39. 21 C.F.R. § 312.23(a)(8).

40. *See* 21 C.F.R. § 312.23.

41. 21 C.F.R. § 312.23(a)(8).

42. *Id.*

43. *Id.*

44. *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm (last updated May 1, 2012) [hereinafter *The FDA's Drug Review Process*]. Pharmacokinetics is the study of the mechanism of absorption and distribution of a drug, whereas pharmacology is the study of a drug's effects on the body. Eva Fernandez et al., *Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults*, 3 PHARMACEUTICS 53, 54 (2011), *available at* http://www.mdpi.com/1999-4923/3/1/53.

45. *The FDA's Drug Review Process*, *supra* note 44.

46. *Id.*

47. *Id.*

48. *Id.*

49. *Id.*

50. *Id.*

common side effects and adverse reactions.[51] The FDA then makes the final drug approval determination based on the drug's overall safety, efficacy, and ability to treat the targeted condition.[52] When a drug is approved, the FDA grants marketing "exclusivity" for a period of years, which prohibits other companies from seeking approval of a comparable drug during that time.[53] "Exclusivity" is a statutory provision granted to applicants if certain statutory requirements are satisfied.[54]

2. REGULATION OF MEDICAL DEVICES

While the CDER regulates drugs, the FDA's Center for Devices and Radiological Health (CDRH) regulates medical devices.[55] Medical devices are classified in a three-tier system based on risk.[56] As the degree of risk increases, manufacturers must adhere to stricter regulations that lengthen the approval process and add significant costs. Class I devices, medical devices of the lowest perceived risk and therefore subject to "general controls," must adhere to basic standards of labeling, proper manufacturing processes and conditions, post-market surveillance, and reporting to the FDA.[57] General controls do not require the submission of clinical data attesting to safety and efficacy, and generally these devices do not need to gain FDA approval before they can be marketed.[58]

Class II devices are higher-risk devices that are subject to "special controls."[59] Special controls may entail performance reviews against established standards, design controls, and post-market surveillance mechanisms.[60] Additionally, the majority of Class II devices require FDA clearance of a Premarket Notification Application (PMA or 510[k])

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51. *See* 21 U.S.C. § 352(f) (2006).

52. *See* 21 U.S.C. § 355(d).

53. 21 U.S.C. §§ 355(c)(3)(E), 355(j)(5)(F); *see also* 21 C.F.R. § 314.108 (2013).

54. 21 C.F.R. § 314.108.

55. *About the Center for Devices and Radiological Health*, FDA, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/default.htm (last updated Aug. 15, 2013).

56. Aaron V. Kaplan et al., *Medical Device Development: From Prototype to Regulatory Approval*, 109 CIRCULATION 3068, 3069 (2004).

57. *Id.* Examples of Class I medical devices include elastic bandages, examination gloves, and hand-held surgical instruments. JUDITH A. JOHNSON, CONG. RESEARCH SERV., R42130, FDA REGULATION OF MEDICAL DEVICES 5 (2012).

58. 21 U.S.C. § 360(k)–(l) (2006), *amended by* 21 U.S.C. § 360(k) (Supp. V 2012).

59. Kaplan et al., *supra* note 56, at 3069.

60. *Id.*

before the manufacturer can sell the device.[61] A PMA requires the medical device manufacturer to show that the device is "substantially equivalent" to a legally marketed device.[62]

Class III devices are those that present the highest safety risk.[63] Devices that involve the highest risk include those that support or sustain human life, prevent impairment of human health, or generally present a high risk of illness or injury.[64] As a result, device manufacturers looking to market a Class III device must, in addition to complying with general and special controls, submit a PMA that includes evidence demonstrating that the device is safe and effective for its targeted use.[65]

B. Patentability of Diagnostic Devices in the Courts

Diagnostic method patents have been a point of contention in the courts since their inception.[66] Under 35 U.S.C. § 101 (Section 101), "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor . . . ."[67] In *Diamond v. Diehr*,[68] the Supreme Court clarified the patent standard and held "laws of nature, natural phenomena, and abstract ideas" to be unpatentable.[69] Further, although the *Diamond* Court reasoned that mathematical formulas in the abstract are not patentable, a physical machine or process that makes use of an algorithm meets the requirements of patentability.[70] Over the next fifteen years, courts ruled on several method patent cases, leading up to a case in which the Federal Circuit held that a method is patentable if it has a "useful, concrete, and tangible result."[71]

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61. *Id.* Examples of Class II devices include powered wheelchairs, joint prosthesis, and infusion pumps. JOHNSON, *supra* note 57, at 5.

62. *Premarket Notification (510k)*, FDA, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm (last updated Sept. 30, 2010).

63. Kaplan et al., *supra* note 56, at 3069.

64. 21 U.S.C. § 360(c) (2006).

65. Kaplan et al., *supra* note 56, at 3069. The FDA must approve the PMA before the manufacturer may release the device commercially. *See* 21 U.S.C. § 360(e).

66. Asher Hodes, *Diagnosing Patentable Subject Matter*, 26 BERKELEY TECH. L.J. 225, 227 (2011).

67. 35 U.S.C. § 101 (2006).

68. 450 U.S. 175 (1981).

69. *Id.* at 185.

70. *Id.* at 192.

71. *State St. Bank & Trust Co. v. Signature Fin. Grp., Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998) (quoting *In re Alappat*, 33 F.3d 1526, 1543 (Fed. Cir. 1994)).

Relaxation of the patent standard caused an explosion in the number of method patents.[72] But in 2008, the Federal Circuit reconsidered the scope of Section 101 in *In re Bilski*[73] and held that a method must be tied to a particular machine or apparatus, or transform an article into a different state or thing.[74] Two years later, the Supreme Court held that the "machine-or-transformation" test is not the only test for determining the patent eligibility of a process, yet it is a "useful and important clue, an investigative tool . . . ."[75]

Because diagnostic method patents utilize individual genomic information, diagnostics manufacturers often try to patent their genomic findings. The Supreme Court has long held that bioengineered living organisms are patentable subject matter.[76] Further, the United States Patent and Trademark Office (USPTO) has generally found isolated and purified genes to be patentable.[77]

On July 29, 2011, the Court of Appeals for the Federal Circuit upheld the patentability of claims on isolated DNA sequences in *Association for Molecular Pathology v. U.S. Patent and Trademark Office* (*AMP v. USPTO*).[78] The diagnostics industry found cause to celebrate after the *AMP v. USPTO* decision, until the Supreme Court handed down their decision in *Prometheus* on March 20, 2012.[79] In *Prometheus*, the Court used new methodology in determining patentability under Section 101, ruling that to be eligible for a patent, "a process that focuses upon the use of a natural law [must] also contain other elements or a combination of elements . . . sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself."[80] Using this methodology, the Court held that relationships between the concentration of metabolites in the bloodstream and the appropriate dose of a drug are "laws of nature," and Prometheus did not add *enough* to the correlations to make the diagnostic

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72. *See* John W. Bagby, *Business Method Patent Proliferation: Convergence of Transactional Analytics and Technical Scientifics*, 56 BUS. LAW. 423, 445–46 (2000).

73. 545 F.3d 943 (Fed. Cir. 2008).

74. *Id.* at 954 (construing the "machine-or-transformation" test).

75. *Bilski v. Kappos*, 130 S. Ct. 3218, 3227 (2010).

76. *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

77. Utility Examination Guidelines, 66 Fed. Reg. 1092, 1092–93 (Jan. 5, 2001).

78. 653 F.3d 1329 (Fed. Cir. 2011). This case concerned the patentability of two isolated DNA segments used in the diagnosis of women for heightened risks of breast and ovarian cancer. *Id.* at 1334. The first segment was a naturally occurring segment as it appears on the human chromosome. *Id.* at 1364. The second, synthetically created complementary DNA (cDNA), was chemically modified to remove portions of the DNA not involved in coding for cell production. *Id.* at 1339, 1364.

79. Stroud, *supra* note 26, at 72.

80. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1294 (2012).

process patent-eligible.[81] As a result, the celebration in the diagnostics industry following the *AMP v. USPTO* decision[82] immediately ceased with the release of Justice Stephen Breyer's opinion in *Prometheus*, as the holding threatened to invalidate future diagnostic method patents.

II. CURRENT REGULATION AND PROTECTION CAPACITY OF DIAGNOSTIC DEVICES HINDER INNOVATION

The future of the diagnostics industry and personalized medicine depends on securing market protection for diagnostics manufacturers and pharmaceutical companies.[83] Given the current regulation of the diagnostics industry, these companies cannot secure the necessary market protection through FDA approval alone.[84] Currently, to prevent competitors from piggybacking off of an idea that diagnostics manufacturers spend millions of dollars to develop, manufacturers rely on patents.[85]

The recent *Prometheus* decision[86] threatens manufacturers' ability to gain protection through patents and thus eliminates incentive to invest in research and development. Although the FDA attempted to improve the regulation of diagnostic devices through a *Draft Guidance*,[87] that

81. *Id.* at 1296, 1303; *see* Stroud, *supra* note 26, at 79–80.

82. Following the *Prometheus* decision, the United States Supreme Court granted the Association for Molecular Pathology's writ of certiorari. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 131 S. Ct. 3027 (2011). On March 26, 2012, the Supreme Court vacated the Federal Circuit decision and remanded the case back to the Federal Circuit. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012). On August 16, 2012, the Federal Circuit again held the isolated DNA molecules to be patent-eligible under Section 101. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1326 (2012). On September 25, 2012, the American Civil Liberties Union and the Public Patent Foundation filed another petition for certiorari with the Supreme Court regarding the second Federal Circuit decision. Petition for a Writ of Certiorari, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398). On November 30, 2012, the Supreme Court agreed to hear the appeal of the ruling. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694, 695 (2012). In a unanimous decision written by Justice Clarence Thomas on June 13, 2013, the Court reversed the Federal Circuit's ruling as to the naturally occurring DNA segment but affirmed with regards to the cDNA. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2111 (2013). The Court stated that while the discovery and isolation of the naturally occurring segment was not patent-eligible, "the lab technician unquestionably creates something new when cDNA is made." *Id.* at 2119–20.

83. *See* Hopkins & Hogarth, *supra* note 13, at 499.

84. *See* Stroud, *supra* note 26, at 77.

85. Hopkins & Hogarth, *supra* note 13, at 499.

86. *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012).

87. DRAFT GUIDANCE, *supra* note 23.

guidance has yet to be finalized. With the FDA dragging its feet, a change in the regulation of diagnostic devices could also come from Congress to ensure that diagnostics manufacturers obtain market protection, but existing draft legislation falls short of what is needed.[88] Because FDA approval does not alone protect diagnostics manufacturers' inventions from market competitors, patent protection is necessary to incentivize further innovation in the industry.

A. Market Exclusivity Is the Key to Incentivizing Development

The research and development necessary to produce quality, cutting-edge diagnostic devices requires large investments from private investors and manufacturing companies.[89] Such investors contribute between 70 and 75 percent of the cost of research and development.[90] Currently, manufacturers and private investors are not guaranteed profits from their technologies. Without market exclusivity, investment in the necessary research and development will come to a screeching halt.[91] As the incentives for investment in diagnostics and necessary subsequent clinical trials disappear, so will the evidence base and development in the industry.[92]

1. TRADE SECRETS ARE NOT THE ANSWER

Pharmaceutical and diagnostics manufacturers could use trade secret protection to gain market exclusivity, but the potential market protection offered by trade secrets is weak and uncertain.[93] The origin of trade secret protection exists in state common law, which arguably serves as part of the cause of its relative weakness compared to, for example, patent protection—created by federal statute.[94] In 1979, the Uniform Law

88. *See* Gottlieb, *supra* note 27, at 7.

89. Johanna Jacob, Comment, *Should Our Genes Be Part of the Patent Bargain? Maximizing Access to Medical Diagnostic Advances While Ensuring Research Remains Profitable*, 28 SANTA CLARA COMPUTER & HIGH TECH. L.J. 403, 434 (2012).

90. *See* Nat'l Sci. Found., *Research and Development: National Trends and International Linkages*, *in* SCIENCE AND ENGINEERING INDICATORS 2008, at 4-5 (2008), *available at* http://www.nsf.gov/statistics/seind08/pdf/c04.pdf.

91. Jacob, *supra* note 89, at 434.

92. Hopkins & Hogarth, *supra* note 13, at 499.

93. Trade secrets protect against the disclosure of secret information of economic value that an owner has taken steps to secure from disclosure. *Trade Secrets 101*, GALLAGHER & DAWSEY (Apr. 2009), http://www.invention-protection.com/ip/publications/docs/Trade_Secrets_101_pf.html. Trade secrets "can include a formula, pattern, compilation, program, device, method, technique or process." *Id.*

94. Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD

Commission published the Uniform Trade Secrets Act (UTSA), and to date forty-six states have adopted it in an attempt to standardize trade secret protection.[95]

Trade secret protection is substantially limited because the owner of a trade secret does not possess exclusive right to that information, and protection from rivals independently acquiring the information (leading to separate development and reverse engineering) does not exist.[96] Further, legal limits on the duration of a trade secret do not exist.[97] As a result, companies can *indefinitely* withhold key information from competitors, preventing the industry as a whole from advancing.[98]

The life-saving nature of these technologies prevents trade secrets from being a viable option. If diagnostics manufacturers rely on trade secrets, they withhold key information from their competitors and inhibit other companies from improving upon the latest technology. This would ultimately harm patient health. Secrecy in science, especially health science, should be avoided.

2. REGULATING DIAGNOSTIC DEVICES AS DRUGS COULD INVITE LITIGATION

One way in which diagnostics manufacturers could gain market exclusivity would be to afford diagnostic devices the same FDA-granted exclusivity as drugs. When the FDA approves a drug, it grants "exclusivity" to the pharmaceutical company for a defined number of

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DRUG L.J. 285, 288 (2011); *see* 1 MELVIN F. JAGER, TRADE SECRETS LAW §§ 2:1–2:4 (2006).

95. Katarzyna A. Czapracka, *Antitrust and Trade Secrets: The U.S. and the EU Approach*, 24 SANTA CLARA COMPUTER & HIGH TECH. L.J. 207, 222 (2008). The UTSA defines a trade secret as:

> [I]nformation, including a formula, pattern, compilation, program, device, method, technique, or process, that: (i) derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or use, and (ii) is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.

UNIF. TRADE SECRETS ACT § 1(4) (amended 1985), 14 U.L.A. 538 (1985).

96. Czapracka, *supra* note 95, at 226 (citing 1 MELVIN F. JAGER, TRADE SECRETS LAW §§ 3:11–3:12 (2006)).

97. Chris J. Katopis, *Patients v. Patents?: Policy Implications of Recent Patent Legislation*, 71 ST. JOHN'S L. REV. 329, 344–45 (1997) ("In theory, trade secret protection can last forever, or at least longer than the practical useful life of an invention.").

98. In other words, if a market competitor does not discover the trade secret through independent research or reverse engineering, the trade secret could remain a secret forever. This differs from patent protection, where the inventor must disclose the "best mode" of carrying out the invention upon approval of the patent. *See infra* Part II.A.3.

years.[99] After the FDA evaluates a drug's safety and efficacy,[100] it approves a drug for a specific use delineated in the official drug label; the FDA never approves a drug for "general" use.[101]

Once a drug is approved and labeled, however, physicians have the discretion to "prescribe any drug for any medical condition, even outside of the parameters of the label, for a so-called 'off-label' use."[102] This common practice has led pharmaceutical manufacturers to *promote* drugs for off-label uses, which is expressly forbidden by the FDA.[103] The FDA restrictions and prosecutions of off-label promotion by pharmaceutical companies have caused significant backlash in the pharmaceutical community.[104] This backlash led to litigation based on the legal principal of commercial speech starting in the 1970s.[105]

Yet, the Second Circuit recently overturned the conviction of a pharmaceutical sales representative for conspiring to introduce a misbranded drug into interstate commerce.[106] In *United States v. Caronia*,[107] Caronia argued that the Federal Food, Drug, and Cosmetic Act's (FDCA) misbranding provisions prohibit off-label promotion and thus violate free speech protections under the First Amendment.[108] In a

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99. *See* 21 C.F.R. § 314.108 (2013).

100. *See supra* Part I.A.1 (discussing the FDA drug approval process and requirements).

101. Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 225 (2011).

102. *Id.*

103. *Id.* at 225–28; *see* Aaron S. Kesselheim & Jerry Avorn, *Pharmaceutical Promotion to Physicians and First Amendment Rights*, 358 NEW ENG. J. MED. 1727, 1727 (2008) (describing off-label promotion rules).

104. *See* Daniel B. Klein & Alexander Tabborok, *Who Certifies Off-Label?: FDA Efficacy Requirements May Do More Medical Harm Than Good*, 27 CATO REV. BUS. & GOV'T REG. 60, 63 (2004) ("The experience with off-label prescribing and the experience of pre-1962 America suggest that initial efficacy requirements may do more harm than good.").

105. *See* Kesselheim, *supra* note 101, at 242–46 (describing the history of the judiciary's perspective on free commercial speech). "Under the First Amendment, which establishes the right to free expression of ideas, the government generally cannot restrict communications based on their content, although it can exert some control over their context." *Id.* at 242; *see also Sorrell v. IMS Health, Inc.*, 131 S. Ct. 2653, 2659 (2011) (holding that "[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment"); *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (discussing the "general rule" that "the speaker and the audience, not the government, assess the value of the information presented"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001) (stating that although it is unlawful for companies to promote FDA-approved drugs for unapproved, or off-label, uses, doctors may lawfully prescribe these drugs for the same unapproved uses).

106. *United States v. Caronia*, 703 F.3d 149, 152 (2d Cir. 2012).

107. 703 F.3d 149 (2d Cir. 2012).

108. *Id.* at 160.

2-1 decision, the Second Circuit held that "the government cannot prosecute pharmaceutical manufacturers and their representatives under the FDCA for speech promoting the lawful, off-label use of an FDA-approved drug."[109]

If the Supreme Court decides to take the case and upholds the *Caronia* decision, it could invite the industry to consider revising current regulations so that drugs and medical devices are regulated in the same manner.[110] If medical devices were regulated in the same manner as drugs, diagnostic devices would enjoy the same statutory "exclusivity" as drugs upon FDA approval; however, as it currently stands, the *Caronia* decision only substantially impacts three states.[111] The case law is by no means settled. If the Supreme Court declines to take on *Caronia* (or reverses the decision), and if the FDA begins to regulate diagnostic devices like drugs and grants market exclusivity upon approval of a diagnostic device for a very specific purpose, the courts would experience a flood of litigation regarding diagnostics manufacturers' ability to advertise their products for off-label uses.[112]

In addition to the flood of litigation that would likely result from regulating diagnostic devices in the same manner as drugs, the regulatory scheme for drugs is not desirable for other reasons. Most significantly, it can take over fifteen years to bring a new drug to market.[113] Also, the FDA "errs on the side of excessive caution," using a rigorous

109. *Id.* at 169.

110. This is because the industry's fear of an outpouring of litigation regarding diagnostics manufacturers' advertising their products for off-label uses would no longer be a barrier for regulating diagnostic devices as drugs (and thereby affording them the same market exclusivity upon approval).

111. New York, Connecticut, and Vermont, which comprise the Second Circuit.

112. Some may argue that the promotion of diagnostic devices for off-label uses is not a real threat given the high degree of personalization and particularity of the devices, but the industry has already acted on the possibility of this threat. For example, in 2000 the FDA sent a letter of warning to a medical device company for attempting to promote a device for an off-label use. Sara E. Dyson, *How to Avoid Off-Label Device Promotion*, MED. DEVICE & DIAGNOSTIC INDUSTRY (Feb. 17, 2010), http://www.mddionline.com/article/how-avoid-label-device-promotion. The FDA approved a product manufactured by the company for use as an *adjunctive* diagnostic screening device for detecting breast cancer, yet the company's promotional materials implied that the device could be used as a *standalone* diagnostic test for breast cancer. *Id.* The FDA deemed the company's website to be misleading, qualifying it as off-label promotion because it implied that the diagnostic device could be used for something other than its cleared purpose. *Id.*

113. Chris L. Waller et al., *Strategies to Support Drug Discovery through Integration of Systems and Data*, 12 DRUG DISCOVERY TODAY 634, 634 (2007).

one-size-fits-all model for the approval of new drugs, which is neither efficient nor desirable.[114]

3. PATENTS SECURE THE BEST INDUSTRY PROTECTION

With trade secrets providing unreliable industry protection and the FDA (currently) unable to realistically regulate diagnostic devices the same way it regulates drugs, the only existing business incentive for diagnostics manufacturers to invest in the high costs of research and development is patent protection. The Constitution grants Congress the power to confer patents,[115] and Congress grants patents through Section 101.[116] Patents give investors "the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States" for a limited time.[117] In exchange, the inventor must publicly divulge the "best mode . . . of carrying out the invention."[118]

Unlike with trade secrets, where information leading to an invention has the potential to be kept secret indefinitely and as a result impede innovation, the grant of a patent requires the patentee to release information.[119] This release of information allows future inventors to improve upon the technology, ultimately promoting progress in the industry.[120] As a result, patents promote investment in research and development because manufacturers know that they will benefit from such protection.

Until recently, an inventor's failure to disclose the best mode was available as a defense in patent infringement litigation.[121] On September 16, 2011, President Barack Obama signed the Leahy-Smith America Invents Act[122] (AIA) into law, causing major changes to the United States patent system. The law caused significant changes to many portions of Title 35 of the United States Code, the main source of patent

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114. Bartley J. Madden, *The Problem with the FDA Drug Approval Process*, HEARTLAND (June 1, 2007), http://news.heartland.org/newspaper-article/2007/06/01/problem-fda-drug-approval-process; *see supra* Part II.A.1.

115. *See* U.S. CONST. art. I, § 8, cl. 8 ("The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . . .").

116. 35 U.S.C. § 101 (2006).

117. 35 U.S.C. § 154(a)(1).

118. *See* 35 U.S.C § 112.

119. Epstein, *supra* note 94, at 288.

120. *Id.*

121. 35 U.S.C. § 282.

122. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

law in the United States.[123] Specifically, the enactment amended 35 U.S.C. § 282 to remove the failure to disclose the best mode as a means to invalidate or cancel an issued patent.[124] Despite this change, the AIA did not amend the statutory requirement to disclose the best mode of Section 112(a); thus, in order to comply with the statutory disclosure requirements, investors must continue to set forth the best mode contemplated by the inventor in carrying out the invention.[125]

Some criticize diagnostics patents, fearing increases in consumer pricing due to the "monopolies" that patents create.[126] They also worry about the impenetrable "patent thickets" that an abundance of diagnostic patents could create, which could thwart innovation.[127] Although patent thickets may be a reasonable concern for certain products, the nature of diagnostic devices significantly limits this concern. Patent thickets occur when a product involves many patents.[128] Unlike smartphones, for example, which can require thousands of patents, arguably creating an impenetrable patent thicket, diagnostic devices require fewer: one for the algorithm, the gene, and perhaps the laboratory setup and reagent.[129] Therefore, the threat of a patent thicket presented by other products is not a reasonable concern for diagnostic devices.

Further, given the way that the diagnostics industry currently stands, the only available channel to commercialization for diagnostics companies is the patent process.[130] To pay for the extensive evidence that is necessary to develop and perfect diagnostic devices, ultimately leading to safe, effective, and potentially life-saving products, companies need to know that there will be a potential for future reimbursement.[131] Today,

123. Ryan Vacca, *Patent Reform and Best Mode: A Signal to the Patent Office or a Step toward Elimination?*, 75 ALB. L. REV. 279, 279, 290–93 (2011–12).

124. 35 U.S.C. § 282; Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 15, 125 Stat. 284, 328 (2011) (stating that "the failure to disclose the best mode shall not be a basis on which any claim of a patent may be canceled or held invalid or otherwise unenforceable").

125. 35 U.S.C. § 112.

126. *See* Hopkins & Hogarth, *supra* note 13, at 498.

127. *Id.*; *see also* David H. Blankfein-Tabachnick, *Intellectual Property Doctrine and Midlevel Principles*, 101 CALIF. L. REV. 1315, 1347 (2013).

128. James Bessen, *Patent Thickets: Strategic Patenting of Complex Technologies* 1 (Research on Innovation, Working Paper No. 0401, 2004), *available at* http://www.researchoninnovation.org/thicket.pdf.

129. Interview with R. Alta Charo, Warren P. Knowles Professor of Law & Bioethics, Univ. of Wis. Law Sch., in Madison, Wis. (Dec. 17, 2012); *see also* Mark A. Lemley, *Software Patents and the Return of Functional Claiming*, 2013 WIS. L. REV. 905, 929 (describing the problem of patent thickets in the smartphone industry).

130. Stroud, *supra* note 26, at 77.

131. *See* Hopkins & Hogarth, *supra* note 13, at 499.

patents serve as the best incentive for investment due to their promise of industry protection.

B. The FDA's Proposed Draft Guidance *Falls Short of Solving the Problem*

If diagnostic manufacturers cannot gain effective market exclusivity through the existing regulatory mechanisms and laws governing the diagnostics industry, a schematic change in the FDA's regulation of diagnostic devices could potentially provide a solution. Currently, the FDA regulates drugs and medical devices in two completely different ways, from two separate offices.[132] The "quick-fix" solution by regulating medical devices in the same manner as drugs is neither practical nor desirable.[133] On July 14, 2011, the FDA issued *Draft Guidance* on in vitro companion diagnostic devices that, when (and *if*) finalized, would reform the regulatory scheme for diagnostic devices.[134]

The *Draft Guidance* begins by narrowly defining in vitro diagnostic (IVD) devices. It excludes "clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product."[135] Focusing on regulatory requirements, the *Draft Guidance* states that the therapeutic products would need to be reviewed and approved under either Section 505 of the FDCA[136] or Section 351 of the Public Health Service Act,[137] while the IVD device would have to be contemporaneously reviewed and approved under Section 510(k) of the Medical Device Amendments[138] to the FDCA.[139]

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132. *See supra* notes 19–47 and accompanying text.

133. *See supra* Part II.A.2.

134. *See generally* DRAFT GUIDANCE, *supra* note 23.

135. *Id.* at 7.

136. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, ch. 675, § 505, 52 Stat. 1040, 1052–53 (1938). Section 505 describes the regulatory pathways for approval for new drugs. *Id.* The New Drug Application (NDA) requirements are set out under § 505(b)(1) and include two adequate and well-controlled clinical studies to support NDA approval. *Id.*; *see also* 21 C.F.R. § 314.50 (2013).

137. Public Health Service Act, Pub. L. No. 78-410, ch. 373, 58 Stat. 682 (codified as amended at 42 U.S.C. §§ 262–300jj, 351 (2006 & Supp. II 2006)). Section 351 of the Public Health Service Act regulates the approval of biologics. *Id.* at 702–03. In order to introduce a biological product into interstate commerce, a manufacturer must file a biologics license application with the FDA. *Id.* As a part of this license, the manufacturer submits to post-market studies and clinical trials, as well as proper labeling and risk evaluation. *Id.*

138. Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539.

139. DRAFT GUIDANCE, *supra* note 23, at 7.

Further, the *Draft Guidance* stipulates that novel therapeutic products whose safe and effective use depends on the use of a diagnostic device *will not be approved* until the device "is properly validated and meets the applicable standard for safety and effectiveness or for substantial equivalence for the use indicated in the therapeutic product's labeling."[140] Therefore, in most circumstances, the proposed *Draft Guidance* requires that the review and approval of a diagnostic device and the corresponding therapeutic product be a collaborative, synchronous effort at the FDA.

Although the *Draft Guidance* (if ever finalized and enacted) could potentially contribute to the diagnostics and personalized medicine industry through increased organization, it does not explicitly (or implicitly) discuss market exclusivity or protection. The *Draft Guidance* shows that the FDA understands that diagnostic devices have become an essential component to the advancement of personalized medicine; but by failing to add business incentives to the funding problem, it falls far short of what is needed to save the industry. In order for new regulations to viably solve the problem in the diagnostics industry, the FDA must explicitly allow diagnostics manufacturers to enjoy market exclusivity for a period of years.

C. Congressional Change Is Possible

Instead of the FDA solely working internally to restructure the regulation of diagnostic devices, Congress could restructure the industry's regulation.[141] If diagnostic devices were regulated under a separate pathway at the FDA, it is possible that the cost of approval would decrease.[142] Importantly, the current regulations and the proposed *Draft Guidance* largely ignore Laboratory-Developed Tests (LDTs), or "home-brews," which are tests that are used solely within a laboratory and not distributed or sold to other laboratories or health-care

140. *Id.* at 8. The *Draft Guidance* gives a few exceptions to this rule, as in the case of products to treat serious or life-threatening conditions or already-approved products. *See id.* at 8–9.

141. Stroud, *supra* note 26, at 77.

142. *Id.* As it stands, the Premarket Notification Application (PMA) process is convoluted and carries high regulatory costs. If diagnostic devices were regulated under a separate pathway at the FDA, the new regulatory requirements could more closely match the perceived risk of the devices, eliminating unnecessary costs.

facilities.[143] Because these tests can slip through the regulatory cracks, their use poses a potentially serious risk to the consumer.[144]

The draft legislation receiving the most attention is Senator Orrin Hatch's Better Evaluation and Treatment through Essential Regulatory Reform for Patient Care (BETTER Patient Care) Act of 2011.[145] The BETTER Patient Care Act would create a new division inside the FDA, the Center for Advanced Diagnostics Evaluation and Research, "which would be responsible for ensuring the safety and efficacy of a new category of tests called 'advanced personalized diagnostics' (APDx)."[146] This new category of tests would encompass in vitro diagnostic devices and LDTs.[147] The BETTER Patient Care Act would require these tests to be categorized according to whether they have a low, moderate, or high health impact, and the FDA would require premarket clearance for high-risk tests.[148]

Similar to the *Draft Guidance*, the draft legislation recognizes the importance and uniqueness of diagnostic tests and devices, and instead of trying to add more provisions to the existing regulatory scheme, it creates a new framework and allows regulatory requirements to be more closely matched to the expected risk of the products.[149] Unfortunately, available information surrounding this draft legislation does not explicitly mention market protection mechanisms. Therefore, similar to the *Draft Guidance*, the key market exclusivity component goes unresolved. In addition to separating diagnostic devices from the current convoluted regulatory scheme, legislation must afford manufacturers a period of years during which other manufacturers in the industry may not duplicate the innovation.

D. Progression in the Diagnostics Industry Depends upon a Narrow Interpretation of Prometheus

Both the *Draft Guidance* for in vitro diagnostic devices and the "most promising" draft legislation are over a year old, and rumblings in the industry indicate low expectations for the finalized versions to be

143. *See* Jennifer Morton, *BRCA1 and BRCA2 Mutations Highlight the Need for Improved Regulation of Laboratory-Developed Tests*, 12 HOUS. J. HEALTH L. & POL'Y 63, 64 (2011).

144. *Id.* at 64.

145. Gottlieb, *supra* note 27, at 7.

146. *Id.*

147. *Id.*

148. *Id.*

149. *Id.*

released anytime soon.[150] Even if the FDA finalizes the guidance or Congress passes new legislation, the current propositions fail to recognize the need for diagnostics manufacturers to gain market exclusivity. For these reasons, how the industry and judicial branch interpret the *Prometheus* decision regarding the ability of diagnostics manufacturers to gain patent protection on their new technologies will be paramount to the future of personalized medicine.

In *Prometheus*, the Supreme Court held that the patented Prometheus claim[151] directed to methods of optimizing the dosing regimen of a specific drug used in the treatment of a specific medical condition was invalid under Section 101 because it pertained to ineligible subject matter.[152] Prometheus's patent involved a method of administering thiopurine drugs to a patient and determining whether the concentration of blood metabolites fell within an optimal therapeutic range.[153]

Rejecting the outdated "machine-or-transformation" test,[154] the Supreme Court constructed a new methodology: "a process that focuses upon the use of a natural law [must] also contain other elements or a combination of elements, sometimes referred to as an 'inventive concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself."[155] The Court determined that the correlation between thiopurine drug dosage and a

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150. Interview with R. Alta Charo, Warren P. Knowles Professor of Law & Bioethics, Univ. of Wis. Law Sch., in Madison, Wis. (Oct. 23, 2012).

151. The following is the text of the now-invalidated Claim 1 of the Prometheus U.S. Patent No. 6,255,623:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine is less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1295 (2012).

152. *Id.* at 1294.

153. *Id.* at 1295.

154. The machine-or-transformation test is a test of patent eligibility under which a claim to a process may be considered for patenting if it (1) is implemented with a particular machine, that is, one specifically devised and adapted to carry out the process in a way that is not concededly conventional and is not trivial; or else (2) transforms an article from one thing or state to another. Stefania Fusco, *Is* In re Bilski *a* Déjà Vu*?*, 2009 STAN. TECH. L. REV. 1, ¶ 2.

155. *Prometheus*, 132 S. Ct. at 1294.

patient's subsequent metabolic response was an unpatentable law of nature.[156] Further, applying the new methodology, the Court concluded that the claims were not patent eligible because "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field" and that Prometheus did not add *enough* to the correlations to allow the processes they described to qualify as patent eligible.[157]

The *Prometheus* decision has many fundamental flaws. First, the Court did not evaluate whether the claimed innovation was a law of nature causing it to be ineligible for patent protection; rather, it *assumed* that the correlation between metabolite levels and the toxicity and efficacy of the drug was a law of nature, considering only what additional elements must be added to a law of nature claim to make it patent eligible.[158] The second, yet related, mistake is that the Court's reasoning supports the opposite ruling. The Court reasoned that a patented process that focuses upon the use of a law of nature must contain an additional "inventive concept."[159] Later in the opinion, the Court concedes that "a new way of using an existing drug" meets the requirements for a patent.[160] Further limiting this decision's future applicability, the Court never defines what Prometheus would have to do to add "enough" to the correlation for the claim to be patent eligible, failing to give the requisite direction needed to guide future innovations.

The fundamental flaws inherent in the *Prometheus* decision require a narrow reading of the ruling and certainly do not warrant the courts to find future diagnostic method patents to be invalid. The first flaw, the assumption that the correlation was a law of nature, is incorrect because the human body metabolizing a drug is at best a natural phenomenon, and the Prometheus patent "does not claim the process of metabolism."[161] Instead, the Prometheus patent aims to determine the relationship of a drug dosage to toxicity.[162] A law of nature that reveals a method of optimizing therapeutic efficacy without harmful side effects does not exist. Even if, for the sake of argument, a natural biological phenomenon determines a patient's response to a therapeutic product, nature does not weigh the potential risks and benefits of increasing or

156. *Id.* at 1292, 1305.

157. *Id.* at 1294.

158. Denise DeFranco, Mayo*: A Force to be Reckoned with*, 4 LANDSLIDE 24, 26 (2012).

159. *Prometheus*, 132 S. Ct. at 1294.

160. *Id.* at 1302.

161. DeFranco, *supra* note 158, at 27.

162. *Prometheus*, 132 S. Ct. at 1294.

decreasing a drug dosage, as does Prometheus's method patent. The Court's expansive approach as to what constitutes a "law of nature" stretches the statutory patentability requirements far too thin to serve the underlying purpose of promoting the invention of useful processes.

Further, when the *Prometheus* Court stated that using an existing drug in a new way meets the patent requirements, it seemingly forgot the basis of the Prometheus patent, thereby leading to the second flaw of the opinion. The Prometheus patent concerned the optimization of dosage of a drug used to treat disorders such as Crohn's disease.[163] In the past, this drug was used ineffectively, either causing harmful side effects or not having any effect at all.[164] By discovering specific levels of the drug metabolite that form guideposts for dosing by a physician, Prometheus's patent claim arguably did precisely what the Court stated would have been necessary to be patent eligible (by discovering a new way of using an existing drug). The lines set forth in the *Prometheus* decision seem arbitrary, and as a result, future courts should limit its application by reading the decision narrowly.

Even if the judicial branch does not agree that the *Prometheus* decision contains several fundamental flaws, the invalidation of the Prometheus patent should not translate into the invalidation of all future diagnostic device patents. The Prometheus patent claim arguably contained drafting weaknesses that can be easily avoided in the future.[165] Prometheus's patent claim, according to the Court, suffered from a lack of new implementation.[166] To avoid patent invalidation, future diagnostic device patent applicants can ensure that the claims indisputably include a new action step.[167] As long as applicants utilize stronger claim drafting, there is no reason that the *Prometheus* decision should invalidate future diagnostic device patents.

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163. *Id.* at 1294–95.

164. *Id.*

165. DeFranco, *supra* note 158, at 27.

166. *Prometheus*, 132 S. Ct. at 1297. The Court stated that the "administering" step "simply refers to the relevant audience," but added nothing else, since doctors administered these drugs long before these particular claims. *Id.* Further, the Court stated that the "wherein" clauses inform the doctors of the natural laws at play, "at most adding a suggestion that he should take those laws into account when treating his patient." *Id.* Lastly, the Court stated that the "determining" clause "tells the doctor to determine the level of the relevant metabolites in the blood" by whatever process he deems appropriate, and these "methods for determining metabolite levels were well known in the art." *Id.* at 1297–98.

167. DeFranco, *supra* note 158, at 27 (stating that the claim format in *Prometheus* can be avoided and "patent applications can simply avoid claiming pure correlations (natural or not) without also reciting action steps based on the correlation").

CONCLUSION

Better patient care and treatment outcomes depend upon the use of in vitro companion diagnostic devices, yet to date only nineteen FDA-approved diagnostic devices exist.[168] Despite a few potential shortcomings of granting patents, allowing diagnostics manufacturers to patent their discoveries is the only current business incentive to invest in the expensive research and development necessary to develop the devices. If Congress or the FDA decides to implement new legislation or regulatory standards that explicitly afford manufacturers the necessary industry protection, it is possible that patents will no longer be the only (or best) option for diagnostics manufacturers to gain market exclusivity.

Without drastic regulatory change, the *Prometheus* decision must not be read to invalidate future diagnostic device patents. The future of the personalized medicine industry and the possibility of improved treatment outcomes necessitate allowing diagnostics and pharmaceutical manufacturers to obtain patents on their inventions.

168. *See supra* note 12.