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Personalized Medicine, *Mayo*, and the Uncertain Future of Integrated Health Care

Peter S. Selness[*]

Personalized medicine is a dynamic and rapidly evolving approach to healthcare that promises to revolutionize the practice of medicine. Personalized medicine allows practitioners to tailor individualized medical treatments to patients based upon their unique genetic code and eliminates the old one-size-fits-all approach to healthcare.[1] There are numerous benefits offered by such an approach, but the recent holding in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* [hereinafter *Mayo*] poses a substantial threat to future development in this area of medicine.[2] *Mayo* held that a patent claiming a diagnostic method for determining the proper dosage of a medication was invalid because it claimed an underlying law of nature.[3] This holding has the potential to make patenting personalized medicine methods extremely difficult under 35 U.S.C. § 101 as many of these methods are closely tied to an underlying law of nature.[4] With personalized medicine methods

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1. Gary E. Marchant, *Personalized Medicine and the Law*, ARIZ. ATT'Y, Oct. 2007, at 12, 13.

2. *See generally* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 66 (2012).

3. *See id.* at 66.

4. *See* 35 U.S.C. § 101 (2012) (describing the boundaries of patentable subject matter); *see also* Christopher Bergin, *Take Off Your Genes and Let the Doctor Have A Look: Why the* Mayo *and* Myriad *Decisions Have Invalidated Method Claims for Genetic Diagnostic Testing*, 63 AM. U. L. REV. 173, 200 (2013) (explaining that a combination of the *Mayo* and *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* decisions "have likely eliminated genetic diagnostic methods as patentable subject matter under § 101").

struggling to fall within the bounds of patentable subject matter, companies' ability to turn a profit on expensive research and development efforts becomes questionable.[5] Without the profit protection granted to companies by a patent, other options need to be explored to ensure that research and development in the field of personalized medicine continues.

This Note seeks to examine the field of personalized medicine, identify any issues that may lead to future research stagnation, and propose several solutions to those issues. Part I will cover relevant background information on DNA, describe the danger posed by *Mayo* to the field of personalized medicine, and describe how personalized medicine operates as a new approach to healthcare. Part II will explain why the field of personalized medicine is threatened and propose ways to lessen the impact of *Mayo*. Part III will then describe ways to incentivize future research in this field without resorting to patent protection. This Note will then conclude by stating that the hazards discussed substantiate a significant threat to personalized medicine and several or all proposed solutions need to be adopted to ensure that research continues to develop in this field.

I. BACKGROUND

The background section will explain the basics of personalized medicine and the law affecting it. First, a brief explanation of DNA and its basic functions will be discussed to provide insight into the genetic component of personalized medicine. Second, a general overview of personalized medicine and its benefits to society will be described. Third, the methodology of personalized medicine will be analyzed. Fourth, the patentability of personalized medicine methods prior to *Mayo* will be explored to summarize the law of that time. Lastly, the *Mayo* decision will be summarized.

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5. *The Promise – and Perils – of Personalized Medicine*, KNOWLEDGE@WHARTON (Dec. 19, 2012), http://knowledge.wharton.upenn.edu/article/the-promise-and-perils-of-personalized-medicine/ (explaining that "the financial challenge is complicated by the motivations of profit-making enterprises . . . [because] companies have to recoup the development costs and see corporate profits").

A. BACKGROUND ON DNA

Understanding *Mayo* and the implications it may have for the future of personalized medicine requires a basic understanding of genetics and the role DNA plays in heredity. "DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms."[6] DNA is comprised of four basic building blocks called nucleotides, "adenine (A), guanine (G), cytosine (C), and thymine (T)."[7] Between these four chemical bases, thymine pairs with adenine and cytosine pairs with guanine.[8] The binding portions of these nucleotides are attached to a backbone structure comprising a phosphate and sugar molecule.[9] Covalent bonds between the sugar group of one nucleotide and the phosphate group of another gives rise to long chains of many nucleotides.[10]

The chains of nucleotides also bind with their matching base pairs through hydrogen bonds, giving rise to a macro structure consisting of two sugar phosphate backbones with nucleotide base pairs holding the chains together through hydrogen bonding.[11] The base pair bonding within the interior of the structure may be thought of as "steps" in a chain.[12] The hydrogen bonding patterns of these steps coupled with other intermolecular forces also cause the overall macro structure to twist, and thus take on the famous double helix structure DNA is known for.[13] "A good analogy for understanding DNA pairing is to think of a spiral staircase . . . [with] [e]ach step . . . bordered by two handrails."[14] The end result is a double helix consisting of two sugar phosphate backbones with hydrogen bound base pairs facing the interior and holding the structure together.[15]

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6. *What Is DNA?*, U.S. NAT'L LIBR. MED, https://ghr.nlm.nih.gov/primer/basics/dna (last visited Nov. 8, 2016).

7. *Id.*

8. *See id.* (illustrating the patterns of binding between base pairs that gives rise to the overall structure of DNA).

9. *Id.*

10. BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL (4th ed. 2002) (ebook), https://www.ncbi.nlm.nih.gov/books/NBK26821/.

11. *See id.*

12. A. JAMIE CUTICCHIA, GENETICS: A HANDBOOK FOR LAWYERS 7–8 (2009).

13. ALBERTS ET AL., *supra* note 10.

14. CUTICCHIA, *supra* note 12.

15. ALBERTS ET AL., *supra* note 10.

"It is because of the physical property of the DNA double-helix that the laws of genetics are made possible."[16] The sequence of nucleotides within a strand of DNA acts as a code containing hereditary information passed on from one generation to another, as well as the instructions for creating proteins.[17] The process of transcription unzips the double helix structure, matches each nucleotide with its corresponding pair, and reproduces a new strand of genetic information called messenger RNA (mRNA).[18] Nucleotides from the mRNA copy are then read in multiples of three and matched with the amino acid that they code for. The amino acids then bind together as more are matched with their coding section of mRNA, and a protein structure is assembled.[19] It is through this relationship between an individual's genetic code and the creation of protein structures that DNA is expressed.[20]

Not all DNA is expressed, however, as some portions do not lead to the creation of proteins. "The nucleotides that code for amino acids are 'exons,' and those that do not are 'introns.'"[21] In total, merely two percent of DNA actually codes for creating proteins.[22] The remaining ninety-eight percent of DNA is non-coding and referred to as introns.[23] So far, scientists have largely been interested in exon sequences of DNA and how genetic variations therein affect disease.[24] "The Centers for Disease Control and Prevention (CDC) states that nine out of the ten leading causes of death in the United States have a genetic / genomic component."[25] Naturally, this relationship between genetics and disease has been of great interest to researchers

16. *See* CUTICCHIA, *supra* note 12, at 7.

17. *See id.* (explaining that a type of four letter alphabet exists due to the nature of the nucleotides).

18. *See* CUTICCHIA, *supra* note 12, at 9–10 (explaining the fundamentals of the transcription process and how proteins are created from the underlying genetic code).

19. *Id.* at 9.

20. *Id.* at 8–9.

21. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2109 (2013).

22. Patchen Barss, *The Dark Corners of Our DNA Hold Clues About Disease*, SCI. AM. (Dec. 18, 2014), https://www.scientificamerican.com/article/the-dark-corners-of-our-dna-hold-clues-about-disease/.

23. *See id.*

24. *See, e.g.*, *Myriad Genetics, Inc.*, 133 S. Ct. at 2109.

25. CUTICCHIA, *supra* note 12, at 96.

and has played a large role in the development of personalized medicine.

B. OVERVIEW OF PERSONALIZED MEDICINE

Personalized medicine has been defined by the President's Council of Advisors on Science and Technology as "the tailoring of medical treatment to the individual characteristics of each patient . . . [and] the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment."[26] This tailoring of medical treatment to an individual is based upon the information contained in their genetic code.[27] Human DNA is roughly 99.9% identical, but the 0.1% that is different may lead to large differences in an individual's susceptibility to disease and response to certain medications.[28] An effective dosage of medication for one patient may have little to no effect on another.[29] By knowing both an individual's genetic make-up and the correlation between the presence or absence of certain genes, some of the guess work in calculating dosages for patients may be eliminated.[30] With personalized medicine, physicians are able to match a specific individual with the optimal dose of a medication based on that individual's genetic code; they can provide "the right patient with the right drug at the right dose at the right time."[31]

Such capabilities raise the question of what impact personalized medicine may have on future healthcare. One very promising benefit to healthcare lies in more favorable patient

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26. PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., PRIORITIES FOR PERSONALIZED MEDICINE 1 (2008), http://cdm266901.cdmhost.com/cdm/ref/collection/p266901coll4/id/1735 [hereinafter PRIORITIES].

27. *See id.* (explaining that physicians' goals have always been to tailor medical treatment to the specific needs of the patient, but recent developments in genomics has vastly changed the scope of what may be accomplished in this area).

28. KEWAL K. JAIN, TEXTBOOK OF PERSONALIZED MEDICINE 1 (2009).

29. *See* PRIORITIES, *supra* note 26, at 12 (illustrating how the drug warfarin was traditionally dosed through trial and error due to its widely varying effects on patients).

30. *See* U.S. FOOD & DRUG ADMIN., PAVING THE WAY FOR PERSONALIZED MEDICINE: FDA'S ROLE IN A NEW ERA OF MEDICAL PRODUCT DEVELOPMENT 6 (2013).

31. *Id.*

responses to medication.[32] Even today favorable responses to medications occur in a mere 30-70% of individuals.[33] With personalized medicine, this portion of the population could be isolated to maximize drug effectiveness.[34] Unfortunately, the correlation between an individual's genotype and the effect of a particular drug are not so simple. Many other factors "including age, sex, body weight, nutrition, organ function, infections, [and] comedications" also play a role, leading to complexities in predicting drug responses.[35] Adding an understanding of genetic predisposition to this list, however, will still lead to more favorable medical outcomes and better healthcare for all.[36]

Additionally, personalized medicine has the potential to: detect diseases at an earlier stage, reduce adverse drug reactions, reduce the time and cost of clinical trials, revive failed drugs, shift the emphasis in healthcare from reaction to prevention, and reduce the overall cost of healthcare.[37] Some of these promising traits of personalized medicine go hand in hand, such as switching from reactive to preventative medical care and an overall decrease in health care costs. Focusing on preventative medicine stems from "the ability to use molecular markers that signal disease risk or presence before clinical signs and symptoms appear."[38] Such a focus prevents diseases from reaching more serious stages, results in less medical treatment,

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32. *See* Wolfgang Sadee & Zunyan Dai, *Pharmacogenetics/Genomics and Personalized Medicine*, 14 HUM. MOLECULAR GENETICS 207, 207–09 (2005).

33. *Id.* at 208 (explaining that a significant portion of the population experiences adverse effects from drug exposure, causing "a poor risk/benefit ratio for a diverse patient population").

34. *See, e.g.*, *id.* at 207 ("If the frequency of an adverse event can be reduced from 5[%] to 2%, by excluding 10% of the targeted population, a drug gains a more favorable risk/benefit ratio and could advance to first-choice treatment, thereby gaining market share.").

35. *See id.* (explaining that the field of pharmacogenomics attempts to integrate genetic factors into this list to further the effectiveness of personalized medicine).

36. *See id.*

37. Edward Abrahams, Exec. Dir., Personalized Med. Coal., Presentation at the American Association of Clinical Chemistry Annual Meeting: Personalized Medicine: The Changing Landscape of Healthcare 5 (July 14, 2007).

38. PERSONALIZED MED. COAL., THE CASE FOR PERSONALIZED MEDICINE 8 (4th ed. 2014), http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_the_case_for_personalized_medicine.pdf.

and lowers the overall cost.[39] These and other benefits make the expansion of personalized medicine an obvious asset to society.

C. PERSONALIZED MEDICINE AS A METHOD

The field of personalized medicine may be thought of as both a diagnostic and therapeutic method for the purposes of patentable subject matter.[40] Personalized medicine has the potential to change the present healthcare system into integrated healthcare.[41] "Advances in medical genetics, molecular diagnostics, and genome-based medicines will enable integrated healthcare systems incorporating genetic screening, preven[]tion, diagnosis, therapy, and monitoring."[42] Such a method will allow physicians to provide comprehensive care for patients in a more effective and cost efficient manner.[43]

Integrated healthcare may be thought of as a unique approach to healthcare consisting of individual steps. The screening step of this method would detect genetic predisposition risk factors for diseases.[44] This step may then be followed by a disease predictive gene testing step to predict "those at risk of developing a certain disease."[45] Once a predisposition to disease has been identified, an early prevention step may be employed to either slow or prevent the disease's development.[46] Such a step may include correcting the risk factors already present, or engaging in preemptive treatment.[47] Lastly, when a disease has manifested itself in a patient, therapy may begin subject to continual monitoring.[48]

Integrated healthcare is the future of personalized medicine, but the current methods employed are somewhat more simplistic. Personalized medicine today generally entails "methods involving diagnostic testing and treatment

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39. *See id.* at 8–9 (explaining that early detection can also eliminate the need for further costly and invasive diagnostic testing later).
40. KEWAL K. JAIN, TEXTBOOK OF PERSONALIZED MEDICINE 55 (2d ed. 2015).
41. JAIN, *supra* note 28, at 54.
42. *Id.*
43. *Id.*
44. *See id.* at 55.
45. *Id.* at 54.
46. *Id.* at 56.
47. *Id.*
48. *Id.*

administration steps."[49] Such a system is aptly illustrated by *Mayo* where the patent in question had "claims covering processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases determine whether a given dosage level is too low or too high."[50] In relation to drug dosing, the basic method utilized consists of administering the drug to the patient and determining the level of resulting metabolite in the patient's bloodstream.[51] Despite the apparent simplicity, the method in *Mayo* is of great importance for personalized medicine and laid the foundation for future integrated healthcare systems.

D. PRE-*MAYO* DECISION PATENTABILITY IN PERSONALIZED MEDICINE

Several cases addressed the patentability of diagnostic methods and laws of nature prior to *Mayo,* and came to differing conclusions about the scope of patentable subject matter. *Diamond v. Chakrabarty* established the general proposition of the time that "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'"[52] In *Chakrabarty*, a plasmid was spliced into a bacterium which then allowed it to degrade hydrocarbon compounds.[53] Chakrabarty's patent application consisted of three claims, one of which claimed the bacterium itself.[54] The Supreme Court held that the bacterium was patentable subject matter under 35 U.S.C. § 101 and interpreted the terms "manufacture" and "composition of matter" broadly, so as to avoid the bar on patenting laws of

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49. Erik P. Harmon, *Promoting the Progress of Personalized Medicine: Redefining Infringement Liability for Divided Performance of Patented Methods*, 42 HOFSTRA L. REV. 967, 970 (2014).

50. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 72 (2012).

51. *See id.* at 74–75 (listing the steps of the claims involved in the *Mayo* patent).

52. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

53. *See id.* at 305 (explaining that the bacterium was human made and possessed characteristics like no other bacteria found in nature).

54. *See id.* at 305–06 (showing that three claims were scrutinized in this decision: a process claim for creating the bacterium, a claim for an inoculum, and a claim to the bacterium itself). Only the third claim was rejected by the Patent Office because bacteria are a product of nature. *Id.*

nature and naturally occurring products.[55] This holding was a severe blow to the product of nature doctrine, and "led at least two commentators to declare the product of nature doctrine effectively a dead letter in biotechnology."[56] It also had a direct impact on gene patents as the United States Patent and Trade Office (USPTO, or PTO) issued "the first patent covering human genetic material" shortly after *Chakrabarty* was decided.[57] Since then, a storm of gene patent applications has withstood the scrutiny of the USPTO.[58]

In contrast, method claims prior to *Mayo* did not enjoy the same level of freedom and deference to patentability. Under 35 U.S.C. § 101, patentable subject matter includes "any new and useful process, machine, manufacture, or composition of matter."[59] These categories are subject to the exceptions in *Diamond v. Diehr*, however, which stated that "[e]xcluded from such patent protection are laws of nature, natural phenomena, and abstract ideas."[60] In *Diehr*, a patent was found valid by the Court despite relying on the use of a mathematical equation, which is commonly classified as a law of nature.[61] Despite the holding in *Diehr*, many other method patents have been held invalidated based on the abstract idea exception to § 101.[62]

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55. *See id.* at 303; 35 U.S.C. § 101 (2012) (explaining three relevant points addressed when interpreting the language of the 1930 Plant Patent Act and 35 U.S.C. § 101).

56. Jonah D. Jackson, *Something Like the Sun: Why Even "Isolated and Purified" Genes Are Still Products of Nature*, 89 TEX. L. REV. 1453, 1455 (2011).

57. *Id.* at 1454.

58. *Id.* at 1454–55.

59. 35 U.S.C. § 101 (stating broadly the categories of patentable subject matter, subject to several exceptions).

60. Diamond v. Diehr, 450 U.S. 175, 185 (1981). Diehr had claimed a process for curing rubber utilizing the Arrhenius equation for calculating ideal rubber curing temperatures. *Id.* at 177–78 (explaining that the method utilized the Arrhenius equation to constantly determine the ideal temperature for the rubber molding process and the amount of time remaining before the rubber press was to open).

61. *See id.* at 175.

62. *See, e.g.*, Bilski v. Kappos, 561 U.S. 593 (2010); Parker v. Flook, 437 U.S. 584 (1978); Gottschalk v. Benson, 409 U.S. 63 (1972) (illustrating examples of method claims that were determined to be unpatentable subject matter based on an abstract idea). Furthermore, these cases show that utilizing a law of nature in a method is by itself insufficient to pass the § 101 bar on subject matter patentability. *Bilski*, 561 U.S. at 593; *Parker*, 437 U.S. at 584; *Gottschalk*, 409 U.S. at 63.

Several trends have emerged from the rejection of method patents based on abstract ideas. First, method claims that largely employ mental steps are generally ruled unpatentable subject matter.[63] Granting patents on purely mental processes has obvious negative connotations, and enforcing such patents would be nearly impossible. Second, method claims applying a law of nature are rarely valid.[64] When applying laws of nature, the patent claim must include something substantially more novel than the mere application of an existing law.[65] Lastly, creating a software program to digitize a method grants no additional level of novelty than would be present if the same process were carried out physically.[66] Taking a previously physical or mental process and coding it to be performed by a computer changes the medium of the process, not its level of novelty.[67] These three general trends concerning method claims had been well established prior to *Mayo*, and ultimately played an important role in the holding.

E. *MAYO* SUMMARY

In *Mayo*, the Supreme Court held that a diagnostic method for determining the proper dosing of thiopurine drugs was invalid as it impermissively claimed the "underlying laws of nature themselves."[68] Prometheus Laboratories held two patents concerning the use of thiopurine drugs for treatment.[69]

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63. *See Bilski*, 561 U.S at 595 ("Petitioners seek to patent both the concept of hedging risk and the application of that concept to energy markets . . . however, these are not patentable processes but attempts to patent abstract ideas."); *Gottschalk*, 409 U.S. at 68 (explaining that the method of hedging risk set forth in *Bilski* was unpatentable subject matter as it was merely a way of thinking for investment purposes). Furthermore, *Gottschalk* shows how a patent claim for a method of converting binary-coded decimal numbers into pure binary form by utilizing a computer was found to be non-patentable subject matter as it was an abstract idea. *Gottschalk*, 409 U.S. at 68.

64. *See Parker*, 437 U.S. at 594–95 (illustrating how a method of constantly updating alarm limits on a catalytic conversion was unpatentable subject matter as it merely applied a known law of nature to a known process).

65. *Id.* at 590 (explaining that merely including a final step of applying a law of nature does not make it patentable subject matter under § 101).

66. *See Gottschalk*, 409 U.S. at 67 (noting that the mathematical process at issue could be performed by older analog computers and by hand).

67. *Id.*

68. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 92 (2012).

69. *See id.* at 67.

These patents were based upon the metabolization of thiopurine when ingested by the human body.[70] The body metabolizes thiopurine drugs at different rates, resulting in different levels of metabolite in the patient's bloodstream.[71] Such differences in metabolization rates leads to difficulty in treating patients with the correct dosage of thiopurine.[72] The patent claimed a method for treating patients with thiopurine drugs based on the relationship between the level of metabolite in the patient's bloodstream and the resulting effectiveness or ineffectiveness of the treatment.[73] The method claims being challenged are largely set forth as follows:

> Each claim recites (1) an "administering" step—instructing a doctor to administer the drug to his patient—(2) a "determining" step—telling the doctor to measure the resulting metabolite levels in the patient's blood—and (3) a "wherein" step—describing the metabolite concentrations above which there is a likelihood of harmful side-effects and below which it is likely that the drug dosage is ineffective, and informing the doctor that metabolite concentrations above or below these thresholds "indicate a need" to decrease or increase (respectively) the drug dosage.[74]

The basis for challenging the patents stated that the method claimed a natural phenomenon relating to "the correlation[] between thiopurine metabolite levels and the toxicity and efficacy of thiopurine drugs."[75] The Court agreed and held the patents invalid because they were largely based upon this natural phenomena with no other steps adding anything to the realm of patentable subject matter.[76] In so doing, the Court analyzed each of the steps in the method looking for an inventive concept that was substantially more than the application of the natural phenomena, and then viewed the method as a whole with the same intent.[77] This two-step test has come to be called the *Mayo* test.

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70. *Id.*
71. *Id.*
72. *Id.*
73. *Id.*
74. *Id.*
75. *Id.* at 68 (illustrating that the human body naturally carries out the process of metabolizing thiopurine drugs in this way whether or not it is part of a method).
76. *Id.* (explaining that the court was also cautious to avoid granting patents on claims that did not genuinely apply the law of nature, but were merely clever drafting techniques to make it appear so).
77. *Id.*

When applying this methodology, the first "administering" step was found to merely identify a group that would be interested in the correlation between metabolite levels in the patient and the effectiveness of treatment.[78] Furthermore, the Court concluded that a "prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment."[79] The "wherein" step simply restated the natural law correlating the effectiveness of treatment with the amount of metabolite measured.[80] The method then relied upon the doctors to use the law in their decision making process.[81] Lastly, the "determining" step essentially instructed the doctors to measure the resulting level of metabolite in the patient's bloodstream.[82] Because the methods and technology used for measuring the metabolite were already well known and routine, this step added nothing that was not conventional or obvious.[83] The Court then viewed the method as an ordered combination and still found nothing that significantly added to the law of nature recited.[84] The Court determined that the process "simply tell[s] doctors to gather data from which they may draw an inference in light of the correlations."[85] As such, the claimed method in *Mayo* was found to be unpatentable subject matter and the patent was invalidated.

II. ANALYSIS

Mayo has potential to cause great harm to the field of personalized medicine, as this part will explain. Part II will begin by pointing out the specific dangers of *Mayo* to personalized medicine. It will then go on to explore the effects of

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78. *Id.* (stating that doctors had been using thiopurine drugs to treat patients with autoimmune disorders long before this patent emerged).

79. *Id.* at 78 (internal quotations omitted).

80. *Id.*

81. *Id.* (suggesting that such a step boils down to the application of the law of nature).

82. *Id.* at 79.

83. *Id.* (explaining that scientists routinely utilized this method of measuring metabolite levels when investigating the toxicity of thiopurine compounds).

84. *Id.*

85. *Id.* (concluding that the claims inform a target audience about a natural phenomenon and contain routine steps already well known by the scientific community that adds nothing to the claims when viewed as a whole).

Mayo when coupled with the *Myriad* decision. Part II will conclude by analyzing the post-*Mayo* effects on the patentability of personalized medicine methods.

A. *MAYO*'S EFFECT ON PERSONALIZED MEDICINE PATENTS

Mayo poses a unique danger to the field of personalized medicine because most personalized medicine patents resemble a more complicated version of the *Mayo* patent.[86] Personalized medicine is unique because it is an overarching process of carrying on healthcare rather than an individual medical procedure as depicted in *Mayo*.[87] It fits into a grey area of patent law that is neither the simplistic method of administering medication illustrated by *Mayo* or a tangible medical invention such as a medication. Instead, it is a hierarchy of steps involving known methods of genetic testing and the administration of existing medication based upon the results of those tests.[88] Such a system has the potential to revolutionize healthcare, but the current approach to the patentability of methods may make obtaining patent protection quite difficult.

The first issue raised by *Mayo* concerns the test set forth by the Supreme Court for dealing with issues of patentability under 35 U.S.C. § 101.[89] This process, known as the *Mayo* test, consists of two steps for determining if the subject matter in question is patentable: "(1) 'whether the claims at issue are directed to one of those patent-ineligible concepts'; and if so, then (2) 'whether it contains an "inventive concept" sufficient to "transform" the claimed abstract idea into a patent-eligible application.'"[90] This was the two-step test used to determine that there was no sufficient inventive concept in the scrutinized claims of *Mayo*.[91] Since its establishment, the *Mayo* test has invalidated numerous

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86. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66 (2012).

87. *See supra* Section I.C.

88. *See* PRIORITIES, *supra* note 26 (explaining the basics of the personalized medicine process).

89. *See* 35 U.S.C. § 101 (2012) (explaining what constitutes patentable subject matter).

90. Steven Swan, *Plugging the Rabbit Hole: The Supreme Court's Decision in* Alice, 2016 UTAH L. REV. 891, 893 (2016) (quoting Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355–57 (2014)) (explaining that the *Mayo* test was first laid forth in *Mayo*, but more formally codified in later cases such as *Alice*).

91. *See Mayo*, 566 U.S. at 66.

other patents for lack of an "inventive concept sufficient to transform the claimed abstract idea into a patent-eligible application."[92]

The *Mayo* two-step test may potentially invalidate a wide array of personalized medicine patents to which it is applied. Personalized medicine combines already established genetic tests, natural phenomena, and the distribution of existing medications.[93] Step one of the *Mayo* test will be satisfied because personalized medicine patents incorporate both laws of nature and abstract ideas.[94] Step two will then be applied to search for an inventive concept when viewing the claim as a whole.[95] It is likely that personalized medicine patents will also have issues passing this second step. Personalized medicine is largely based upon statistical correlations between subpopulations expressing a particular genetic variation and the resulting efficacy of medications.[96] This statistical correlation results from an underlying law of nature, leading to complications with patentability under the *Mayo* test. Thus, the resulting similarity between the claims invalidated in *Mayo* and the claims of personalized medicine patents will likely sway court opinion toward invalidation.[97]

The problem with the *Mayo* test lies in its failure to appreciate the dramatic impact personalized medicine will have on today's health care system. The truly innovative concept of personalized medicine lies in its ability to switch healthcare from reactive to preventative medicine tailored to each individual.[98] However, a simplistic application of the *Mayo* test to personalized medicine claims would likely fail to capture this innovative concept. As such, the *Mayo* test poses a significant

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92. *Alice*, 134 S. Ct. at 2355; *see, e.g.*, Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1377–79 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 2511 (2016); OIP Techs., Inc. v. Amazon.com, Inc., 788 F.3d 1359, 1362 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 701 (2015).

93. *See supra* Section I.C.

94. *See Alice*, 134 S. Ct. at 2355 (illustrating the criteria that trigger step one of the *Mayo* test).

95. *See id.* (showing that step two is an exception to invalidation under step one of the *Mayo* test, but case law has shown that it is a relatively high bar to meet).

96. *See Mayo*, 566 U.S. at 66.

97. *See id.*

98. Marchant, *supra* note 1, at 14.

threat to personalized medicine patents and may potentially invalidate the resulting method claims.

The second issue facing personalized medicine lies in the direct implication of declaring personalized medicine patents unpatentable subject matter. Patents are enabled under Article I, Section 8 of the United States Constitution.[99] The relevant language states that "Congress shall have power . . . [t]o 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."[100] The patent system, as it is today, has been derived directly from this constitutional language, and has been vital in promoting the development of technology.[101]

The underlying rationale for having a patent system, as stated directly in the Constitution, is to promote the progress of technological advancement.[102] This purpose may be further broken down into three theories: reward theory, disclosure theory, and specialization theory.[103] Reward theory considers patents to be a motivating factor for inventors to develop new technologies.[104] From a reward theory perspective, "patents are utilitarian tools employed via government action to enlist potential inventors in serving societal needs."[105] Disclosure theory focuses on the societal gain experienced from forcing inventors to disclose the inner workings of their inventions to the rest of the world as a result of the patent application process.[106] Lastly, specialization theory states that patents help with the organization and specialization of individuals in

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99. U.S. CONST. art. I, § 8.

100. *Id.* (showing that the importance of patents to the development of technological discoveries has long been recognized, dating all the way back to the United States Constitution).

101. *See* Richard S. Gruner, *Why We Need A Strong Patent System and When: Filling the Void Left by the* Bilski *Case*, 28 SANTA CLARA COMPUTER & HIGH TECH. L.J. 499, 499–503 (2012).

102. *See id.*

103. Gruner, *supra* note 101, 504–13.

104. *See id.* at 504–05 (explaining that reward theory is the oldest and most economically based theory for having a patent system).

105. *Id.* at 505.

106. *See id.* at 508 (stating that in many cases, inventors would otherwise keep the specifics of their inventions to themselves and others would be unable to benefit from the discoveries made).

bringing products to market.[107] For the purposes of personalized medicine, reward theory and disclosure theory are most relevant and play the most significant role in future technological advancement.[108]

Applying the *Mayo* test to personalized medicine patents will likely lead to the conclusion that those patents cover unpatentable subject matter, but why is this important? It has been argued that patenting discoveries in the field of personalized medicine or genetics is unnecessary or may even inhibit future innovation.[109] However, there are also several perspectives contrary to this point of view. The first argument in favor of patent protection for personalized medicine is based on the reward theory. Private companies are profit driven, and without a reasonable probability of profiting from research expenses, it is unlikely that any research will be conducted in the first place.[110] Patents play a vital role in a company's ability to ensure that they will be able to recoup the losses they sustain from research.[111] Furthermore, from an investor's perspective, "patents serve as a leading indicator of profits."[112] Attracting investors to a company also plays a significant role in a company's success, and "[c]ompanies with strong patent portfolios routinely outperform the S&P 500."[113] The bottom line is that patent protection for a company's inventions matters, and with little hope of obtaining a personalized medicine patent, research in this area will likely dwindle.

The second argument in favor of granting personalized medicine patents is based upon the disclosure theory. If a company is unable to obtain patent protection for their

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107. *See id.* at 511–12 (explaining the benefits patents confer to businesses in the organizational structure of the company).

108. *See id.* at 507, 509 (emphasizing the importance of reward and disclosure theories for future advances in patentable materials).

109. Marchant, supra note 1, at 19 (explaining that "excessive patenting in the genomics field . . . is impeding innovation by creating . . . a thicket of overlapping patent rights [that] precludes anyone from fully developing the patented technologies").

110. *See* Louise Basenese, *Patents Mean Profits . . . for Firms and Investors*, WALL ST. J. (July 14, 2016), https://www.wallstreetdaily.com/2016/07/14/asia-tech-patents/ (explaining that there are "wars" being fought in Asia over patent protection due to what patent protection means for the profitability of a company).

111. *Id.*

112. *Id.*

113. *Id.*

inventions, a logical alternative form of protection is resorting to trade secret.[114] Resorting to trade secret protection is less beneficial to society as it prevents the flow of information obtained from discoveries and does not allow others to build upon those discoveries.[115] Patents have the "twin purposes of encouraging new works and adding [knowledge] to the public domain."[116] If trade secret protection becomes widely utilized by personalized medicine researchers due to the unobtainability of patent protection, no new knowledge will be added to the public domain and the technological progress within this field will be greatly slowed.

Mayo will have a direct impact on the future development of personalized medicine unless patent law in this area is modified or alternative forms of incentives are pursued. The *Mayo* test as adopted by the Supreme Court is essentially a death sentence for personalized medicine patents, and will continue to affect the industry for years to come. In an attempt to remain profitable, companies will either abandon research in this area or seek trade secret protection to ensure no competitors benefit from their research. Either way, personalized medicine will be negatively impacted by *Mayo* to the detriment of society.

B. *MYRIAD*'S IMPLICATIONS COUPLED WITH *MAYO*

Shortly after *Mayo*, a second decision was handed down by the Supreme Court that also has a direct impact on the field of personalized medicine.[117] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* [hereinafter *Myriad*] considered the patentability of human genes.[118] In *Myriad*, Myriad Genetics discovered and isolated the location of the BRCA1 and BRCA2 genes.[119] These genes held importance as mutations in them had

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114. EarthCam, Inc. v. OxBlue Corp., 49 F. Supp. 3d 1210, 1224 (N.D. Ga. 2014) (defining trade secrets as "information . . . which is not commonly known by or available to the public . . . [which] [d]erives economic value . . . from not being generally known to . . . other persons who can obtain economic value from its disclosure or use").

115. *See id.* (explaining that the information must be kept with reasonable efforts at secrecy from others who could economically gain from this information in order to qualify for trade secret protections).

116. Eldred v. Ashcroft, 537 U.S. 186, 227 (2003).

117. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2107 (2013).

118. *Id.*

119. *Id.* at 2112.

been linked to an increase in both breast and ovarian cancer for women.[120] Knowing the location and the specific nucleotide sequence of these genes allowed Myriad to develop a medical test for ascertaining a patient's risk of developing cancer.[121] Myriad then patented their discoveries, and claimed the BRCA1 and BRCA2 genes in their patent application.[122] *Myriad* was filed when the patentability of isolated human DNA was brought into question for being a product of nature.[123] In the end, the Court concluded that cDNA[124] was patentable subject matter, but isolated DNA was not, as it existed in nature.[125]

Myriad imposes an additional road block to the patentability of personalized medicine. Personalized medicine is based upon the specific genetic code of each individual patient and any predisposition to disease or the effectiveness of medication that may result.[126] Therefore, one of the steps in a personalized medicine method requires identifying genetic mutations that may lead to these predispositions.[127] As previously noted, the personalized medicine method itself will likely be unpatentable due to *Mayo*. When seeking an alternative route to securing patent protection for personalized medicine methods, companies may have attempted to patent the genes utilized as part of each method. Holding a gene patent (when still allowable before *Myriad*) allowed the patentee to prevent others from isolating and manipulating the patented gene outside the body, and prevented competitors from performing genetic testing on that gene. Such a patent would have allowed the patent owner to exclude others from conducting genetic tests on those genes and would have made carrying out the personalized medicine method impossible. However, because of *Myriad*, this approach is no longer possible and personalized medicine methods cannot obtain patent protection through the

120. *Id.*

121. *Id.* (stating that a mutation in one of these genes could signal up to a sixty-five percent increase in the risk of developing cancer).

122. *Id.* at 2113 (explaining that Myriad claimed both the isolated DNA and cDNA of the BRCA genes).

123. *See id.* at 2114.

124. *Id.* at 2115.

125. *Id.* at 2116 (explaining that Myriad had not invented or discovered the isolated DNA, they had merely located its position on the BRCA genes).

126. JAIN, *supra* note 28, at 2.

127. *See* JAIN, *supra* note 40, at 55.

genes of interest, nor the method used.[128] Thus, *Mayo* and *Myriad* together block many avenues to patent protection for personalized medicine methods.

C. POST *MAYO* DECISION

Mayo was decided several years ago, and the effects it has had on diagnostic method patents, such as those in the field of personalized medicine, have been immense.[129] *Myriad* also illustrates a sharp change in the Supreme Court's view of patents involving a genetic component, and was a significant departure from the "anything under the sun" philosophy held before.[130] Besides *Myriad*, however, several other cases illustrate just how significant the impact of *Mayo* has been. In *Alice Corp. Pty. Ltd. v. CLS Bank International* [hereinafter *Alice*], the two-step test conceptualized in *Mayo* was solidified and applied to another method claim.[131] The patent at issue in *Alice* concerned a computer system that acted as an intermediary to negate settlement risk for two parties.[132] The patent claimed "a method for exchanging financial obligations."[133] The Court applied the *Mayo* two-step test to this claim and found that it was directed toward the abstract idea of intermediary settlement, and that digitizing this idea added nothing to transform an abstract idea into patent-eligible subject matter.[134] *Alice* thus further solidified and expanded the bounds of the *Mayo* test and reaffirmed the policy of subjecting method claims to additional scrutiny when abstract ideas are present.

In addition to *Alice*, *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* invalidated yet another diagnostic method patent,[135] and

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128. *See Myriad Genetics, Inc.*, 133 S. Ct. at 2107.

129. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 91 (2012).

130. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (internal quotations omitted); *see also Myriad Genetics, Inc.*, 133 S. Ct. at 2109.

131. Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347, 2350–51 (2014).

132. *See id.* at 2349 (explaining that the computer system would act as a third party that could assure the other parties that all financial obligations would be fulfilled).

133. *Id.*

134. *See id.* at 2350 (stating that the same issue from *Mayo* was present in this case and that applying an abstract idea is not enough to obtain patent protection).

135. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1378 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 2511 (2016).

made obtaining such patents even more difficult. *Ariosa* scrutinized a patent that utilized cell-free fetal DNA (cffDNA) in a woman's bloodstream to determine if she is pregnant.[136] The patent claimed a method for obtaining a sample of cffDNA, amplifying the sample, detecting the sample, and then determining certain characteristics of the fetus such as gender and possible genetic defects.[137] The Court applied the *Mayo* test and found that the method began and ended with a naturally occurring phenomenon: the presence or absence of cffDNA in the mother's bloodstream.[138] Moving on to step two of the *Mayo* test, the Court found that the method simply applied commonly known techniques to a naturally occurring phenomenon, and that the only innovation stemming from the patent came from the discovery of cffDNA.[139] The Court thus invalidated the patent for claiming unpatentable subject matter.[140] Of particular relevance to personalized medicine, however, Sequenom argued that their patent should be upheld as it "combined and utilized man-made tools of biotechnology in a new way that revolutionized prenatal care."[141] A very similar argument may be made for the effects of personalized medicine on general healthcare, but the Court found such revolutionary discoveries still unworthy of patent protection.[142]

Since *Mayo* was decided, further decisions have continued to chip away at the chances of a personalized medicine method obtaining a patent. The *Mayo* test has become more broad and encompassing, striking down more and more diagnostic method patents. These effects have also been felt within the United States Patent and Trade Office. "[F]ollowing a key Supreme Court decision in 2012, the US Patent and Trademark Office (USPTO) was nearly four times more likely to deem . . . [applications of laws of nature] unpatentable — and applicants were less than half as likely to overcome those

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136. *Id.* at 1373.

137. *See id.* (explaining that only the method was claimed in the patent, not the cffDNA itself).

138. *See id.* at 1376.

139. *See id.* at 1377 (stating that discovering cffDNA was the only innovative part of the method, but as cffDNA is naturally occurring it is not patent eligible subject matter).

140. *See id.* at 1378.

141. *Id.* at 1379 (internal quotations omitted).

142. *See id.*

rejections."[143] Indeed, some view the *Mayo* decision as "the death knell for patents relating to personalized medicine, diagnostics, and biotechnology."[144]

III. SOLUTIONS FOR INCENTIVIZING FUTURE RESEARCH

Part III will attempt to address the issues facing the field of personalized medicine raised in Part II. It will start by proposing possible forms of claims drafting that may confer a greater deal of patentability on personalized medicine methods. Next, the benefits of increased funding for a central genetic database will be discussed. Short periods of regulatory exclusivity from the Food and Drug Administration (FDA) will also be analyzed as a possible way to grant a temporary market monopoly to the developer of a personalized medicine method without issuing a patent. Also, a cash incentive program will be explored as a way to fill in present short comings in the patent system. Lastly, this Part will conclude by proposing a modified compulsory licensing system to further incentivize research in the field of personalized medicine.

A. NEW FORMS OF CLAIMS DRAFTING

One possible avenue for circumventing the statutory bar imposed by 35 U.S.C. § 101 on unpatentable subject matter lies in new and innovative forms of drafting patent claims. It may be possible to obtain a patent on a personalized medicine method if the language of the patent's claims provides an avenue for step two of the *Mayo* test to find a substantially innovative concept. The chances of creative lawyering being a viable solution in the eyes of the Court depends upon how broadly *Mayo* is interpreted. If *Mayo* leads courts to presume that diagnostic method claims are unpatentable subject matter as a rule with few exceptions, then no amount of creative claims drafting will be able to convince them otherwise. As the lower court's interpretation of *Mayo* is still being established, however, some methods of claims drafting may aid in the patent approval process.

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143. Heidi Ledford, *US Personalized-Medicine Industry Takes Hit from Supreme Court*, NATURE (Aug. 17, 2016), http://www.nature.com/news/us-personalized-medicine-industry-takes-hit-from-supreme-court-1.20436.

144. Sanjesh P. Sharma, *Patent-Eligible Subject Matter in Light of* Mayo v. Prometheus, 24 INTELL. PROP. & TECH. L.J. 9, 9 (2012).

First, guidance from the PTO has stated that claiming a law of nature or other exception to patentable subject matter is impermissible, and claims "should include other elements or combination of elements such that, in practice, the claimed product or process amounts to significantly more than a law of nature[.]"[145] The wording from this memorandum indicates that certain combinations of elements added to a claim involving a law of nature may be enough to transform the nature of the claim to cover patentable subject matter.[146] Toward this end, the inclusion of nonobvious elements in the claim may well aid in this transformation.[147] In the *Mayo* decision, the "Court found it relevant and important that the additional steps . . . were 'well understood, routine, and conventional.'"[148] Therefore, by including non-routine or unconventional steps in the diagnostic method, it may be possible to pass step two of the *Mayo* test when viewing the claim as a whole.[149] Possibilities for achieving this in the field of personalized medicine include using a novel genetic test for the screening step, using a novel antibody for the monitoring step, or administering a novel medication for the therapy step. As such, the inclusion of non-obvious elements in a diagnostic method has potential to transform the claim into patentable subject matter.

A second way to draft more patentable subject matter friendly claims lies in narrowing the scope of those claims.[150] In *Mayo*, the Court viewed the claims unfavorably because the breadth of the claims appeared to partially encompass a law of nature.[151] If a claim necessitates the use of a law of nature, "one must do more than simply state the law of nature while adding

145. Memorandum from Andrew H. Hirshfield, Associate Comm'r, U.S. Patent & Trademark Office, on Supreme Court Decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* to Patent Examining Corps (Mar. 21, 2012), www.uspto.gov/patents/law/exam/mayo_prelim_guidance.pdf.

146. *Id.*; *see* Angela L. Morrison, Mayo v. Prometheus*: Patent Eligibility of Claims Covering Natural Laws*, 41 COLO. LAW. 77, 82 (2012).

147. *See* Morrison, *supra* note 146, at 82.

148. *Id.*

149. *See id.* at 82–83.

150. *See id.* at 83 (stating that it is important to use active steps when drafting claims and be specific as to what is required by each step).

151. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 72–73 (2012).

the words 'apply it.'"[152] Narrowing the scope of the claims sets forth a more specific method with limits on what is being claimed, and may distance the method from the law of nature.[153] While it is important to distance the patent application from claiming the underlying law of nature, however, this also must be balanced with the value lost to the patent through excessive narrowing. For personalized medicine, claims may be narrowed by stating exactly what genetic test is to be used, what antibody is to monitor results, and what medication is to be administered for therapy, based upon specific criteria. Coupling this specificity with the previously mentioned novel elements may yield a claim that, when viewed in its entirety, is substantially more than the application of a natural law and satisfies the *Mayo* test's second step.

A third possibility for drafting claims around the *Mayo* test lies in focusing claims on a man-made component integral to the diagnostic method, rather than the method itself.[154] This approach comes with some obvious limitations, namely, the method must at some point rely on the use of a man-made sample. Creation of such a sample for purposes of personalized medicine would most likely necessitate the binding of DNA probes to the patient's genetic material during the genetic sequencing step.[155] Such a step would result in the creation of a non-naturally occurring complex that could be patented as part of the method. Despite the Supreme Court invalidating the machine or transformation test as the sole test of patentability for methods in *Bilski*, it was still acknowledged that "the machine-or-transformation test is a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101."[156] Therefore, including a step that transforms a sample into something man-made and

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152. *See* Hirschfield, *supra* note 145 (explaining that the distinction between patentable and unpatentable subject matter lies in applying the law in a limited fashion rather than claiming the law itself).

153. *See, e.g.*, Morrison, *supra* note 146, at 80.

154. Holly Atkinson et al., *Personalized Medicine Patents at Risk: Tips for Battling* Prometheus *and* Myriad *to Obtain Claims to Diagnostics*, FINNEGAN (Mar. 2013), http://www.finnegan.com/resources/articles/articlesdetail.aspx?news=d71205da-cb48-4827-9a8c-fde729146046.

155. *See id.* (stating that the creation of a non-naturally occurring antibody-biomarker complex as an intermediate should convey patentability).

156. Bilski v. Kappos, 561 U.S. 593, 604 (2010).

non-naturally occurring may give more weight to a finding of patentability for a diagnostic method claim.

In summary, it may still be possible to obtain a patent for a personalized medicine method through creative claims drafting techniques. Such a possibility still depends largely upon the manner in which the Court interprets and applies the *Mayo* test. A combination of the discussed techniques may aid in distancing the patent application from claiming an underlying law of nature and grant the claims a certain degree of novelty. If personalized medicine patents remain unobtainable under this approach, however, other forms of incentives may need to be explored.

B. INCREASED DEVELOPMENT OF GENETIC DATABASES

Additionally, some "scholars have proposed a variety of fixes that wouldn't require overturning *Mayo* but which might compensate for its potential negative impact on investment."[157] One method for supporting the field of personalized medicine without delving into the issue of patentability lies in providing funding for genetic databases.[158] The human genome and the implications of genetic differences between individuals is an extremely complex area of science. Sequencing a single patient's exome results in roughly sixty million data-points.[159] All of that data must be analyzed to determine the genetic implications for a single patient. Furthermore, trends in the expression of specific genetic variations only emerge when dealing with a large sample size including numerous individuals who share the same genetic variation. "Ideally, doctors could tap into a single, large database filled with anonymous genetic information — biomarkers tied to patient demographics tied to specific drugs and treatments — to help doctors make decisions about each individual's medical path."[160]

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157. Thomas Cotter, Patent Wars: How Patent Disputes Impact Our Daily Lives (Nov. 4, 2016) (unpublished book) (on file with Thomas Cotter of the University of Minnesota Law School).

158. *See id.* (listing the subsidization of genetic databases among other suggestions for offsetting the negative impact of *Mayo*).

159. Vojtech Huser et al., *Developing Genomic Knowledge Bases and Databases to Support Clinical Management: Current Perspectives*, 7 PHARMGENOMICS & PERS. MED. 275, 276 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4175027.

160. Dawn McMullan, *What Is Personalized Medicine?*, GENOME (Jan. 19, 2017), http://genomemag.com/what-is-personalized-medicine.

Having one central database all practitioners could consult for guidance in the interpretation of genetic variations would greatly aid practitioners' ability to make informed decisions in the field of personalized medicine.[161] Understanding the basics of what genetic variations mean for an individual's health is central to practicing personalized medicine, and having a single genetic database to aid in physicians' decisions would lead to better medical care for all. Databases help in this area because they reduce the typical number of relevant variants in a patient's exome from roughly twenty thousand to a more workable number.[162] Knowing which variants in a patient's genetic code carry significance plays a pivotal role in the process of personalized medicine, and the development of genetic databases will play a large role in the future success of personalized medicine.

There are several ways to improve the existing genetic databases to aid in the development of personalized medicine. First, all genetic data contained in existing databases should be consolidated into a single location.[163] A recent study concluded that there are 314 distinct genetic databases maintained by a variety of institutions.[164] Consolidating all the information contained in these databases into a single, well maintained database would significantly aid practitioners in their understanding of genetic variation implications. A second way to improve the function of genetic databases for personalized medicine is to tailor the accessibility and interface toward physicians and genetic counselors rather than researchers.[165] Lastly, databases should be adapted to contain information on not just a patient's genotype, but also their long term phenotype to better understand how genetic variants are expressed over a long period of time.[166] Such changes would greatly aid in

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161. *See* Huser, *supra* note 159, at 275.

162. *See id.* (stating that unfortunately there is no one central database that provides a complete set of variants).

163. *See id.*

164. *See id.* at 278 (explaining that some of these databases may no longer be maintained, however).

165. *See id.* at 281 (stating that a combination of targeting physicians as the primary platform users and establishing training programs on the platform's functions would aid in adapting genetic databases for use in the field of personalized medicine).

166. *See id.* at 280 (explaining that such a change raises data privacy issues that will need to be addressed as patient-level data is retained).

understanding the genetic component of personalized medicine, but most likely could only be carried out by government action due to the size and financial constraints of such a project.

C. SHORT PERIODS OF REGULATORY EXCLUSIVITY

An additional possibility for ensuring sufficient incentive exists to spur research in the field of personalized medicine lies in making modifications to the existing regulatory scheme governing this area. Several organizations play a role in regulating personalized medicine. The Centers for Medicare and Medicaid Services (CMS) was established by Congress and granted the power to regulate "all clinical laboratories performing genetic testing"[167] to ensure compliance with applicable standards.[168] The goal of the CMS was to guarantee quality in the procedures used for clinical testing.[169] As such, the genetic testing utilized in personalized medicine falls squarely within the regulatory powers of the CMS.[170] This is but a small portion of a personalized medicine method, however, giving the CMS a relatively small regulatory role in this area.

The regulatory body tasked with the most significant responsibility pertaining to personalized medicine is the Food and Drug Administration.[171] The FDA is tasked with the regulation of all drugs and medical devices.[172] The FDA thus regulates the safety and efficacy of any drugs utilized in personalized medicine methods, as well as diagnostic testing, effectively granting it jurisdiction over the entire method.[173] Despite regulatory difficulties that most certainly will arise when applying the current regulatory scheme to personalized medicine, the FDA has demonstrated an eagerness to tackle the challenge.[174] The FDA has stated: "From FDA's perspective, personalized medicine promises to increase benefits and reduce risks for patients by improving both the safety and efficacy of

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167. *Regulation of Genetic Tests*, NAT'L HUM. GENOME RES. INST. (June 21, 2016), https://www.genome.gov/10002335/regulation-of-genetic-tests/.

168. *See* 42 C.F.R. § 493.551 (2016) ("CMS may deem a laboratory to meet all applicable CLIA program requirements.").

169. *See Regulation of Genetic Tests*, *supra* note 167.

170. *See id.*

171. *See id.*

172. *See id.*

173. *See id.*

174. U.S. FOOD & DRUG ADMIN., *supra* note 30, at 11.

medical products."[175] Furthermore, personalized medicine has the potential to allow medications tailored for use in a particular population of medical candidates to pass FDA regulatory processes where the medication may previously have failed to meet FDA standards under the one-size-fits-all approach.[176] As such, the FDA is in the best position to incentivize continued research in this area from a regulatory standpoint.[177]

Per 21 C.F.R. 314.108, a period of exclusivity may be granted by the FDA to a newly developed drug.[178] This period of exclusivity prevents other drugs similar in composition and purpose from attaining FDA approval for a set period of time.[179] In effect, a market monopoly is granted to the holder of the FDA exclusive drug as without FDA approval, drugs created by competitors cannot be marketed to consumers.[180] The extent of the period of exclusivity granted varies depending upon the chemical composition of the new drug.[181] The FDA's Center for Drug Evaluation and Research exclusivity board was established to determine appropriate time frames of exclusivity on a case to case basis for new drugs.[182] Under the current system, time frames of exclusivity may range from 180 days to seven years.[183] Patents play no role in the FDA's decision to grant exclusivity, placing the FDA in an excellent position to grant a market monopoly of a similar nature to that of a patent

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175. *Id.*

176. *See id.* at 11–12.

177. *See id.* at 13 (explaining that many drug development failures stem from the failure to meet efficacy levels and that improving the understanding of the underlying causes of these failures should increase the number of drugs shown to be safe and effective).

178. 21 C.F.R. § 314.108 (2016) (stating that exclusivity does not require a pre-existing patent and does not prolong the life of patents).

179. *See generally Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm (last visited Feb. 28, 2017).

180. *See id.*

181. *See* Renu Lal, *Patents and Exclusivity*, FDA/CDER SBIA CHRON., May 19, 2015, at 2–3, http://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf.

182. *See id.* at 3 (stating that the focus of the board is on "whether and what type of exclusivity should be granted and the appropriate scope of exclusivity grants").

183. *See id.* at 2–3.

without adhering to the rules that govern patentable subject matter.

The FDA's exclusivity system could easily be expanded to include personalized medicine methods, creating an alternative pathway to achieving a temporary market monopoly to incentivize continued research in this field. The exclusivity board would have to create new standards for determining appropriate time frames of exclusivity, but could otherwise continue functioning normally. In practice, a new personalized medicine method could be granted FDA exclusivity protection upon passing FDA regulations and prevent competitors from immediately marketing a similar method. The period of exclusivity would not last as long as a patent, but still would provide additional peace of mind to researchers and be a viable incentive to potentially replace that of a patent.

D. CASH INCENTIVE PROGRAM

Additionally, research on personalized medicine may be further incentivized through establishing an incentive program that offers cash rewards to researchers for their discoveries. A prize system would incentivize researchers in the personalized medicine profession to continue their work despite the financial uncertainty associated with the inability to obtain a patent.[184] It would allow researchers to recoup the expenses incurred during the research process without granting them patent protection.[185] Offsetting research costs through prizes rather than patents would also not impede the use of other discoveries within the personalized medicine field.[186]

A cash incentive system would award prizes for contributions to the field of personalized medicine, and prizes are an extremely effective incentive. "After all, if there's one thing that defines modern economics, it's that incentives matter,

184. *See, e.g.*, Joesph E. Stiglitz, *Prizes, Not Patents*, PROJECT SYNDICATE (Mar. 6, 2007), https://www.project-syndicate.org/print/prizes--not-patents (arguing that prizes could be part of a portfolio of incentives including patents which would encourage investment into drugs that have been overlooked by the current system).

185. *Id.*

186. *Id.*

and a prize is as obvious an incentive as one could imagine."[187] A prize system carries several distinct advantages in comparison to the patent system. Primarily, as it relates to personalized medicine, prizes may be awarded for research in areas typically off limits for patent protection. Such capabilities would negate the significance of *Mayo* in relation to the field of personalized medicine.[188] The flexibility of a prize system would allow the government to incentivize research in any area of interest without being restricted by the limitations of the patent system.[189] Prizes would also allow the government to set firm boundaries on what discoveries would be eligible for the prize, and thus grant greater specificity in what can be incentivized. "A prize is for a particular accomplishment specified in advance, while one can get a patent for anything that meets the relevant statutory definition."[190] Specific areas of personalized medicine most in need of technological development could therefore be prioritized through granting larger prizes in those areas.

A prize system would be particularly beneficial for the field of personalized medicine, as *Mayo* has made it difficult to obtain patents on diagnostic methods.[191] The adoption of such a monetary reward system has been previously considered to compensate for shortcomings in the patent system.[192] A prize system was proposed for research on drugs and other healthcare products by The Medical Innovation Prize Act of 2005 (MIPA).[193] In this proposal, 0.5% of the country's total GDP was to be pooled each year to form a prize fund that could be awarded to researchers.[194] The goals established were "1) to provide incentives for R&D investment in new and significantly better

187. Timothy J. Brennan, *Prizes Versus Patents: A Comment on Jonathan Adler's* Eyes on a Climate Prize: Rewarding Energy Innovation to Achieve Climate Stabilization, 42 ENVTL. L. REP. NEWS & ANALYSIS 10719 (2012).

188. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 66 (2012).

189. *See* Brennan, *supra* note 187, at 10720.

190. *Id*.

191. *See* Jenny Shmuel & Megan Chacon, *Diagnostics Patent Eligibility: A Turning Point Approaches*, LIFE SCIS. INTELL. PROP. REV. at 4 (Jan. 27, 2016), http://www.lifesciencesipreview.com/article/diagnostics-patent-eligibility-a-turning-point-approaches.

192. Marlynn Wei, *Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005*, 13 B.U. J. SCI. & TECH. L. 25, 25–26 (2007).

193. *Id*. at 28.

194. *See id*. (explaining that strict criteria would be established to determine when a prize would be awarded).

medicines; 2) to enhance access to medicines; and 3) to focus more resources in non-profitable areas such as global infectious diseases, 'orphan drugs' and neglected diseases."[195] The MIPA was never approved by Congress,[196] but substantially the same system could be adopted as an alternative to patents in the field of personalized medicine.

Several concerns with the MIPA lead to its ultimate downfall in Congress. Primarily, there was a great deal of uncertainty surrounding the abandonment of the patent system utilized since the drafting of the United States Constitution in favor of a prize system.[197] A complete abandonment of the patent system in favor of a prize system appeared too dramatic a solution to many.[198] A second issue raised in relation to a prize system concerned determining the appropriate size of the monetary reward.[199] A fine line had to be established so that prizes would be large enough to create a significant incentive for researchers, without being so large as to be a significant economic burden on the country.[200] These issues would not be a problem if a prize system were adopted for personalized medicine, however, because the patent system would still be in place and the prizes would merely act as a way to incentivize areas of research not qualified for patent protection. Therefore, the adoption of a prize system would likely be a significant form of incentive for research in the field of personalized medicine without impeding or abolishing the existing patent system.

E. COMPULSORY LICENSING

Personalized medicine may also benefit from the adoption of a modified compulsory licensing system. Under such a system, a type of pseudo-patent on personalized medicine methods could

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195. *See id.* (stating that a prize system would allow for significant prizes for large innovative contributions to society and lesser prizes for smaller contributions).

196. *H.R. 417-Medical Innovation Prize Act of 2005*, CONGRESS.GOV, https://www.congress.gov/bill/109th-congress/house-bill/417/all-actions (last visited Mar. 3, 2017) (showing that the bill was last referred to the Subcommittee on the Courts, the Internet, and Intellectual Property on Mar. 2, 2005).

197. *See* Wei, *supra* note 192, at 31.

198. *See id.* at 32.

199. *See id.* at 32–33 (explaining that administrative difficulties were the greatest roadblock to the prize system).

200. *See id.* (stating that excessive prize awards could lead to "resource duplication and favoritism").

be issued with the caveat that the patent is subject to mandatory compulsory licensing. Compulsory licensing is a type of exception to the exclusionary rights granted to the holder of a patent.[201] One form of compulsory licensing grants the government the ability to convey licenses on patented inventions to third parties without the consent of the patent holder.[202] It prevents patent holders from failing to utilize their patents while also preventing competitors from benefiting from the relevant invention.[203] In such a situation, the government may force the offending patent holder to license the invention to a third party who may benefit from it.[204] The United States has never implemented a formal compulsory licensing scheme, but many foreign countries have made use of compulsory licenses to varying degrees.[205] Compulsory licensing has been utilized sparingly within the United States and only in relation to matters of national interest, such as the Atomic Energy Act of 1948.[206]

Compulsory licenses have been criticized within the United States for several reasons. First, the level of required patent misuse that would allow a third party to obtain a compulsory license is a fairly high standard to meet and would rarely occur, making a compulsory licensing system largely useless.[207] There have been very few cases of patent suppression within the United States due to the large time and monetary investment required to obtain a patent in the first place.[208] Second, it is argued that forcing a compulsory license on a patent holder would prevent them from recouping their research expenses and

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201. Paul Gormley, *Compulsory Patent Licenses and Environmental Protection*, 13 TUL. ENVTL. L.J. 131, 135–36 (1993).

202. *See id.*

203. *See id.*

204. *See id.* (explaining that compulsory licensing has also been used for issues such as defense and security, in addition to atomic energy).

205. Cole M. Fauver, *Compulsory Patent Licensing in the United States: An Idea Whose Time Has Come*, 8 NW. J. INT'L L. & BUS. 666, 674 (1988).

206. *See id.* at 670 n.21 (explaining that this provision was later amended to eliminate the compulsory licensing portion).

207. *See id.* at 674–75.

208. *See id. But see* Cont'l Paper Bag Co. v. E. Paper Bag Co., 210 U.S. 405, 424–29 (1908) (showing one of the few instances where an important patent was not sufficiently worked by the patent holder).

devalue the entire patent system.[209] This is particularly relevant as compulsory licenses would play a large role in combating high prices on products that are cheap to create, but stem from expensive research and development investments.[210] Lastly, language from the Constitution is frequently cited to fight compulsory licenses.[211] Under Article I, Section 8 of the United States Constitution, "The Congress shall have power . . . [t]o 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."[212] This section states that Congress may grant the "exclusive" rights of an invention to the holder of the patent. It is argued that a constitutionally backed exclusive right is not one that may be diminished because the government thinks that right may be put to better use elsewhere.[213] These arguments have held compulsory licensing at bay, and the United States has never adopted such a system.

When applied to personalized medicine, however, there is a more compelling argument for adopting a compulsory licensing system. Incentivizing personalized medicine research through a modified compulsory licensing system could be one way to address the issue of unpatentability currently facing the industry. The primary difference between the proposed system and those adopted by other countries lies in the unpatentability of personalized medicine methods. *Mayo* blocks the issuing of patents on diagnostic methods, such as those employed in personalized medicine, making it impossible to obtain a compulsory license on a patent that doesn't exist.[214] However, if a type of "pseudo-patent" (for lack of a better term) were to issue on personalized medicine methods, under the caveat that the pseudo-patent is subject to obligatory licensing, this issue may be avoided.

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209. *See* Gormley, *supra* note 201, at 136 (stating that the pharmaceutical industry would be particularly vulnerable to these concerns due to the substantial research costs associated with bringing a new drug to market).

210. *See id.*

211. *See* Fauver, *supra* note 205, at 677–78.

212. U.S CONST. art. I, § 8 (capitalization in original omitted).

213. *See* Fauver, *supra* note 205, at 678.

214. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 92 (2012).

Such a system would grant researchers the ability to obtain some form of protection on their invention, but wouldn't grant them the ability to exclude others from utilizing it. Instead, if a third party wished to work the patent, they could apply for a compulsory license, given that specific criteria are met, and the compulsory license would issue. The third party would then be obligated to pay royalties to the holder of the pseudo-patent. Furthermore, the societal detriments of market monopolies would not exist, but the original inventor would still be placed in a superior financial position to competitors from the royalties collected. Thus there would still be a financial incentive to conduct research in the field of personalized medicine, but there would be no fear of granting a patent that essentially monopolizes the underlying law of nature relied upon.

Pseudo-patents would also not run into any of the problems associated with a regular compulsory licensing scheme as they would fill in gaps where patents cannot issue in the first place. The first argument against compulsory licensing would not apply as it relates to the difficulty of proving that a patent holder is failing to sufficiently utilize a patent. The second argument would also be inapplicable as pseudo-patents would most certainly help inventors recoup their losses through the royalty payments received, whereas without a pseudo-patent scheme they would have no additional source of income. Lastly, the constitutional argument would not apply as it relates to the rights of patent holders and pseudo-patents would be an entirely different form of property right. Therefore, adoption of a modified compulsory licensing scheme would provide strong incentive for continued research on personalized medicine without running afoul of the problems that typically plague such a system.

IV. CONCLUSION

Personalized medicine has the potential to revolutionize the current healthcare system and offers numerous benefits to individuals seeking medical attention. However, *Mayo* presents a road block to future development of technology in this field and poses a significant threat to the future of personalized medicine. To ensure the continued development of personalized medicine, multiple solutions were proposed to either aid researchers in obtaining patents on personalized medicine methods despite *Mayo*, or to lessen the financial blow presented by the inability

to obtain patent protection. Several or all proposed solutions should be adopted to ensure that the field of personalized medicine continues to develop and expand for the benefit of society.