Saint Louis University Journal of Health Law & Policy

Volume 14
Issue 1 *Health Inequities and Employment: The New Civil Rights Struggle for Justice*

Article 9

2020

Expanding Patient Access to Breast Cancer Genetic Testing Through Incentive Regimes

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EXPANDING PATIENT ACCESS TO BREAST CANCER GENETIC TESTING THROUGH INCENTIVE REGIMES

ABSTRACT

It is estimated that 268,600 women were diagnosed with breast cancer in 2019 alone, and as many as 26,860 of these women could have developed breast cancer due to a genetic disposition.[1] *While over one million women have undergone genetic testing to identify variations in the BRCA1 and BRCA2 genes, the test results are often ambiguous due to identified variations for which the breast cancer development risk is unknown.*[2] *A new technology known as CRISPR has the potential to change this state of uncertainty due to its capability to identify thousands of BRCA1 and 2 gene variations and accurately predict the associated breast cancer development risk.*[3] *However, access to this innovative technology for the accurate classification of breast cancer predictors has been impeded by the emergence of proprietary rights over breast cancer predictors and the inconsistent regulation of genetic testing by the Food and Drug Administration. This article proposes a single regulatory pathway for all genetic tests that requires clinical validity for approval, allowing the use of technology such as CRISPR to supplement clinical patient data with accurate laboratory data. This proposal provides incentives for companies to enter the genetic testing market, making breast cancer predictors available to the women who need them.*

1. *Breast Cancer Facts & Figures 2019-2020*, AM. CANCER SOC'Y (2019), https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf; Tamsen Valoir, *Breast Cancer, Politics, and Patents*, 44 AIPLA Q. J. 63, 73 (2016).

2. Jay Shendure et al., *What CRISPR Genome Editing Means for BRCA Breast Cancer Testing*, INVERSE (Oct. 1, 2018), https://www.inverse.com/article/49465-what-crispr-genome-editing-means-for-breast-cancer-research.

3. Sarah Zhang, *With CRISPR, Scientists Engineered Nearly 4,000 Mutations of a Breast-Cancer Gene*, THE ATLANTIC (Sep. 12, 2018), https://www.theatlantic.com/science/archive/2018/09/4000-brca1-variants/569827/.

I. INTRODUCTION

A woman in the United States has a one in eight chance of developing breast cancer in her lifetime.[4] Of the women who develop breast cancer, five to ten percent are more likely to have developed breast cancer due to a genetic disposition related to a variation in the BRCA1 and BRCA2 genes.[5] However, a significant number of identified BRCA gene variations have not been classified as breast cancer predictors due to the unknown breast cancer development risk associated with these variations.[6] There is a new technology that has the capability to not only identify the complete range of BRCA gene variations but to also accurately classify these variations as breast cancer predictors.[7] This emerging technology, called CRISPR, is a gene-editing technology.[8] However, as this Article will demonstrate, there are two phenomena that are likely to hinder the application of CRISPR to breast cancer predictors, rendering the development and availability of this technology problematic. The first is the level of incentives in the form of proprietary rights, and the second is regulatory uncertainty. In order for women to benefit from this technology, companies need to enter the genetic testing market so that this technological advance can be used to make breast cancer predictors accessible.

Proprietary rights through patent protection, the first phenomena, is the default incentive regime to innovation.[9] Thus, innovation hinges on the patentability of genes and genetic tests. The problem is that the Supreme Court has held that genes and genetic tests are not eligible for patent protection, based on the finding that an isolated deoxyribonucleic acid (DNA) segment is a naturally occurring product that is not made by man.[10] Trade secrecy is also a factor in this area because it operates separately from patent protection.[11] As an example, due to the exclusiveness of these two systems, the company that held the only BRCA gene patents developed a proprietary breast cancer predictor database and this trade secret was not impacted by the invalidation of the patents.[12] This results in an even higher proprietary rights barrier for companies

4. *Breast Cancer Risk in American Women*, NAT'L CANCER INST., (last updated Oct. 3, 2019).

5. Valoir, *supra* note 1.

6. Anny Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 566–67 (1998).

7. Zhang, *supra* note 3.

8. *Id.*

9. While there are alternative incentive regimes to innovation, this article focuses on patent protection because it is the primary mechanism of innovation in the United States. *See* Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L.R. 303, 311–12 (2013) (explaining that incentive regimes include patents as well as prizes, government grants to offset research and development cost, and tax incentives).

10. *See* Diamond v. Chakrabarty, 447 U.S. 303, 309–10 (1980).

11. Valoir, *supra* note 1 at 98.

12. *Id.*

looking to enter the genetic testing market, a consequence of the inability to exclude others via patent protection as well as the significant disadvantage companies have in classifying identified BRCA gene variations without the use of the largest repository of breast cancer predictor patient data.[13] The ultimate consequence is the negative impact on women's access to breast cancer predictors.[14]

Regulation, the second phenomena, is the method by which the FDA oversees the safety and effectiveness of genetic tests.[15] The FDA has the authority to regulate genetic tests as medical devices because the tests are used in the diagnosis and prevention of disease.[16] There are stark differences in the validity required for FDA approval of genetic tests based on the method of test administration, either administration by the laboratory that created the test or by a laboratory following a purchase from the manufacturer.[17] These regulation differences hinder the accessibility of breast cancer predictors because companies must contend with regulatory uncertainty, which can impede market entry.[18] Even the introduction of direct-to-consumer genetic tests did not improve breast cancer predictor accessibility, as this third method of test administration only further complicated the regulation.[19]

If one out of every eight women in the United States is at risk of developing breast cancer, there certainly is a significant number of women who would benefit from access to breast cancer predictors in order to identify treatment options before it is too late.[20] While CRISPR has made more comprehensive and accurate genetic testing a reality, women cannot benefit from this technology if companies do not market genetic testing that utilizes the full range of breast cancer predictors.[21] In order to overcome the impediments to breast cancer predictor accessibility, proprietary rights and regulation, a uniform regulatory pathway for genetic testing is needed that requires proof and disclosure of clinical validity to ensure the safety and effectiveness of the genetic tests. This Article argues that the FDA must establish a single regulatory pathway for genetic testing, balancing the requirement of clinical validity with the supplementation of patient data by technologies such as CRISPR in order to

13. *Id.* at 101.

14. *Id.* at 109.

15. *FDA Fundamentals*, U.S. FOOD & DRUG ADMIN., (last updated Feb. 9, 2018).

16. Suneel Arora et al., *The Interplay between FDA and Patent Law: Infusing Organizational Knowledge for Medical Device Companies*, 39 WM. MITCHELL L. REV. 1176, 1177 (2013); Patricia J. Zettler et al., *23andMe, the Food and Drug Administration, and the Future of Genetic Testing*, 174 JAMA INTERNAL MED. 493, 493 (Apr. 2014).

17. *See* Kayte Spector-Bagdady & Elizabeth R. Pike, *Consuming Genomics: Regulating Direct-to-Consumer Genetic and Genomic Information*, 92 NEB. L. REV. 677, 702–03 (2014).

18. *See id.* at 703.

19. *See id.* at 705.

20. NAT'L CANCER INST., *supra* note 5.

21. Spector-Bagdady & Pike, *supra* note 18, at 691.

overcome the inaccessibility of breast cancer predictors due to proprietary rights protection.

Part II of this Article starts by outlining the reasons breast cancer predictors are not only relevant but also crucial for the medical treatment of women. This is followed by a discussion of how proprietary rights over breast cancer predictors emerged in the form of patent case law, leading to a substantial decrease in available patent protection for genetic tests, and a discussion of how the regulation of genetic tests is inconsistent. The discussion of both of these issues will illustrate how a lack of incentive for companies to enter the genetic testing market ultimately results in inaccessibility of breast cancer predictors.

Part III of this Article analyzes how trade secrecy and the introduction of direct-to-consumer genetic tests have further impeded breast cancer predictor accessibility. This analysis starts with an assessment of how, even though patent protection over genetic tests has been substantially reduced, trade secrecy continues to disadvantage companies that lack years of patient data for establishing clinical validity. This is followed by an analysis of the complication of genetic testing regulation by the advent of direct-to-consumer tests, highlighting the negative impact of regulation variability on breast cancer predictor accessibility.

Part IV proposes a novel solution that draws on existing literature to promote accessibility of breast cancer predictors: a single regulatory pathway for all genetic tests that requires clinical validity for FDA approval regardless of the method of test administration. This clinical testing requirement is balanced by the utilization of technology such as CRISPR to supplement patient clinical data with accurate laboratory data, incentivizing companies to enter the genetic testing market so that breast cancer predictors are accessible to the women who need them.

II. PROPRIETARY RIGHTS AND REGULATION OF BREAST CANCER PREDICTORS

A. Relevance of Breast Cancer Predictors

DNA is a genetic sequence that is formed by pairs of nucleotide bases, the order of which determines the structure and hereditary material of a living organism.[22] The complete DNA sequence is known as the genome and contains approximately 20,000 to 25,000 genes, located on chromosomes in the nucleus of each human cell.[23] The purpose of genetic testing is to identify variations in human genes that are linked to a genetic disease, in order to determine whether an individual is at an increased risk of disease development.[24] Specific to breast

22. *What is DNA?* U.S. NAT'L LIBR. MED. (June 23, 2020).

23. *A Brief Guide to Genomics*, NAT'L HUM. GENOME RSCH. INST., (last updated Nov. 7, 2019).

24. Huang, *supra* note 7, at 555.

cancer, women who undergo genetic testing are interested in determining whether they have a breast cancer predictor, a BRCA1 or BRCA2 gene variation that is associated with breast cancer development.[25] The BRCA genes impede tumor growth in breast cells and women want to know if they are at risk of a breast cancer predictor suppressing these genes.[26] The BRCA1 and BRCA2 genes were discovered in 1990 and 1995 respectively, and the significance of this discovery was the identification of risk predictors for a disease that scientists understood to be hereditary without knowing the genes that indicated a risk.[27] Myriad Genetics, Inc., discovered the precise location of the BRCA2 gene, which allowed Myriad to not only determine the nucleotide sequence but to also use this sequence information in order to develop medical tests for the detection of breast cancer predictors.[28]

Although this information can be extremely helpful to patients in making treatment decisions, genetic testing provides only an estimate of the probability of genetic disease development because gene expression is a factor of inheritance and of an individual's environment.[29] This is further complicated by the fact that there are identified gene variations for which the genetic disease risk is not known, making these "variants of unknown significance," or VUS.[30] As technology has advanced, allowing for large portions of DNA to be sequenced quickly, the scientific understanding of the significance of gene variations has been outpaced by technological discovery.[31] The BRCA1 gene is an illuminating example, as there are still thousands of VUS despite the pervasiveness of research.[32] The consequence of this uncertainty is that women are making the private decision to undergo genetic testing for breast cancer predictors, understanding that the test results could be emotionally challenging, without the confidence that the results will be meaningful.[33] Based on test results, a woman might choose to have a double mastectomy, or even to not have children to avoid the risk of passing on the gene, decisions that would be made based on uncertain test results.[34]

The emergence of a new technology, called CRISPR, introduced the capability to not only identify thousands of BRCA gene variations but to also

25. *Id.* at 567.

26. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 583 (2013).

27. Jacob S. Sherkow & Henry T. Greely, *The History of Patenting Genetic Material*, 49 ANN. REV. GENETICS 161, 172 (2015); *Myriad Genetics, Inc.*, 569 U.S. at 583.

28. *Myriad Genetics, Inc.*, 569 U.S. at 583.

29. *See* Huang, *supra* note 7, at 564–65.

30. Zhang, *supra* note 3.

31. Spector-Bagdady & Pike, *supra* note 18, at 685.

32. Zhang, *supra* note 3.

33. Huang, *supra* note 7, at 567–68.

34. *Id.*

accurately classify these variations as breast cancer predictors.[35] CRISPR is a gene-editing technology that enables scientists to edit the DNA of human cells, using the Cas9 enzyme as "molecular scissors" to cut and modify DNA.[36] Before CRISPR, scientists had spent decades attempting to catalog the many variations of the BRCA gene in order to classify the variations as breast cancer predictors.[37] As the BRCA1 gene sequence is 5,600 nucleotide bases in length, the process of looking at only one variation at a time would have taken decades.[38] The CRISPR technology radically changed this approach, allowing scientists to genetically engineer 3,893 BRCA1 variations in a single study, based on only twenty-five percent of the BRCA1 coding sequence.[39] This is already a significant increase from the 1,800 BRCA1 variations that had been identified as of 2016, and this doesn't include the potential thousands of additional variations that could result from the analysis of the remaining seventy-five percent of the BRCA1 coding sequence.[40]

Even more importantly, CRISPR is yielding accurate disease development risk prediction results.[41] An early comparison of the risk prediction accuracy of variations identified by CRISPR with those BRCA1 variants for which patient data was already available is yielding an almost exact match.[42] This means that CRISPR not only has the capability to identify BRCA gene variations but to also turn these identified variations into accurate breast cancer predictors. With the potential to significantly decrease the number of women who receive genetic testing results of unknown significance, which is as many as 5 out of 100 tested women today, it is crucial to make the CRISPR technology accessible to the women who need more comprehensive and accurate breast cancer genetic testing.[43] In order for women to have this access, companies will need to navigate different layers of legal and regulatory frameworks.

B. Emergence of Proprietary Rights over Breast Cancer Predictors

In order to incentivize inventors to engage in costly and time-consuming research and development, as well as to produce socially valuable information, the patent system provides exclusivity of an invention to allow inventors to

35. Zhang, *supra* note 3.

36. STEPHAN RIXEN, BETWEEN MORAL HAZARD AND LEGAL UNCERTAINTY 18 (Matthias Braun et al. eds., 2018).

37. Zhang, *supra* note 3.

38. *Id.*

39. *Id.*

40. Valoir, *supra* note 1, at 76.

41. Shendure et al., *supra* note 2.

42. *Id.*

43. *See* Zhang, *supra* note 3.

recover the innovation cost.[44] Patent protection originated with the U.S. Constitution, which grants Congress the 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."[45] An invention must meet three requirements in order to be eligible for patent protection.[46] First, an invention must be useful, meaning it is classified as a "process, machine, manufacture, or composition of matter."[47] Second, an invention must be novel, indicating it is the first of its kind to be patented.[48] Third, an invention must be nonobvious, signifying it is sufficiently different from any prior inventions to not be obvious to a "person having ordinary skill in the art to which the claimed invention pertains."[49]

The application of these requirements to biological material occurred in 1980, when the case *Diamond v. Chakrabarty* came before the Supreme Court for resolution of whether a human-made micro-organism was eligible for patent protection.[50] Chakrabarty's patent application for a human-made bacterium was rejected by the U.S. Patent and Trademark Office (USPTO) on the grounds that the created micro-organism was a "product of nature."[51] This rejection was based on precedent that "laws of nature, physical phenomena, and abstract ideas" are not patentable subject matter, because a micro-organism, like the discovery of a new mineral or Newton's discovery of the law of gravity, is a discovery of a manifestation of nature that is "free to all men and reserved exclusively to none."[52] The USPTO reasoned that because a micro-organism exists in nature, purification alone does not make it a "process, machine, manufacture, or composition of matter" as required to meet the usefulness requirement.[53] Chakrabarty appealed to the Patent Office Board of Appeals but the Board affirmed the rejection, maintaining that the usefulness requirement does not incorporate living things.[54]

44. In addition to recouping research and development costs, the exclusivity granted by patent protection also accounts for the cost of previous failed invention iterations. Roland E. Dukes et al., *Accounting for Research and Development Costs: The Impact on Research and Development Expenditures*, 18 J. ACCT. RES.1, 1–2 (1980). *See* Sherkow & Greely, *supra* note 28, at 162. *See also* Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 JURIMETRICS J. 117, 117–18 (2016).

45. U.S. CONST. art. I, § 8, cl. 8.

46. Sherkow & Greely, *supra* note 28, at 163.

47. 35 U.S.C. § 101.

48. *See id.* § 102.

49. *Id.* § 103.

50. Diamond v. Chakrabarty, 447 U.S. 303, 305 (1980).

51. *Id.* at 306.

52. *Id.* at 309 (quoting Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)).

53. *Chakrabarty*, 447 U.S. at 306; 35 U.S.C. § 101.

54. *Chakrabarty*, 447 U.S. at 306.

In reviewing the Board's decision, the Supreme Court focused on whether Chakrabarty's micro-organism was covered by a "manufacture" or "composition of matter" classification.[55] The Court interpreted 35 U.S.C. § 101 to include "anything under the sun that is made by man," holding that the micro-organism was patent eligible because it had been created by Chakrabarty to have "markedly different characteristics from any found in nature."[56] As Chakrabarty's invention was "not nature's handiwork, but his own," it was patentable subject matter because it was not a "product of nature."[57] Based on this case, the USPTO decided that isolated and purified DNA was eligible for patent protection because the separation of DNA from the cell environment, like the creation of a micro-organism in a laboratory, created a product that was sufficiently different from the natural product to no longer be a manifestation of nature.[58] This USPTO decision led to the issuance of thousands of patents for genetic material that had been isolated from the cell environment, including patents for the BRCA1 and BRCA2 genes.[59]

Myriad Genetics, the discoverer of the BRCA2 gene, was granted patent protection for the BRCA1 and BRCA2 genes in 1998.[60] The patents included composition claims, detailing the DNA nucleotide sequences that cause a cell to produce specific BRCA1 and BRCA2 variations, and method claims, detailing the isolation of the DNA sequences contained in the composition claims.[61] Collectively, these patent claims distinguished Myriad as the sole holder of the right to isolate the DNA sequences contained in the BRCA1 and BRCA2 genes.[62] This allowed Myriad to enforce its BRCA gene patents against any other company that was conducting breast cancer genetic testing because genetic testing requires the isolation of DNA sequences.[63] In light of these patent challenges, the American Civil Liberties Union filed a suit in 2009 against Myriad in federal district court, alleging that Myriad's patents were invalid as patents for "products of nature" under 35 U.S.C. § 101.[64] By filing this suit, the petitioners hoped to invalidate Myriad's patents, which would in turn allow other

55. *Id.* at 307.

56. *Id.* at 309–10.

57. *Id.* at 310.

58. Valoir, *supra* note 1, at 81.

59. *Id.* at 81–82.

60. Sherkow & Greely, *supra* note 28, at 172.

61. A patent composition claim covers a mixture of two or more substances, the combination of which creates composition properties not held by the substances when separate. WILLIAM C. ROBINSON, LAW OF PATENTS FOR USEFUL INVENTIONS 278 (1890). A patent method claim, also known as a process claim, covers the steps required to bring about a specific result. *Id.* at 230. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 584 (2013). *See also* Ass'n for Molecular Pathology v. USPTO, 653 F.3d 1239, 1352 (Fed. Cir. 2011).

62. *Myriad Genetics*, 569 U.S. at 585.

63. *Id.*

64. Ass'n for Molecular Pathology v. USPTO, 669 F. Supp. 2d 365, 369–70 (S.D.N.Y. 2009).

companies to isolate BRCA1 and BRCA2 DNA sequences in the process of conducting breast cancer genetic testing.[65]

The District Court granted summary judgment in favor of the petitioners for the composition claims, holding that the claims were invalid as "products of nature."[66] However, the Federal Circuit reversed based on the above-mentioned holding in *Chakrabarty*, reasoning that isolated DNA is not a product of nature because it consists of "molecules that are markedly different – have a distinctive chemical identity and nature – from molecules that exist in nature."[67] After granting certiorari, the Supreme Court vacated the judgment and remanded the case to the Federal Circuit for a decision consistent with the newly decided *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*[68]

The Court in *Mayo* recognized that while a law of nature is not patentable, an application of it could be eligible for patent protection if the application transforms "unpatentable natural laws into patent-eligible applications of those laws."[69] This means that if a law of nature, as applied, is sufficiently different from the product as found in nature, it can be eligible for patent protection. The Court held that the patent method claims at issue did not meet this standard because the process steps involved "well-understood, routine, conventional activity."[70]

On remand, the analysis of the BRCA patents was expanded to look at not only whether the composition claims covered products of nature, but also whether the composition claims were transformed by the method claims into patent-eligible subject matter.[71] The Federal Circuit held that the isolated BRCA1 and BRCA2 DNA sequence claims were eligible for patent protection because "the act of isolating DNA … is an inventive act that entitles the individual who first isolates it to a patent."[72] When the case again reached the Supreme Court, the Court reversed and unanimously held that "a naturally occurring DNA segment is a product of nature and [is] not patent eligible merely because it has been isolated."[73]

The Supreme Court's holding that genes and genetic tests are not eligible for patent protection has significant consequences for companies in the genetic testing market.[74] Without the ability to exclude others from a potential genetic testing invention via patent protection, it can be assumed under contemporary

65. *Id.* at 369.
66. Ass'n for Molecular Pathology v. USPTO, 702 F. Supp. 2d 181, 232 (S.D.N.Y. 2010).
67. Ass'n for Molecular Pathology v. USPTO, 653 F.3d 1239, 1351 (Fed. Cir. 2011).
68. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 566 U.S. 902 (2012).
69. Mayo Collaborative Servs. v. Prometheus Labs., Inc. 566 U.S. 66, 72 (2012).
70. *Id.* at 73.
71. Ass'n for Molecular Pathology v. USPTO, 689 F.3d 1303, 1324 (Fed. Cir. 2012).
72. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 586–87 (2013).
73. *Id.* at 580.
74. *See id.* at 585.

intellectual property regimes that companies will lack the incentive to produce innovative genetics tests that are valuable to society.[75] However, patent protection does not work alone in the field of innovation. While patent protection encourages inventiveness, public health regulation encourages the production of inventive data during the progression from idea to market.[76] The problem is that the lack of regulatory uniformity is impeding companies from entering the genetic testing market, resulting in a lack of access to innovation for patients.[77]

C. Inconsistent Regulation of Breast Cancer Predictors

In order for these products to be made available to patients, the product must be approved by the FDA.[78] The FDA is a regulatory agency that is part of the U.S. Department of Health and Human Services and is tasked with assuring the safety and effectiveness of drugs, biological products, and medical devices.[79] Congress authorized the FDA to regulate medical devices, products that are "intended for use in the diagnosis … or in the cure, mitigation, treatment, or prevention of disease," with the passage of the Federal Food, Drug, and Cosmetic Act in 1938.[80] This empowered the FDA to monitor medical devices that are on the market in order to identify potential risks to patient safety and track adverse patient events.[81] The passage of the Medical Device Amendments in 1976 expanded FDA oversight of medical devices, authorizing the FDA to enforce safety and effectiveness standards that medical devices must meet before being placed on the market.[82]

Since genetic tests are used in the diagnosis and prevention of disease, the FDA regulates these tests as medical devices.[83] Depending on how a genetic test is produced and marketed, it can be regulated as either an in vitro diagnostic device (IVD) or a laboratory developed test (LDT).[84] IVDs are "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease" and as such, are "intended for use in the

75. *See* Laakmann, *supra* note 45, at 118.

76. *Id.* at 119.

77. *See* Kirk Willmarth, *The FDA and Genetic Testing: Improper Tools for a Difficult Problem*, 2 J.L. & BIOSCIENCES 158, 164 (2015).

78. U.S. FOOD & DRUG ADMIN., *supra* note 16.

79. *Id.*

80. Federal Food, Drug, and Cosmetic Act, § 201(h), 21 U.S.C. § 321(h); John E. Meyer, *The Future of the FDA's Application of Enforcement Discretion on Laboratory Developed Tests*, 12 J. HEALTH & LIFE SCI. L. 43, 47 (2019).

81. *See Regulatory Controls*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls (last updated Mar. 27, 2018).

82. Meyer, *supra* note 81.

83. Zettler et al., *supra* note 17.

84. Andrew S. Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access*, 9 NW. J. TECH. & INTELL. PROP. 377, 393 (2011).

collection, preparation, and examination of specimens taken from the human body."[85] A genetic test is classified as an IVD when it is manufactured by a company and then purchased by a laboratory to be used for testing.[86] LDTs are a category of IVDs and a genetic test is classified as an LDT when it is manufactured and used by the same laboratory.[87]

For a consumer, the main difference between IVDs and LDTs is how each is regulated by the FDA, as there is a significant difference in the standards that must be met before being placed on the market.[88] The FDA plays a direct role in the regulation of IVDs, requiring proof of both analytic and clinical validity.[89] As related to genetic testing, analytic validity is proof that a test correctly identifies gene variations and clinical validity is proof that a test accurately reports the predictions of disease development risk that correlate to those variations.[90] The level of review of IVDs, as medical devices, is contingent on the device classification assigned by the FDA.[91] Medical devices can be classified as Class I, Class II, or Class III, based on the risk the device could pose to the consumer.[92] Increased risk to the consumer requires additional oversight by the FDA in order to assure the public's safety, with Class III being the highest risk class.[93] Genetic tests have been classified as either Class II or Class III, both of which can require costly clinical testing and submission of clinical data for evaluation prior to FDA approval and subsequent market placement.[94]

LDTs, on the other hand, have historically been regulated by the FDA only at its discretion because LDTs are also regulated by the Centers for Medicare & Medicaid Services (CMS) via the Clinical Laboratories Improvements Amendments Act (CLIA).[95] Congress passed CLIA in 1988, authorizing CMS to regulate laboratory tests that are conducted on human subjects for non-research purposes.[96] Under CLIA, CMS requires proof of only analytic validity, focusing on the reliability of the laboratory performing the LDT, as compared to the requirement of analytic and clinical validity for IVDs.[97] This means that a genetic test classified as an LDT only requires proof that the test correctly

85. 21 C.F.R. § 809.3 (2019).
86. Robertson, *supra* note 85, at 394.
87. Spector-Bagdady & Pike, *supra* note 18, at 702.
88. Robertson, *supra* note 85, at 394.
89. Zettler et al., *supra* note 17, at 493–94.
90. *Id.* at 493.
91. Huang, *supra* note 7, at 587–88.
92. Spector-Bagdady & Pike, *supra* note 18, at 699.
93. *Id.*
94. Gail H. Javitt, *In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests*, 62 FOOD & DRUG L.J. 617, 629–30 (2007); Meyer, *supra* note 81, at 48–49.
95. Meyer, *supra* note 81, at 45–46.
96. *Id.* at 56.
97. *Id.* at 56–57.

identifies gene variations, with no requirement of proof that the test accurately reports the predictions of disease development risk that correlate to those variations.[98]

The stark differences between regulating a genetic test as an IVD or an LDT illustrate how patient access to genetic testing is hindered by the variability in regulation, as this makes it difficult for companies to determine the validity data required for FDA approval. This decision might then impact the choice of whether to enter the genetic testing market.[99] The resulting negative impact on women's access to breast cancer predictors is in addition to the access barrier created by the lack of proprietary rights for genes and genetic tests.[100] This Article will first analyze these two legal considerations separately, illustrating that the lack of impact of the *Myriad* holding on the trade secrecy of its breast cancer predictor data, as considered with the inconsistent regulation by the FDA following the introduction of direct-to-consumer genetic tests, presents an urgent issue that is difficult to ignore. This Article will then propose a solution that promotes accessibility of breast cancer predictors, a single regulatory pathway for all genetic tests that requires both proof and transparency of clinical validity data.

III. IMPEDIMENTS TO WOMEN BENEFITTING FROM BREAST CANCER PREDICTORS

A. Problematic Trade Secrecy of Breast Cancer Predictors

As discussed, the case law history of Myriad's BRCA gene patents established that genes and genetic tests are not eligible for patent protection.[101] Due to the invalidation of its patents, Myriad no longer can exclude other companies from entering the breast cancer genetic testing market.[102] However, these other potential companies are at an extreme disadvantage. Although the holding in *Myriad* addressed the patentability of genes and genetic tests, it did not impact the trade secrecy of BRCA gene variations known exclusively to Myriad.[103] As the holder of the only BRCA gene patents, Myriad was the primary provider of BRCA1 and BRCA2 genetic tests for sixteen years, allowing Myriad to accumulate patient data on identified BRCA gene variations.[104] The consequence of this data monopolization was that Myriad was the only company that had sufficient data on identified BRCA gene variations

98. Zettler et al., *supra* note 17, at 493–94.
99. *Id.*
100. *Id.* at 493.
101. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 580 (2013).
102. *See id.* at 585.
103. Valoir, *supra* note 1, at 98.
104. *Id.* at 96.

to turn these variations into accurate breast cancer predictors.[105] This placed Myriad in a position to offer superior breast cancer genetic testing as compared to its competitors because the collection of patient data for sixteen years allowed Myriad to offer a more comprehensive breast cancer development risk analysis.[106]

While patents and trade secrecy share the same goal of encouraging invention, the incentives offered by these two systems remain separate.[107] In contrast to the federal patent system, trade secrecy operates at the state level.[108] The Uniform Trade Secrets Act has been implemented in forty-seven U.S. states and protects information as a trade secret if it is valuable for competition, subject to reasonable efforts of confidentiality, and not generally known by others in the trade.[109] The Supreme Court held in *Kewanee Oil Co. v. Bicron Co.* that inventions that are eligible for patent protection can also be classified as trade secrets, stating that "the patent policy of encouraging invention is not disturbed by the existence of another form of incentive to invention."[110] Based on the Court's conclusion that the patent and trade secrecy regimes are not in conflict, Myriad's proprietary breast cancer predictor data can be protected as a trade secret even though its patents have been invalidated.[111]

Myriad's monopolization of breast cancer predictor data is significant when considered as a vital source of data to help classify the nearly 4,000 BRCA1 gene variations discovered thus far by CRISPR.[112] While an initial analysis of the breast cancer development risk of these variations has been completed, yielding accurate results, the medical community remains hesitant to base patient treatment decisions on only laboratory data.[113] While the CRISPR technology has the potential to bridge the gap between the interest of women in undergoing breast cancer genetic testing and the need for accurate breast cancer predictors, women cannot utilize the comprehensive genetic testing made possible by CRISPR without doctor endorsement.[114] If the only alternative to laboratory data to classify breast cancer predictors is patient data, companies will be forced to conduct years of clinical testing in order to collect patient data

105. *Id.*

106. *Id.* at 96–97.

107. Karl F. Jorda, *Patent and Trade Secret Complementariness: An Unsuspected Synergy*, 48 WASHBURN L.J. 1, 5 (2008).

108. *Id.*

109. *Id.* at 2. *See generally* UNIF. TRADE SECRETS ACT, 14 U.L.A. 372 (1990).

110. Jorda, *supra* note 108; Kewanee Oil Co. v. Bicron Co., 416 U.S. 470, 484 (1974).

111. *See Kewanee Oil Co.*, 416 U.S. at 484. *See also* Conley et al., *supra* note 4, at 616.

112. Zhang, *supra* note 3.

113. Gregory M. Findlay et al., *Accurate Classification of BRCA1 Variants with Saturation Genome Editing*, 562 NATURE 217, 221 (Oct. 2018); Zhang, *supra* note 3.

114. Zhang, *supra* note 3.

that is likely duplicative of the data already known to Myriad.[115] This is in direct conflict with the reality that women simply do not have the luxury of waiting.

B. Complication of Breast Cancer Predictor Regulation Due to Direct-to-Consumer Tests

Historically, women have undergone breast cancer genetic testing as administered by either a physician or a laboratory technician.[116] As noted above, companies must grapple with the differing standards in genetic test regulation based on a classification of a genetic test as either an IVD or an LDT.[117] Companies are now faced with an additional potential classification for when a woman decides to conduct the genetic test herself, using a direct-to-consumer (DTC) test.[118] The regulation of breast cancer predictors was already uncertain and the new classification of genetic tests by administration method instead of risk further complicates an already inconsistent regulatory environment.[119]

Following the FDA approval of the first breast cancer predictor DTC test in 2018 for the company 23andMe, women gained the option to use a DTC test for three specific BRCA1 and BRCA2 gene variations.[120] This approval came four years after the FDA issued a draft guidance for the regulation of LDTs that far from clarified the regulatory standards applicable to DTC tests.[121] The FDA decided that, even if a DTC test met the definition of an LDT, enforcement discretion would not be exercised and the FDA would regulate all DTC tests as IVDs.[122] The practical implication of this decision is that companies that create and market DTC tests will be required to prove both analytic and clinical validity in order to obtain FDA approval, as opposed to only analytic validity as required for LDTs.[123] While classifying DTC tests as IVDs means that the FDA has recognized the increased risk of DTC tests due to patients making their own treatment decisions, the requirement of clinical validity for DTC tests emphasizes the contrast between IVDs and LDTs.[124]

Notwithstanding the advent of DTC tests, there are still 11,000 laboratories in the United States that are authorized to perform LDTs.[125] It is well recognized

115. *Id.*

116. *BRCA Gene Test for Breast and Ovarian Cancer Risk*, MAYO CLINIC (Sept. 19, 2019).

117. Robertson, *supra* note 85, at 394.

118. *FDA Authorizes, With Special Controls, Direct-to-Consumer Test that Reports Three Mutations in the BRCA Breast Cancer Genes*, U.S. FOOD & DRUG ADMIN. (Mar. 6, 2018).

119. Willmarth, *supra* note 78, at 159.

120. U.S. FOOD & DRUG ADMIN., *supra* note 119.

121. Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) Draft Guidance, 79 Fed. Reg. 59776 (Sept. 30, 2014).

122. *Id.*

123. Zettler et al., *supra* note 17, at 494.

124. Spector-Bagdady & Pike, *supra* note 18, at 705.

125. Willmarth, *supra* note 78, at 163.

that without requiring clinical validity prior to FDA approval, a genetic test classified as an LDT is at risk of producing inaccurate or misleading results.[126] Even the FDA has acknowledged that the public needs increased oversight of LDTs in order to ensure genetic tests are accurate and reliable.[127] Yet, the FDA has only issued two draft guidance documents regarding the discretionary regulation of LDTs, both in 2014, prior to the 2017 publication of a discussion paper stating that a final guidance would not be issued.[128] While this discussion paper mentions a focus on clinical validity, showing that the FDA is aware of the regulatory standards gap between IVDs, including DTC tests, and LDTs, the discussion paper is merely a suggestion as opposed to binding FDA regulation.[129]

Women need to be confident that the choice to undergo breast cancer genetic testing will yield results that accurately reflect not only the identified BRCA gene variations but also any present breast cancer predictors. It is hard to see how women can have this confidence when making the choice between testing performed by a doctor, a laboratory technician, or at home can change the validity of the results. Thus, a defined regulatory pathway for breast cancer genetic testing is needed for both the women who are at risk of developing the disease and the health care providers responsible for advising these women of their treatment options. This becomes even more crucial in light of the exponential increase in the number of BRCA gene variations discovered thus far by CRISPR.[130] This regulatory pathway needs to balance the need for clinical validity for each variant with the understanding of how making this approval requirement too onerous might make genetic testing an impracticable pursuit due to the required time and company resources.[131] The proposal that follows combines this need for a single regulatory pathway with the reality of the unavailability of breast cancer predictor patient data due to trade secrecy, balancing a requirement for clinical validity for all genetic tests with the use of technology such as CRISPR to supplement patient clinical data.

IV. A PROPOSAL TO REGULATE GENETIC TESTING TO PROMOTE ACCESSIBILITY OF BREAST CANCER PREDICTORS

In order for women to gain access to breast cancer predictors, companies need to have incentives to enter the genetic testing market. The following analysis details a proposed solution to grant women this needed access. This

126. Meyer, *supra* note 81, at 57.

127. U.S. FOOD & DRUG ADMIN., DISCUSSION PAPER ON LABORATORY DEVELOPED TESTS (LDTS) 2 (2017).

128. Spector-Bagdady & Pike, *supra* note 18, at 703; Meyer, *supra* note 81, at 62, 65.

129. Meyer, *supra* note 81, at 66.

130. Zhang, *supra* note 3.

131. Zettler et al., *supra* note 17, at 494.

proposal is for a single regulatory pathway for all genetic tests that balances the requirement of clinical validity with the supplementation of patient data, by technology such as CRISPR, in order to overcome the inaccessibility of breast cancer predictors due to proprietary rights protection.

The first component of the proposed regulatory pathway is a requirement for clinical validity for both LDTs and IVDs, including DTC tests. The FDA could pursue this requirement in two ways – it could regulate all genetic testing as IVDs, thereby requiring clinical validity prior to FDA approval, or it could require proof of clinical validity for LDTs.[132] Both of these options would result in a uniform approach for all genetic tests that requires both analytic and clinical validity prior to FDA approval. This would allow women to feel confident in their breast cancer genetic testing results, as all genetic tests would be required to prove not only the correct identification of BRCA gene variations but also the accurate predictions of disease development risk correlated with those variations.[133] Without the standardized requirement of clinical validity, genetic tests are at risk of producing inaccurate and misleading results due to the lack of FDA oversight.[134] There is simply too much at stake to allow for even the possibility of inaccurate results considering the private and personal treatment decisions women are making based on the test results.[135]

While these two options are both viable, the FDA has implied that it is open to requiring clinical validity for LDTs.[136] This is because this route would provide an impartial confirmation of the quality of genetic test results, providing assurance the test works as intended.[137] Although it could be argued that uniformity of validity data in this instance is minimizing the uniqueness of LDTs, a product that might be better off with product-specific regulation, the FDA itself has acknowledged that heightened oversight of LDTs is needed in order to ensure test accuracy.[138] In addition, while some LDT advocates have expressed concerns that requiring clinical validity for LDTs would duplicate CLIA regulation efforts by CMS, the FDA has stated that this requirement would be complementary to, and not duplicative of, CMS regulation requirements.[139] This suggests that the FDA is willing to keep both the LDT and IVD classifications for genetic tests and that this route will best meet the breast cancer predictor accessibility needs of women.

If clinical validity is required for all genetic tests, companies will need to know what data can be used to meet this requirement in order to bring genetic

132. *Id.* at 493.
133. *Id.*
134. Meyer, *supra* note 81, at 57.
135. Huang, *supra* note 7, at 567–68.
136. U.S. FOOD & DRUG ADMIN., *supra* note 128.
137. *Id.* at 5.
138. *Id.* at 2.
139. *Id.* at 5.

tests to the patients who need them. While the FDA has historically required patient data, it stated in 2017 that it was willing to consider clinical validity that is "supported by literature, well-curated databases, or other appropriate sources that meet the valid scientific evidence standard."[140] As applied to breast cancer genetic testing, this could mean that studies performed with CRISPR might be an option to classify identified BRCA gene variations as breast cancer predictors, as opposed to needing actual patient data for this classification. The use of scientific data to supplement patient data also offsets the significant clinical testing costs that can be incurred by companies, helping to incentivize companies to pursue the genetic testing market.[141] This is even more salient due to Myriad's monopolization of breast cancer predictor patient data.[142] The availability of scientific data has the potential to decrease the time and cost of clinical validity data collection significantly, as illustrated by the single study that identified nearly 4,000 BRCA1 gene variations and accurately classified these variations as breast cancer predictors.[143]

Although this Article focuses on breast cancer genetic testing, the analysis can extend to not only other hereditary diseases but also to other technology. The "nearly perfectly accurate" results of the BRCA1 variation CRISPR study as related to breast cancer predictors is a promising start, for both the classification of future BRCA gene variations and the wide array of other hereditary diseases.[144] Even though the number of people who have received uncertain genetic testing results has been downplayed by some, with claims that uncertain results only occur in a minority of genetic tests, it cannot be denied that even one variation of unknown significance is too many when human lives are at stake.[145] In addition, the technological advance demonstrated by CRISPR has essentially guaranteed that the number of identified gene variations will only continue to grow, illustrating that the identification of variations of unknown significance is just beginning. While doctors may prefer patient data as opposed to laboratory data for classifying gene variations as disease predictors, the confidence of the scientists who conducted the CRISPR study and the willingness of the FDA to consider scientific sources for clinical data illustrates a potential shift that could lead to doctor endorsement of this alternative source of clinical validity.[146]

The second component of the proposed regulatory pathway is a requirement for disclosure of breast cancer predictors as part of the FDA approval process.

140. *Id.* at 6.

141. *See* Robertson, *supra* note 85.

142. Valoir, *supra* note 1, at 98.

143. Findlay et al., *supra* note 114, at 217.

144. Shendure et al., *supra* note 2.

145. *See* Robert Cook-Deegan et al., *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets*, 21 EUR. J. HUM. GENETICS 585, 585 (2012). *See also* Zhang, *supra* note 3.

146. Zhang, *supra* note 3.

Transforming BRCA gene variations into breast cancer predictors requires as much data as can be compiled due to the seriousness of the decisions women are making in light of their test results.[147] Genetic tests should only be made available when both the companies and the FDA are confident that the tests provide a scientifically supported disease development risk prediction, and this requires the collation of breast cancer predictor data in order to ensure both data accessibility and accuracy.[148] By requiring the disclosure of breast cancer predictors as part of genetic test approval, the FDA could incentivize companies to enter the market by lowering the clinical testing barrier to entry based on the data already available for review and analysis.

If companies could access breast cancer predictors shared by others in the industry, women could more readily gain access to the entire range of breast cancer predictors, keeping pace with the advancement of technology. Although the FDA has been criticized because of industry financial conflicts of interest, it is the federal regulatory agency that currently has the authority and responsibility to ensure the safety and effectiveness of genetic tests.[149] As such, it is in the unique position to make breast cancer predictors accessible via market incentives. Market incentives can include motivations rooted in private profits via commercialization, societal improvement, or public safety.[150] In addition, the requirement to share breast cancer predictors as part of FDA approval would remove the trade secrecy disadvantage caused by Myriad's proprietary breast cancer predictor data. By requiring disclosure of breast cancer predictors, in addition to allowing for the use of laboratory data in the classification of these predictors, the FDA would be strengthening the incentive for companies to enter the genetic testing market through the provision of not one but two sources of clinical testing cost offset. If women are going to gain access to breast cancer predictors, they need companies to pursue this market.

The required disclosure of breast cancer predictor data incentivizes accessibility more than public databases because the current public databases depend on the voluntary sharing of data in order to make correlations between gene variations and disease development risk.[151] Voluntary sharing of data is just not enough for the women and health care providers who need access to breast cancer predictors in order to make informed treatment decisions, as this voluntary sharing has led to multiple databases with inconsistent and variable data from which it is difficult to extract reliable information.[152] Similarly, health care payors are also not the solution for data disclosure, as there are hundreds of

147. Michael J. Malinowski et al., *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 TUL. L. REV. 1211, 1248 (1997).

148. *Id.* at 1219.

149. Zettler et al., *supra* note 17; Dukes et al., *supra* note 45, at 1.

150. *See* Laakmann, *supra* note 45, at 125.

151. Cook-Deegan et al., *supra* note 146, at 586.

152. *Id.*

existing contracts between genetic testing firms and health care payors that do not require this disclosure.[153] If the need for accessible breast cancer predictors cannot depend on voluntarily shared research or health care payor contracts, this places the FDA at a crucial junction to meet this need. Additionally, the FDA would not need to start from scratch for a breast cancer predictor database because it could utilize an existing partnership with the National Institutes of Health in order to develop the needed database infrastructure.[154]

This proposed solution of a single regulatory pathway for all genetic tests is the first step in the delivery of innovative health care to patients afflicted with hereditary diseases. While this Article does not address the affordability of this innovation, relevant to both patients and society at large, innovation starts with incentive. Incentive is not limited to private profits but also includes a motivation to improve society and further public safety.[155] In order for breast cancer predictors to be accessible to the women who need them, companies need the incentive to enter the genetic testing market and this Article examines how proprietary rights and regulation can impact this incentive and, ultimately, patient access. Accessibility of breast cancer predictors requires a solution to overcome these impediments to innovation and the solution in this Article is a good place to start.

V. CONCLUSION

There are millions of women at risk of developing breast cancer in the United States and over one million women have already undergone genetic testing of the BRCA1 and BRCA2 genes in order to determine whether they are at risk of disease development due to variations in these genes.[156] There is clearly patient interest in breast cancer genetic testing, but accurate genetic testing requires companies to produce and market genetic tests that utilize the entire range of breast cancer predictors. While the CRISPR technology has been used to not only identify thousands of BRCA1 gene variations but also accurately classify these variations as breast cancer predictors, proprietary rights and regulation are stopping companies from utilizing this technological advance to provide women the accurate genetic tests they need.[157] Therefore, a single regulatory pathway is needed for all genetic tests that balances the requirement of clinical validity with the supplementation of patient data, by technology such

153. *Id.* at 587.

154. Rachel E. Sachs, *Regulating Intermediate Technologies*, 37 YALE J. ON REG. 219, 261 (2020).

155. *See* Laakmann, *supra* note 45, at 125.

156. Valoir, *supra* note 1 at 65; Shendure et al., *supra* note 2.

157. Zhang, *supra* note 3.

as CRISPR, in order to overcome the inaccessibility of breast cancer predictors due to proprietary rights protection.

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* Juris Doctor, Saint Louis University School of Law (anticipated May 2021); Bachelor of Science in Biomedical Engineering, Purdue University (December 2012). This Comment is published with heartfelt gratitude to my husband, Benjamin Hart, for his unwavering support, without whom I would not be pursuing this dream. I would also like to thank my mentor, Professor Ana Santos Rutschman, for her invaluable guidance and feedback throughout the writing process. Finally, I would like to thank the Staff and Editorial Board of Volume 14, for their diligence and dedication. It has been my honor to serve as their Editor-in-Chief.