Gene Patents: Incentive or Impediment for Pharmaceutical Innovation?

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This research explores biopharmaceutical companies' behavior of obtaining patent protection under the tightened patentability standard for biotechnology innovation. To explore the importance of innovations, we collected time-series data from twenty firms over two decades and examined the role of biotechnology on a firm's operating performance and profit via an empirical regression model. The results suggest that greater R&D investment brings firms higher revenue and profit, but a more influential patent does not seem to reward all companies. The possession of biotechnology can help companies increase revenue. For large-scale R&D firms, marketing involvement is particularly important to boost revenue, but low-scale R&D firms should avoid having a high ratio of biotechnology in their patent portfolio strategy.

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I. INTRODUCTION

The California Gold Rush began after gold was discovered in 1848, spurring individual gold-seekers to find their own wealth with a pick and a pan.[1] Wishing to strike it rich, hundreds of thousands of people flocked to California from inside and outside the U.S. from 1848 to 1850, stimulating the local economy and transforming it from a thinly populated ex-Mexican territory to statehood.[2] At the beginning of the California Gold Rush, there were no clear rules of private property.[3] Gold-miners treated "the mining region[s] . . . as a commons from which anyone could gather gold [side by side], so long as he did not interfere physically with other miners."[4] The dream of striking it rich lured a significant labor force

1. Bancroft G. Davis, *Fifty Years of Mining Law*, 50 HARV. L. REV. 897, 897 (1937).
2. Andrea G. McDowell, *From Commons to Claims: Property Rights in the California Gold Rush*, 14 YALE J.L. & HUMAN. 1, 1-2 (2002).
3. *Id.* at 2-3; Davis, *supra* note 1, at 897-99.
4. McDowell, *supra* note 2, at 11.

into California, as many employment contracts that tied employers to employees before 1848 were dissolved.[5] When individuals could no longer collect gold by hand, the first stage of this industry soon ended.[6] By 1851, individual placer deposits were producing only a fraction of their former yields and extracting gold started to require much greater capital.[7] Industry growth in terms of effective gold extraction, transportation infrastructure, and market transaction mechanisms all required inputs from capital investment, talent, and the coordination of production activity.[8] Real social and economic progress would not happen until capital and human resources took over from the earlier placers.[9]

The boom of the biotechnology industry since the 1990s following the Human Genome Project tells an almost identical story. Started in 1990, the United States "Human Genome Project (HGP) [was] an internationally collaborative venture" that encompassed both public sectors and commercial companies.[10] The HGP identified and mapped the human genome, which was vital to unveil the disease mechanism associated with a particular gene.[11] It spurred the race of gene patenting by research institutions and commercial companies.[12] After the completion of the HGP in 2003, private pharmaceutical companies obtained most of the patents in the United States that now claim or mention human genes.[13]

In the biotech boom of the 1990s and early 2000s, the United States's judicial system and administrative practices held a positive attitude toward gene patents. The Federal Circuit held that a claim to "[a] purified and isolated DNA sequence consisting essentially of a DNA sequence

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5. *Id.* at 10.

6. RODMAN W. PAUL, CALIFORNIA GOLD: THE BEGINNING OF MINING IN THE FAR WEST 171 (1947).

7. *See* McDowell, *supra* note 2, at 2 n.1, 10 (citing PAUL, *supra* note 6, at 116) ("The first flush period, when gold could be picked up with relatively little labor, lasted until 1851. From 1851 onwards it took capital and labor to extract the gold.").

8. *See* PAUL, *supra* note 6, at 195.

9. McDowell *supra* note 2, at 10 ("[C]oncentrations of capital and a supply of wage-labor were necessary for progress—that is, for effective gold mining, road building, and the growth of industry—agreed that nothing of the kind could take place until the placers were exhausted." This point of view is later proved.).

10. Daniel Melaas, *Human Genome Project*, N.D. ST. U. (1999), http://www.ndsu.edu/pubweb/~mcclean/plsc431/students99/melaas.

11. *Id.*

12. *See* Robert Cook-Deegan & Christopher Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. GENOMICS & HUM. GENETICS 383, 403 (2010).

13. *See* Christopher M. Holman, *Will Gene Patents Impede Whole Genome Sequencing?: Deconstructing the Myth That 20% of the Human Genome Is Patented*, 2 IP THEORY 1 (2011).

encoding human erythropoietin" was valid.[14] The Patent and Trademark Office (PTO) "endorsed Judge Learned Hand's opinion" in the *Park-Davis* case that an isolated DNA sequence is patentable subject matter "because that DNA molecule does not occur in that isolated form in nature[,]" and that "synthetic DNA preparations are eligible . . . because their purified state is different from a naturally occurring compound."[15]

Public opinion seems uneasy about the rising number of gene patents. Critics argue that gene patents inadvertently hinder academic research, diminish patient care quality, restrict access to genetic diagnostics, slow new medicine development, and discourage investment in downstream R&D.[16] In response, the judicial system has tightened the patentability standard of eligibility, non-obviousness, utility, and enablement for gene patents in its case series since 2007.[17]

The Federal Circuit affirmed written description as a separate requirement from the enablement requirement to establish an applicant's possession of the claimed scope in *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* in 2011.[18] The written description requirement applies to chemical inventions as well as biotechnology inventions.[19] Isolated gene sequences were held to be patent ineligible by the U. S. Supreme Court in 2013 in *Association for Molecular Pathology v. Myriad Genetics, Inc*.[20] In view of the requirement of non-obviousness, the Supreme Court elaborated upon a tightened standard in its 2007 *KSR International Co. v. Teleflex Inc.* decision.[21] In the same year of the Supreme Court's *KSR* decision, the Federal Circuit affirmed through *In re Kubin* that the "obvious-to-try" is an appropriate test to render an isolated gene sequence molecule obvious where a specific protein is disclosed and a specific DNA isolation method is taught.[22]

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14. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1204, 1209 (Fed. Cir. 1991).

15. ROBERT PATRICK MERGES & JOHN FITZGERALD DUFFY, PATENT LAW AND POLICY: CASES AND MATERIALS, 180-81 (5th ed. 2011); Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001).

16. Stephen H. Schilling, *DNA as Patentable Subject Matter and a Narrow Framework for Addressing the Perceived Problems Caused by Gene Patents*, 61 DUKE L.J. 731, 742-43, 745-46 (2011) (alleging gene patents: 1. Diminish Patient Access; 2. Diminish Quality of Patient Care; 3. Impede Research and Innovation).

17. *Id.* at 742.

18. 598 F.3d 1336, 1340 (Fed. Cir. 2010).

19. MERGES & DUFFY, *supra* note 15, at 332-33.

20. 569 U.S. 576, 580 (2013).

21. 550 U.S. 398, 407 (2007).

22. 561 F.3d. 1351 (Fed. Cir. 2007). The skilled artisans have motivation and reasonable expectation to try to obtain the isolated DNA molecule, and the isolated DNA molecule is obvious.

The case series after 2007 may create a barrier for biotechnology and pharmaceutical industries to receive patent protection for genetic related innovations. A recent empirical study found that biotechnology patents suffer the highest invalidity rate when challenged based on enablement and written description in courts and the lowest win rate when adjudicated, compared to other fields of innovation.[23] Scholars have raised questions about whether the lack of strong patent protection would jeopardize the research and downstream development of medical service and therapeutics.[24] A question arises: Is the biotechnology industry doing just fine despite the difficulty in receiving patent protection?[25]

We first note that individual companies within the biotechnology industry are very different from each other. Most studies in the literature interpret biotechnology and pharmaceutics as an evenly developed unity. In fact, individual companies in the industry express heterogeneity in terms of company size, product, and competing strategy.[26] To evaluate the effect of a change in patent law within the industry, we borrow the narrative of the gold rush, differentiate gold placers with finite resources from those with large capital, and measure the effect. We also take into consideration the different types of gene patents and their role in an individual company's therapeutic or diagnostic product R&D.

The rest of this Article runs as follows. Part II provides background information, presents the definitions of various types of gene patent, and summarizes the change of gene patentability requirement of the U.S. patent system. Part III discusses the design of the empirical study, presents the sample companies and categorization criteria, and explains the results. Part IV interprets the empirical results and offers implications of these findings on patent law.

The Federal Circuit revitalized the "obvious to try" doctrine that was previously restricted except for two impermissible "obvious-to-try" scenarios: (1) skilled artisans have to try all parameters in the absence of indications about the choice of the parameter before he or she arrives the successful result; (2) the prior arts only provide "general guidance as to the particular form of the claimed invention" when the skilled artisans are exploring new technology. *Kubin*, 561 F.3d. at 1359 (quoting *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)).

23. John R. Allison et al., *Our Divided Patent System*, 82 U. CHI. L. REV. 1073, 1105-07 (2015).

24. *See id.* at 1140.

25. *See id.* at 1139.

26. *See* Omar Israel González Peña et al., *Pharmaceuticals Market, Consumption Trends and Disease Incidence Are Not Driving the Pharmaceutical Research on Water and Wastewater*, 18 INT'L J. ENV'T RES. & PUB. HEALTH 2532 (2021).

II. GENE PATENTS AND PATENT LAW

A. The Distinction of Gene Patents

"Gene patents [ordinarily] cover three distinct types of invention: (1) diagnostics [uses], (2) compositions of matter[,] and (3) functional uses" for small molecule drugs or personalized drugs.[27]

> (1) *Diagnostics Use Type*. Claims for a diagnostic use type patent cover statistical observations of how a genetic difference or mutation correlates to a certain disease. [28] For example, "[m]utations in [BRCA1 and BRCA2] genes can dramatically increase an individual's risk of developing breast and ovarian cancer."[29] Patents claiming well-known gene-disease correlations include "colon cancers . . . , hemochromatosis (HFE) . . . [,] late-onset Alzheimer's disease (Apo-E), Canavan disease, Charcot-Marie-Tooth disease (CMT-1A, CMT-X), spinal muscular atrophy (SMN1), spinocerebellar ataxia (SCA1–12), and others."[30] In 2012, the U.S. Supreme Court decided that a method of determining the dosage change based on a metabolite concentration in the patient's blood is not patent-eligible in *Mayo Collaborative Services v. Prometheus Laboratories, Inc*.[31] In light of the Mayo Test in the United State Patent and Trademark Office's (USPTO) Manual of Patent Examining Procedure (MPEP), a patent claiming diagnostic uses that merely cover conventional testing methods will be scrutinized more strictly.[32]
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> (2) *Compositions of Matter Type*. The compositions of a matter type gene patent cover isolated and purified genes,

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27. Jon F. Merz & Mildred K. Cho, *What Are Gene Patents and Why Are People Worried About Them?*, 8 CMTY. GENETICS 2 (2005).

28. *Id.*

29. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 582-83 (2013).

30. Merz & Cho, *supra* note 27, at 3; *see, e.g.* U.S. Patent No. 8,101,349 B2 (issued Jan. 24, 2012); U.S. Patent No. 7,368,531 (issued May 6, 2008); U.S. Patent No. 6,812,339 B1 (issued Nov. 2, 2004); U.S. Patent No. 5,767,337 (issued June 16, 1998); U.S. Patent No. 7,432,355 B2 (issued Oct. 7, 2008); U.S. Patent No. 5,679,635 (issued Oct. 21, 1997); U.S. Patent No. 8,975,020 B2 (issued Mar. 10, 2015); U.S. Patent No. 7,727,717 B2 (issued June 1, 2010); U.S. Patent No. 6,245,963 B1 (issued June 12, 2001); U.S. Patent No. 7,727,952 B2 (issued June 1, 2010); U.S. Patent No. 8,163,483 B2 (issued Apr. 24, 2012); U.S. Patent No. 6,855,497 B2 (issued Feb. 15, 2005).

31. 566 U.S. 66, 73 (2012).

32. U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2106 (9th ed., rev. 10, June 2020).

complementary DNA (cDNA), and all derivative products.[33] Examples of patents on the human genome sequence include: "recombinant proteins or drugs, [human insulin, human growth hormone,] viral vectors and gene transfer therapies, transfected cells, cell lines, and higher order animal models in which the patented gene has been inserted or knocked out."[34]

(3) *Functional Use Type for Small Molecule Drug*. A small molecule drug is one "that can enter cells easily because it has low molecular weight."[35] It is clearly "different from drugs that have a large molecular weight."[36] "Once [the small molecule drug is] inside the cells, it can affect other molecules, such as proteins, and may cause cancer cells to die."[37] In contrast, drugs with large molecular weight cannot enter the cells easily.[38] "Many targeted therapies [utilize] small molecule drugs."[39] For example, a small molecule drug is used for targeted cancer therapies "that block the growth and spread of cancer by interfering with specific molecules . . . that are involved in the growth, progression, and spread of cancer."[40]

The functional use type gene patent is important for a small molecule drug. "Small molecule drugs and therapeutic proteins differ substantially" in physiochemical properties.[41] They produce a therapeutic protein, and scientists need to work on the protein-coding sequence to generate a new cDNA molecule.[42]

Accelerated by cancer genome sequencing, the development of small molecule cancer drugs has shifted the paradigm "from a one-size-fits-all [treatment] approach that emphasized cytotoxic chemotherapy to a personalized medicine

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33. Merz & Cho, *supra* 27, at 4.
34. *Id.*
35. Nat'l Inst. Health, *Small-Molecule Drug*, NAT'L CANCER INST., http://www.cancer.gov/publications/dictionaries/cancer-terms/def/small-molecule-drug (last visited Oct. 11, 2021).
36. *Id.*
37. *Id.*
38. *Id.*
39. *Id.*
40. Nat'l Inst. Health, *Targeted Cancer Therapies*, NAT'L CANCER INST., http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet (last updated Sept. 15, 2021).
41. Scientific Writing Team, *Points to Consider in Drug Development of Biologics and Small Molecules*, NUVENTRA (May 13, 2020), http://www.nuventra.com/resources/blog/small-molecules-versus-biologics/.
42. *Id.*

> strategy that focuses on the discovery and development of molecularly targeted drugs . . . ."[43] These drugs often require substantial investment to develop novel approaches "to exploit [particular genetic] addictions, dependencies, and vulnerabilities [of] cancer cells."[44] "One such example is the use of Tamoxifen in the treatment of women with ER+ breast cancer."[45] In reaction, 65% of patients receiving this medicine developed resistance.[46] "Research[ers] later [discovered] that women with certain mutations in their CYP2D6 gene, a gene that encodes the metabolizing enzyme, were not able to efficiently break down Tamoxifen . . . ."[47] Breast cancer patients nowadays routinely receive a genome test to detect such specific mutations, and physicians can accordingly decide the treatment strategy.[48]

B. The Patentability Requirement of Gene Patents

1. The Patent Eligibility Requirement

The first threshold that gene patents have to overcome is the patent eligibility requirement. Before the United States Supreme Court's *Myriad* decision, the most dominant legal standard governing the naturally occurring but isolated and purified substance was handed down by the highly respected Judge Learned Hand in the *Parke-Davis & Co. v. H.K. Mulford & Co.* decision almost a century ago.[49] Judge Hand held that the applicant of the patented invention, a purified form of the naturally occurring hormone, is "the first to make it available for any use by removing it from the other gland-tissue in which it was found, it became for every practical purpose a new thing commercially and therapeutically" and "[t]hat was a good ground for a patent."[50] A century later, the so-called

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43. Swen Hoelder et al., *Discovery of Small Molecule Cancer Drugs: Successes, Challenges and Opportunities*, 6 MOLECULAR ONCOLOGY 2, 155 (2012).

44. *Id.* at 171; *see also* Lisa Larrimore Ouellette, *How Many Patents Does It Take to Make a Drug? Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 302 (2010).

45. Alexander G. Albrecht et al., *Personalized Medicine: Patentability Before the European Patent Office and the USPTO*, 64 GRUR INT. 1, 2 (2015).

46. *Id.* at 2-3.

47. *Id.* at 3.

48. *Id.*

49. Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95 (C.C.S.D.N.Y. 1911), *aff'd in part*, *rev'd in part* 196 F. 496 (2d Cir. 1912).

50. *Parke-Davis*, 189 F. at 103.

"good ground for a patent" of the purified or isolated form of a naturally occurring substance was reversed by the Supreme Court in the *Myriad* decision.[51]

Before the *Myriad* decision was made, the Federal Circuit held that a claim to "[a] purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin" was valid.[52] The PTO examination guideline endorsed Judge Learned Hand's opinion in the *Park-Davis* case that an isolated DNA sequence is patentable subject matter.[53]

In *Myriad*, the U.S. Supreme Court unanimously held that "a naturally occurring DNA segment is a product of nature and not patent-eligible" under 35 U.S.C.S § 101, but that synthetic genes, such as complementary DNA (cDNA), are patent-eligible.[54]

When the Supreme Court made the *Myriad* decision, it became widely recognized that the utility between isolated genomic DNA and cDNA is distinctive.[55] With genomic DNA, most genes consist of exons and introns.[56] Exons are coding sequences providing a "blueprint for the protein encoded by the gene," whereas introns are non-coding sequences.[57] When transcribed into RNA, introns are removed from RNA, and RNA can be used to produce cDNA.[58] The uninterrupted coding sequence of cDNA is more utilizable than isolated genomic DNA to facilitate gene-based diagnostic and therapeutic applications. By separating from the interrupting coding sequence, the researcher can combine the uninterrupted coding sequence with a new regulatory sequence, thus enabling the "manipulation of when, where, and at what level the gene is expressed."[59] The manipulation of gene expression is essential for recombinant-protein therapeutics and gene therapy.[60]

The United States government also expressed its policy consideration in its amicus curiae about whether human genes are "patent-

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51. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 580 (2013).
52. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1204, 1219 (Fed. Cir. 1991).
53. *See* MERGES & DUFFY, *supra* note 15, at 180-81; *see* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001).
54. *Myraid*, 569 U.S. at 580.
55. Schilling, *supra* note 16, at 753.
56. *See id.* at 750 (footnote omitted).
57. *Id.*
58. *Id.*
59. *Id.* at 752.
60. *See id.*

eligible [subject matter] under [35 U.S.C. §] 101."[61] The solicitor general opposed the patentability of isolated forms of unmodified gene sequence, but argued that "synthesized genetic materials such as cDNA are patent-eligible subject matter," because their production requires human intervention.[62]

The *Myriad* decision thwarted diagnostic type gene patents, yet sustained the composition of matter type gene patents.[63] The functional use type gene patent is less influenced by the *Myriad* decision, since this type of gene patent is indeed a chemical composition.[64]

2. The Non-Obviousness Requirement: The Revival of the "Obvious to Try" Doctrine, and the Rationalization of the Non-obviousness Test After *KSR*

a. The Revival of the "Obvious to Try" Doctrine

Some time before the Supreme Court made the *KSR* decision in 2007, the Federal Circuit had rejected the use of "obvious to try" in its non-obviousness analysis. In *Deuel*, the prior arts disclosed a particular protein's amino acid sequence and the method that can isolate the DNA sequence once the amino acid sequence is known. [65] Despite the teaching in the prior arts, the Federal Circuit held that the DNA sequence coding for the particular protein is not obvious.[66] The court disagreed with the precedent case, *Amgen Inc. v. Chugai Pharmaceutical Co*.[67] There, the Federal Circuit sustained the "obvious to try" doctrine.[68] The court held that when a compound may be defined by its process of preparation, and when the isolation method provides a definition for it, the process of preparation can render it obvious.[69]

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61. *See* Br. for the United States as Amicus Curiae in Supp. of Neither Party at 12, Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013) (No. 12-398).

62. *Id.*

63. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 591, 595 (2013).

64. *Id.* at 596.

65. *In re* Deuel, 51 F.3d 1552, 1557 (Fed. Cir. 1995).

66. *Id.* at 1558-59.

67. *Id.* at 1559-60.

68. Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1209 (Fed. Cir. 1991).

69. *Id.* at 1208-09 ("While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious.").

In opposition to *Amgen*, the Federal Circuit in *Deuel* rejected the "obvious to try" doctrine, holding that "the fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned and therefore obvious."[70] The "obvious to try" doctrine was later revived. As the Supreme Court rationalized the non-obviousness factors in its 2007 *KSR* decision, the Federal Circuit reaffirmed that "obvious-to-try" is an appropriate test to render an isolated gene sequence molecule obvious where a specific protein is disclosed and a specific DNA isolation method is taught.[71]

Kubin "presents a claim to a classic biotechnology invention-the isolation and sequencing of a human gene that encodes a particular domain of a protein."[72] Scholars have noted that there are two crucial dates worth our attention in *Kubin*, which reflect the fast-changing reality of the biotechnology industry.[73] The prior art patent, U.S. Patent No. 5,688,690 ("Valiante"), was filed in September 1994 and issued on November 18, 1997.[74] "Valiante disclose[d] a receptor protein called 'p38' that is found on the surface of human N[atural] K[iller] cells."[75] "Valiante's patent further described a five-step cloning protocol for 'isolating and identifying the p38 receptor," but "disclos[ed] neither the amino acid sequence of p38 . . . nor the polynucleotide sequence that encodes p38."[76]

Valiante incorporated another prior art as reference, which is a laboratory manual written by Sambrook et al.[77] "Sambrook does not discuss how to clone any particular gene, but provides detailed instructions on cloning materials and techniques."[78]

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70. 51 F.3d at 1559.

71. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 419-21 (2007); *In re* Kubin, 561 F.3d. 1351, 1359-60 (Fed. Cir. 2007). The skilled artisans have motivation and reasonable expectation to try to obtain the isolated DNA molecule, and the isolated DNA molecule is obvious. The Federal Circuit revitalized the "obvious to try" doctrine that was previously restricted except for two impermissible "obvious-to-try" scenarios: (1) skilled artisans have to try all parameters in the absence of indications about the choice of the parameter before he or she arrives the successful result; (2) the prior arts only provide general guidance as to the particular form of the claimed invention when the skilled artisans are exploring new technology; *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995) (citing *In re* O'Farrell, 853 F.2d 894, 901 (Fed. Cir. 1988)).

72. *In re Kubin*, 561 F.3d at 1352.

73. MERGES & DUFFY, *supra* note 15, at 693.

74. *Id.*

75. *In re Kubin*, 561 F.3d at 1354.

76. *Id.* (quoting U.S. Patent No. 5,698,690 col.18 l.6-col.19 l.28 (issued Dec. 16, 1997)).

77. *Id.* (citation omitted).

78. *Id.* (citation omitted).

"Kubin's application on the DNA sequence encoding the [p38] protein was filed on September 20, 2000."[79] The Board of Patent Appeals and Interferences found that Kubin "used conventional techniques 'such as those outlined in Sambrook' to isolate and sequence the gene that codes for [Natural Killer Cell Activation Inducing Ligand] [(]NAIL[)]."[80] "The Board also found that [Kubin's] claimed DNA sequence is 'isolated from a cDNA library . . . using the commercial monoclonal antibody C1.7 . . . disclosed by Valiante.'"[81]

In reviewing the Board's decision on non-obviousness and written description, the Federal Circuit found that despite the modest difference in the methodology disclosed in Valiante and Kubin for isolating NAIL p38 DNA, the technique in Valiante would not yield the same polynucleotide as the representative claim of Kubin.[82] Moreover, the court noted that even if Kubin had claimed a method of DNA isolation, "[t]he difference between Valiante's and . . . [Kubin's] techniques might be directly relevant to [the] obviousness . . . ."[83] However, since Kubin claimed a gene sequence, "any putative difference in Valiante's/Sambrook's and [Kubins]' *processes* does not directly address the obviousness of representative claim . . . ."[84] In regard to the inventor's motivation, the court noted that "[b]ecause of NAIL's important role in the human immune response, . . . 'one of ordinary skill in the art would have recognized the value of isolating NAIL cDNA, and would have been motivated to apply conventional methodologies, such as those disclosed in Sambrook and utilized in Valiante, to do so.'"[85]

The Federal Circuit properly recognized the growing demand for gene-based therapeutic applications. The Federal Circuit declined "to cabin KSR [in]to the 'predictable arts,' (as opposed to the 'unpredictable art' of biotechnology)."[86] It took into consideration the fast-changing nature of biotechnology industry.[87]

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79. MERGES & DUFFY, *supra* note 15, at 693.

80. *In re Kubin*, 561 F.3d at 1355 (quoting *Ex parte* Kubin, No. 2007-0819, 83 U.S.P.Q.2d 1410, at 5 (B.P.A.I. 2007)).

81. *Id.*

82. *Id.* at 1356.

83. *Id.*

84. *Id.*

85. *Id.* (quoting *Ex parte* Kubin, No. 2007-0819, 83 U.S.P.Q.2d 1410, at 6-7 (B.P.A.I. 2007)).

86. *Id.* at 1360.

87. *Id.* at 1361.

b. The *KSR* Effect on the Non-Obviousness of the Gene Patent

It is worth noting that while discrediting *Deuel*, the Supreme Court in *KSR* resurrected the Federal Circuit's holding in *O'Farrell*.[88] In *O'Farrell*, the Federal Circuit cautioned that the "obvious to try" doctrine might be misused.[89] "To differentiate between proper and improper applications of 'obvious to try,'" the Federal Circuit cited its own analysis in *O'Farrell* and outlined two situations where "obvious to try" is improperly applied in determining obviousness under § 103:

> (1) "[C]ourts should not succumb to hindsight claims of obviousness," when the inventor "would have . . . var[ied] all parameters or tr[ied] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful."
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> (2) It is "'obvious to try' [while exploring] a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it."[90]

The achieved invention is obvious, unless "the improvement is more than the predictable use of prior art elements according to their established functions."[91]

The Supreme Court in *KSR* cast doubts on the Federal Circuit's application of the "obvious-to-try" doctrine. More explicitly, "[t]he Supreme Court . . . invoked *Deuel* as a source of the discredited "obvious-to-try" doctrine."[92] The Federal Circuit in *Kubin* agreed with the Supreme Court in *KSR*, affirming the obviousness analysis in *KSR* that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."[93] The cost of discovering a drug or a therapy is

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88. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 414 (2007) (citation omitted); *see In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

89. *Id.*

90. *In re Kubin*, 561 F.3d. at 1359 (quoting *O'Farrell*, 853 F.2d at 903).

91. KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007).

92. *In re Kubin*, 561 F.3d. at 1358.

93. *Id.* at 1359 (quoting *KSR*, 550 U.S. at 421).

expensive, the market competition is intensive, and clinical trials and FDA approval are lengthy. Under market pressure, a skilled artisan is motivated to pursue every options within his technical grasp to isolate the DNA molecule that is disclosed by his or her peers.[94] After *Kubin*, the "obvious to try" test became a minimum threshold that biotechnology research and development must meet and more than an abstract legal doctrine.[95]

3. The Utility and Written Description Requirement

An inventor must, within the specification, provide "a written description of the invention, and of the manner and process of making and using it . . . ." [96] The inventor shall also disclose "the best mode contemplated by the inventor or joint inventor [for] carrying out the invention." [97] The written description, enablement, and best mode requirements under 35 U.S.C. §§ 111 and 112 comprise the basic disclosure that entitle the inventor to the patent. The requirements must be satisfied at the time of filing.[98] The written description under 35.U.S.C. § 112 has been raised recently and limited the availability for a gene patent of compositions of matter type.[99]

In *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, the Federal Circuit stated that where a patent claims a broad genus of antibody that would achieve an identical result, representative examples should be described in the specification to support the full scope of the claims.[100] Specifically, the MPEP provides that if a biomolecule sequence is only described by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, then the functional characteristic does not serve as a sufficient identifying characteristic for written description purposes.[101] To fulfill the written description requirement, an applicant must describe the core structures or representative examples in the specification if the patent claims a genus.[102]

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94. *See id.*
95. *See* Schilling, *supra* note 16, at 742.
96. 35 U.S.C. § 112.
97. *Id.*
98. *Id.* § 111.
99. *See also* Karshtedt et al., *The Death of the Genus Claim*, 35 HAR. J.L. TECH. 1, 50 (2021).
100. 759 F.3d 1285, 1299-300 (Fed. Cir. 2014).
101. U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 2163 (9th ed., rev. 10, June 2020).
102. *Id.*

C. Research Question

The case law of *Myriad*, *KSR*, and *Kubin* affects the three types of gene patents differently. The compositions of matter type gene patent cover "the isolated and purified gene (cDNA)" and "all derivative products."[103] The isolated and purified gene patent was held to be non-patentable subject matter by the Supreme Court in *Myriad*, while cDNA was patentable subject matter.[104] However, *Myriad* does not involve method claims, patents on new applications of knowledge about the isolated genes, or "the patentability of DNA in which the order of the naturally occurring nucleotides has been altered."[105] Thus, the *Myriad* decision does not affect the other two types of gene patents: diagnostic type gene patent, which covers "statistical observations of [how] a genetic difference" or mutation correlates to a certain disease, and the functional use type gene patent for small molecule drugs.[106] However, any gene patent types that remain patentable subject matter shall also meet the higher standard of obvious-to-try and written description set by *Kubin* and other case law.[107]

The inability to obtain adequate patent protection or uncertainty in the outcomes of litigations are recognized as risk factors for the biotechnology industry operation.[108] "If our intellectual property positions are challenged, invalidated, circumvented, or expire, or if we fail to prevail in present and future intellectual property litigation, our business could be adversely affected," as stated in the annual report of Amgen in the fiscal year of 2007.[109] By the time the Federal Circuit invalidated Kubin's patent, Amgen Inc., which is the real party in interest of Kubin's isolated DNA sequence, acutely observed that "[t]o date, there has emerged no consistent policy regarding [the] breadth of claims allowed in [the pharmaceutical and biotechnology] companies' patents."[110]

Modern pharmaceutical and biotechnology companies may not be parallel to the gold placers in the California Gold Rush, but the tightened limitation on patentability and the change of policy have made it more

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103. Merz & Cho, *supra* note 27, at 4.
104. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 580 (2013).
105. *Id.* at 595-96.
106. Merz & Cho, *supra* note 27, at 2, 4.
107. *See also* Schilling, *supra* note 16, at 742.
108. Allison et al., *supra* note 23, at 1136-38.
109. Amgen Inc., Annual Report (Form 10-K), 33 (Feb. 28, 2008), http://investors.amgen.com/static-files/c6251be0-ae2f-407b-b131-58c23226db92.
110. *Id.* at 49.

difficult for these companies to obtain gene patents.[111] Isolating a DNA sequence using a known method is like placer gold mining, and fabricating a therapeutic protein or antibody is like hard rock mining. In hard rock mining, gold is encased "in rock instead of [as] fragments in loose sediment."[112] Hard rock mining took place of placer gold mining and became the mainstream. Similarly, small molecule drugs or therapeutic proteins helped make a paradigm shift from the one-size-fits-all drug.

Biotechnology and pharmaceutic companies employ a large amount of capital to develop and commercialize therapeutic proteins or small molecule drugs.[113] If a company fails to complete the costly process from drug discovery to product launch, then it will have exhausted all the investment without rewards. This is like if a gold miner, whereby if he or she lacks skills or capital to extract the gold deeply encased in rock, were to leave the mining spot when the gold fragments on the ground surface are exhausted.

Patent protection provides incentives that lead to creations and discoveries. The exclusivity conferred by patent protection is more important for biotechnology and pharmaceutic companies because it is indispensable to recoup the economic return necessary to sustain the expensive drug development and commercialization. Conversely, exclusivity may impede the flow of information that might spur more inventions. The patent policy's main consideration is to strike a delicate balance between incentives and impediments.[114] We shall study if the rule against patents on naturally occurring DNA segments, while sustaining patents on cDNA or functional use of DNA in small molecule drug or therapeutic protein, falls short of the incentive effect for biotechnology invention. We assume that isolating the naturally occurring DNA molecule by the known methods can be compared to collecting gold fragments on the ground surface, and developing and commercializing the small molecule drug or therapeutic protein can be compared to extracting gold encased in hard rock. The policy that rules against a patent on a naturally occurring DNA segment tends to remove impediments to the flow of information that might spur more invention. The policy may also prevent

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111. *See* Schilling, *supra* note 16, at 736-39.

112. *Mining: What Is Gold Mining? How Is Gold Mined?*, GEOLOGY PAGE (Nov. 10, 2021, 8:50 AM), http://www.geologypage.com/2019/04/what-is-gold-mining-how-is-gold-mined.html.

113. *See* Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL DECISION ECON. 469, 470 (2007).

114. *See* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Inovation? The Anticommons in Biomedical Research*, 280 SCI 698 (1998).

small-size companies from investing in expensive drug development since they usually lack the resources to sustain a protracted war from drug discovery to product launch. More adversely, small-size companies often lack the resources to yield R&D results that fulfill the more stringent patentability standards of the obvious-to-try doctrine and written description under 35 U.S.C 103 and 112.[115]

It is widely perceived that strong patent protection is critical for biotechnology and pharmaceutic companies.[116] Such companies rely on the exclusivity conferred by the patent protection to prevent counterfeits and to recoup their investment in the costly and lengthy product development. This concept needs to be examined based on economic data.

In this study, we examine whether there is a correlation (not causality) between the patent data and the revenue of a company that owns a patent. We identify patents that claim or describe gene sequence in the specifications as a gene patent and further specify whether the correlation is positive or negative. If the relationship exists, then it could be a change in revenue that caused the change in patent numbers, or there might be a confounder that was responsible for the correlation between the change in patent number and revenue.[117]

The empirical result of a correlation will allow us to examine the proposition that the biotechnology industry is suffering from a lack of strong patent protection. The result might also provide some clues about how the patent policy of *KSR* and *Myriad* strikes a balance between incentivizing innovation and encouraging information flow in the biotechnology field.

In the next parts of this Article we present the empirical study, the result, and the implication. Part III is the empirical data and the methodology. Part IV is the empirical result. Part V is the implication of the result. Finally, in the conclusion remarks, we present an observation on the policy effect in the biotechnology industry.

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115. Schilling, *supra* note 16, at 756-57.

116. *Id.* at 754 n.174 ("Because the development of biotechnology and pharmaceuticals can be time intensive, unpredictable, and expensive, life sciences innovators need the mechanisms provided by the patent system to recoup their investments and ensure a steady revenue stream for further research and development." Robert J. Paradiso & Lisa K. Schroeder, *District Court Holds Myriad's Gene Patents Invalid*, 18 METROPOLITAN CORP. COUNS. 25, 25 (2010)).

117. Gray Watson, *Correlation Versus Causality*, http://homepage.ntu.edu.tw/~ntut019/ecomicro/Corr-Causation.pdf (last visited Sept. 16, 2020).

III. METHODOLOGY AND DATA

A. Data Source and Dataset

We use empirical data to examine the correlation between a patent and a patent owner's revenue. The empirical dataset comprises patent data and financial data of pharmaceutical and biopharmaceutical companies in the United States during a twenty-year period from 2000 to 2019.

The financial data are collected from the annual reports filed by the observation companies to the U.S. Securities and Exchange Commission (SEC). We record each observation company's annual revenue, net income, R&D expenses, and selling and administrative expenses in each year during the observation period.

The patent data are obtained from The Lens's database. It is a joint initiative of an international non-profit organization (Cambia) and Queensland University of Technology and supported by the Rockefeller Foundation. The Lens's database allows free searching of over 10 million full-text patent documents and scholarly works, which can be aggregated, annotated, exported, and analyzed. We record each company's grant patent, biotechnology patents, and their forward citation counts in every year of the observation period. The dataset consists of twenty publicly-traded companies listed in Table 1.

Table 1. Summary of Observation Companies

Period	**2000-2019**	
Company	**Industry Field***	**Country**
Johnson & Johnson	Pharma.	U.S.
Pfizer	Biopharma	U.S.
Bayer AG	Pharma.	Germany
Novartis	Pharma.	Switzerland
F. Hoffmann-La Roche AG	Pharma.	Switzerland
GlaxoSmithKline	Pharma.	UK
Merck & Co. Inc.	Pharma.	U.S.
Sanofi	Pharma.	France
AstraZeneca	Biopharma	UK
Abbott Laboratories	Pharma.	U.S.
Eli Lilly and Company	Pharma.	U.S.
Bristol-Myers Squibb	Pharma.	U.S.
Amgen Inc.	Biopharma	U.S.
Gilead Sciences Inc.	Biopharma	U.S.
Biogen Inc.	Biopharma	U.S.
Celgene	Biopharma	U.S.
Regeneron	Biopharma	U.S.
Incyte Corporation	Biopharma	U.S.
Myriad Genetics, Inc.	Biopharma	U.S.
IonisPharma.	Biopharma	U.S.

*: Pharma: pharmaceutical company; Biopharma: bio-pharmaceutical company.

This dataset includes information covering 20 years from the 20 companies for empirical analysis. Most samples (14) are from the U.S.; others are from Germany, Switzerland, UK, and France (Table 1). According to the company description on financial reports and official websites, half of the companies define themselves as pharmaceuticals and the other half define themselves as biopharmaceutical.

B. Variables

Table 2 shows the dependent and independent variables. Since every company aims to earn profit, profit is the incentive. We use annual revenue and profit as dependent variables in the empirical models. To avoid extreme values, we take exponential values of the two dependent variables.

The revenue variable measures a company's scale, and the profit variable tests the company's ability in earning returns.

Patent data and R&D expenditure are recognizable proxies for a company's efforts on innovation activities.[118] In order to investigate the contribution of biotechnology patent (patent that covers or describes gene sequences in its claims or specification), the biotechnology patent is distinguished as an independent variable ("Bio_Patent"). The patent data also includes forward citation counts of patent and biotechnology patent to measure the quality of innovation.

Patents are less likely to contribute to revenue in the year when they are granted, but are more likely to contribute in coming years. Therefore, we use lagged variables, which are the average numbers of patents and biopatents the firm received in the past three years (3Y_Patent and 3Y_BioPatent).

The model also considers the percentage of biotechnology patents to all patents in the year, which is represented by the variable Bio_Ratio. This variable serves as an indicator to measure how much biotechnology is involved in the company innovation. For marketing activities, we collect data about a firm's efforts in sales and administrative activities (i.e., SGA). To determine the level that the company places emphasis to marketing and administrative activity compared to R&D activity, we use the variable S-Ratio (i.e., SGA expenditure/R&D expenditure) instead of direct SGA expenditure.

118. Sadao Nagaoka et al., *Patent Statistics as an Innovation Indicator*, *in* HANDBOOK OF THE ECONOMICS OF INNOVATION at 1085, 1105 (Bronwyn H. Hall et al. eds., 2010); *see also* You-Na Lee, *Evaluating and Extending Innovation Indicators For Innovation Policy*, 24 RES. EVALUATION 417, 472-73 (2015).

Table 2. Variables

Variable	Description	Data source
Dependent variables		
LnREV	Exponent of annual revenue in the observation year LnREV=Ln (Revenue)	Company Annual Report
LnProfit	Exponent of annual net profit in the observation year LnProfit = Ln(Profit)	Company Annual Report
Independent variables		
3Y_Patent	Average number of patents granted over the past three years 3Y_Patent = average patent numbers in the observation year and previous two years	LENS
Citation	Total number of patent forward citations received in the observation year	LENS
3Y_Biopatent	Average number of biotechnology patents granted over the year and previous two years	LENS
Bio_Citation	Total number of biotechnology patent forward citations received in the observation year	LENS
Bio_Ratio	Ratio of biotechnology patent number to total patent number	LENS
RD	R&D expenditure in the observation year	Company Annual Report
S_Ratio	Ratio of SGA expenditure to R&D expenditure **SGA: expenditure used in sales, marketing, and relevant administrative works*	Company Annual Report
RD x S_Ratio	The effort a company spent in commercializing its research output	Company Annual Report

C. Methodology

This study utilizes the panel data regression model to estimate the degree to which company revenue corresponds to changes in the strengths and characteristics of patent quantity, R&D expenses, and operation expenses. The data form a multi-dimensional dataset observed over a long time period.

Previous studies of the biopharmaceutical industry lay a foundation for the hypothesis of this study. In this industry, the term biotechnology patent refers to the patent claiming or describing a gene sequence in its specification.[119] This is identical to the definition in prior literature, but relatively straightforward for data collection purposes. Biotechnology patents cover the use of medical diagnostics, medical tests, and pharmaceutical products, verified by the fact that biotechnology patents are mostly owned and used by biomedical companies, pharmaceutical companies, and universities.[120]

Patent protection is effective at securing rewards for costly and expensive research and development, and patents with higher scientific values are more desirable. Therefore, we assume factors, including patent applications, patent qualities, technology characteristic, R&D expenses, and operation expenses (including selling expenses), have certain levels of determinacy in revenue. Thus, we denote a regression model as:

$$LnRevit = \alpha it + \beta 1(3Y\_Patent) + \beta 2(Citation) + \beta 3(3Y\_BioPatent) + \beta 4(BioCitation) + \beta 5(RD) + \beta 6(Bio\_Ratio) + \beta 7(RD \times S\_Ratio) + \varepsilon it$$

$$LnProfitit = \alpha it + \beta 1(3Y\_Patent) + \beta 2(Citation) + \beta 3(3Y\_BioPatent) + \beta 4(BioCitation) + \beta 5(RD) + \beta 6(Bio\_Ratio) + \beta 7(RD \times S\_Ratio) + \varepsilon it$$

To reduce the interference of company size, we use the exponent of revenue and profit, because the revenue or profit of large-size companies is far larger than that of small-size companies. For example, in our sample, the average revenue of Pfizer from 2000 to 2019 is $48.714 billion, while the average revenue of Celgene over the same period is $4.509 billion. If we use revenue as the variable, then the result is probably misled by the variation among all revenues.

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119. Allison et al., *supra* note 23, at 1086; *see also* Merz & Cho, *supra* note 27, at 4.

120. Examples of the top 20 applicants of U.S. biotechnology patents include Univ. of California, Genentech Inc., Du Pont, Monsanto Technology LLC, Isis Pharmaceuticals Inc. (Ionis), Amgen Inc., Novartis Ag, Regeneron Pharma, Harvard College, Human Genome Sciences Inc., and Smithkline Beecham Corp.

We assume that patents granted to a company correlate to its profit and revenue, but a company may not generate profit in the granted year. It takes time to negotiate a patent licensing or settle a litigation, and the patent owner starts to receive the royalty or infringement damages after several years from the patent grant. Therefore, we use the delayed variables 3Y_Patent and 3Y_Biopatent to measure the effect of the average number of patents granted to the company over the past three years.[121]

The variables Citation and Bio_Citaion are not delayed variables because the forward citation of the patent measures the impact on scientific research and development. Since the patent application is publicized eighteen months from its filing date, researchers can access the information of the patent before the patent is granted.[122] The variable S_Ratio is the ratio of Selling, General and Administrative (SG&A) expenditure to R&D expenditure. We use the product of the variables RD and S_Ratio instead of SG&A to eliminate the interference of company size, because large-size companies usually spend more on SG&A not only for product commercialization, but also to maintain operations.

IV. THE RESULTS OF EMPIRICAL DATA

A. Description of Dataset

We select the sample from all biopharmaceutical and pharmaceutical companies that are publicly traded in the U.S. stock market that have considerable annual revenue, R&D expenditure, and patent numbers. To verify if the dataset represents the U.S. biotechnology statistics, we collect biotechnology patent numbers filed in the U.S during the observation period 2000-2019 and make a comparison. We find that despite our dataset

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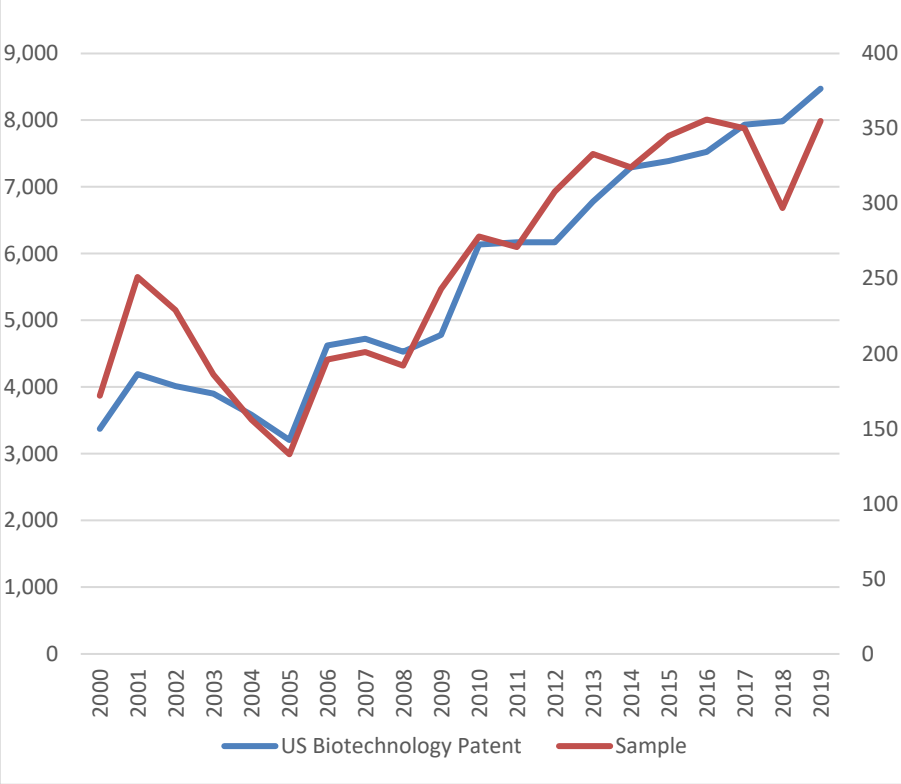
121. For example, before the expiration of Pfizer's original composition of matter patent on its blockbuster brand name drug "Viagra" in early 2000s, Pfizer filed a "method patent" using Viagra to treat Erectile Dysfunction (ED) in 2001. U.S. Patent No. 6,469,021B1 (issued October 22, 2002). On the same day when the method patent was granted, Pfizer sued direct competitors GlaxoSmithKline, Bayer AG, Eli Lilly and Company for patent ingringement. Merz & Cho, *supra* note 29, at 5. In March of 2010, Pfizer sued Teva Pharmaceutical Industries Ltd. (Teva) and Sun Pharmaceutical Industries Ltd.(Sun) for patent infringement of its method patent of treatment of ED. Pfizer, Teva, and Sun settled in 2013. "As of December 31, 2013, the remaining receivables from Teva are . . . US $512 million." Tava agreed to "launch [the] generic version of *Viagra* in the U.S. in December 2017 . . . ." Pfizer Inc., Annual Report (Form 10-K), at 20, 307 (Feb. 28, 2014); *see also* David Teather, *GSK and Bayer's Orange Pill Challenges Viagra*, GUARDIAN (Sept. 18, 2020, 10:09 AM), http://www.theguardian.com/business/2003/aug/21/glaxosmithklinebusiness.

122. 35 U.S.C. § 122(b)(1)(A) (2018).

containing only twenty firms, the correlation index between the dataset and the total biotechnology patent numbers highly correlates (correlation coefficient = 0.9). It is clear that the dataset is representative.

Figure 1. U.S. Biotechnology Patent (Grant) Trend Over 2000-2019



Before the empirical test starts, Table 3 lists the general statistics about the observation companies in the dataset, which is composed of twenty years of data from twenty companies. The yearly average revenue ranges from $208 million to $59.955 billion. Some profit rates are as high as 20%, and some are negative. In other words, both remunerative and unprofitable companies are included in the dataset. In the dataset, about half of the sample companies spend several thousands millions of US dollars in R&D every year. The patent yield also varies among the sample companies, ranging from hundreds to units digit. The gene patent percentage for most of the sample companies is double-digits. We consider these innovation

indicators for exploring the impacts on revenue and profit in different models and demonstrate the regression result in the next section.

Table 3. General Statistics of Observation Companies

Period Company	2000-2019 Revenue (Yearly Average) ($mn)	Profitability (%)	R&D Exp. (Yearly Average) ($mn)*	U.S. Patent (Yearly Average)	Gene Patent Percentage (Yearly Average) (%)
Johnson & Johnson	59955.6	18.2%	7291.0	84.9	2.67 %
Pfizer	48714.2	22.2%	7460.5	47.6	22.04 %
Bayer AG	42721.2	6.6%	3858.8	89.0	3.38 %
Novartis	39741.5	21.3%	6864.1	184.8	17.42 %
Roche AG	39696.3	27.3%	7621.8	72.9	16.09 %
GlaxoSmithKline	39429.1	25.8%	5557.0	29.2	21.58 %
Merck & Co. Inc.	37077.5	15.4%	6401.0	69.1	32.52 %
Sanofi	32759.8	18.4%	5025.9	60.8	21.94 %
AstraZeneca	24735.1	17.5%	4689.0	66.1	9.23 %
Abbott Laboratories	23229.2	14.4%	1957.1	93.7	15.12 %
Eli Lilly	18438.1	16.6%	4024.2	52.3	20.91 %
Bristol-Myers Squibb	17872.6	17.3%	3828.3	85.8	18.91 %
Amgen Inc.	15108.5	24.6%	2924.8	45.9	47.72 %
Gilead Sciences Inc.	11028.1	24.3%	1938.1	33.1	11.94 %
Biogen Inc.	5735.4	17.1%	1208.6	34.6	59.57 %
Celgene	4509.3	7.1%	1680.6	13.2	2.97 %
Regeneron	1891.3	-71.2%	823.5	26.3	81.63 %
Incyte Corporation	475.3	-537.4%	358.8	25.4	38.80 %
Myriad Genetics, Inc.	379.2	-2.9%	53.4	6.6	49.52 %
Ionis Pharma.	208.2	-78.5%	186.2	36.8	82.99 %

B. Regression Result of All Observation Companies

We first demonstrate the regression result of the empirical data for 2000-2019 in Table 4 containing the revenue model and the profit model. In the revenue model, the exponent of revenue is the dependent variable. The variable 3Y_Patent with a coefficient of 0.0037 is significant at the 0.05 level ($p< 0.05$). The variables Biocitation with a coefficient of -0.0016 and RD with a coefficient of 0.0002 are significant at the 0.01 level ($p < 0.01$).

In the profit model, the exponent of profit is the dependent variable. The variable RD with a coefficient of 0.0002 is significant at the 0.1 level ($p < 0.1$).

Table 4. Regression Result of 2000-2019

Period: 2000-2019	Revenue Model DV: LnRev		Profit Model DV: LnProfit	
	ß coefficient	P-value	ß coefficient	P-value
3Y_Patent	0.0037	**	0.0076	
Citation	0.0002		0.0005	
3Y_Biopatent	0.0067		0.0107	
Biocitation	-0.0016	***	-0.0018	
RD	0.0002	***	0.0002	*
Bio_Ratio	-0.0014		-0.0024	
RDxS_Ratio	0.0000		0.0001	
R-sq(between)	0.7124		0.5669	
N	199		199	

* P<0.1; ** P<0.05; *** P<0.01.

The regression result shows a positive correlation between granted patent and revenue. For a company receiving one more patent each year in the past three years, the revenue increases by 0.0037% each year. There is a negative correlation between the forward citation received by the biotechnology patent and the revenue. For a company receiving one more forward citation of the biotechnology patent each year, the revenue decreases by 0.0016% each year. In both revenue and profit models, there is a positive correlation between R&D expenditure and the revenue or profit. A company that spends one more dollar on R&D each year receives a 0.0002% increase in revenue or profit.

Bear in mind that a correlation is not causation. It might be that companies generating more income are more willing to or capable of spending more on R&D and filing patents. It might be that less profitable companies are more willing to improve their patent quality (in terms of forwarding citation). It might also be that increasing the biotechnology patent's citation fails to reward the patent owner and diminishes the revenue. The puzzle of the correlation between biotechnology patent quality and company revenue requires further investigation.

The results briefly suggest that the devotion of a company's wealth and time to research and development reaps patents and boosts revenue growth for all biopharmaceutical companies. However, it seems counterintuitive that the influence of biotechnology patents, in turn, jeopardizes revenue. In the next section we further investigate whether it is common for all companies to suffer a loss by developing prestige biotechnology patents, or whether it depends on certain company characteristics.

C. A Comparison Between the Two Groups of Companies

The variable R&D expenditure is the only factor showing a positive contribution in the model. We observe in our samples that R&D expenditure varies on a large scale. For example, the average R&D expenditure of Pfizer from 2000 to 2019 is $7.460 billion, while the average revenue of Myriad Genetics, Inc. over the same period is $53.4 million. We then take into consideration the nature of R&D and its huge cost in biotechnology and pharmaceutical industry and categorize the sample companies accordingly.

1. Categorization

Innovation in biotechnology and pharmaceutical is both time-consuming and abrupt progress. On average, it takes more than a decade to bring a therapeutic product to market with the cost ranging from $500 million to $2 billion.[123] The discovery of potential therapeutic material bears notable uncertainty and the research efforts are not cumulative. One study finds that there are only 3.5 to 5 patents covering a small-molecule

123. *See* Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 20 (2016).

drug, far fewer than the patents covering an Apple iPhone.[124] In other words, only a small portion of patents successfully transform into the final product that reaches the market. A success in one drug product does not promise the success of the next drug product.

To sustain such uncertainty, a pharmaceutical company is expected to expend considerable resources until the product is ready to reach the market. We suggest categorizing the sample companies in view that R&D expenditure may provide some clues.

We assume that each firm's annual R&D expenditure is normally distributed, and hence we categorize the sample companies by the criterion of standard deviation. According to the empirical rule in statistics, 67% of data lays within one standard deviation of the mean. If a company's mean annual R&D expenditure minus one standard deviation exceeds $2 billion, then 84% of its annual R&D expenses during 2000-2019 exceed $2 billion. In other words, the company has R&D resources to carry out various products through different R&D stages.

We categorize our sample companies whose 84% of annual R&D expenses during 2000-2019 exceed $2 billion as group A. The other sample companies are Group B, whose R&D expenditures fluctuate over the period. Group A is more financially robust to complete the R&D cycle from drug discovery to product distribution. Table 5 shows the categorization of Group A and Group B companies.

124. Ouellette, *supra* note 44; *see also* Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1183-85 (2002).

Table 5. Categorization of Observation Companies

Group A* (High R&D)	Group B (Low R&D)
F. Hoffmann-La Roche AG	Celgene
Johnson & Johnson	Gilead Sciences Inc.
Novartis	Amgen Inc.
Merck & Co. Inc.	Incyte Corporation
Pfizer	Abbott Laboratories
Sanofi	Biogen Inc.
GlaxoSmithKline	Regeneron
AstraZeneca	Ionis Pharma.
Bristol-Myers Squibb	Myriad Genetics, Inc.
Eli Lilly	
Bayer AG	

* Companies with 84% of annual R&D expenses during 2000-2019 over $2 billion.

We apply the same regression model to both high R&D (group A) companies and low R&D (group B) companies, where:

$$LnRevit = \alpha it + \beta 1(3Y\_Patent) + \beta 2(Citation) + \beta 3(3Y\_BioPatent) + \beta 4(BioCitation) + \beta 5(RD) + \beta 6(Bio\_Ratio) + \beta 7(RD \times S\_Ratio) + \varepsilon it$$

$$LnProfitit = \alpha it + \beta 1(3Y\_Patent) + \beta 2(Citation) + \beta 3(3Y\_BioPatent) + \beta 4(BioCitation) + \beta 5(RD) + \beta 6(Bio\_Ratio) + \beta 7(RD \times S\_Ratio) + \varepsilon it$$

The regression results are presented in Part V.C.2 (where revenue is the dependent variable) and Part IV.C.3 (where profit is the dependent variable). The comparisons of high R&D and low R&D companies are demonstrated in Part V.

2. Revenue Regression Model

High R&D companies in Group A are more financially robust than low R&D companies in Group B. In the long term, the high R&D companies in Group A spend more than $2 billion annually most times. The revenue regression result in Table 6 shows that as the number of biotechnology patent increases, so do the revenues of both high R&D and low R&D companies. For all companies, there is a positive correlation between the biotechnology patent numbers and revenue in the long term. It is noticeable that increasing the forward citation of biotechnology patents is not a virtue for low R&D companies. For low R&D companies, increasing the forward citation of biotechnology patents leads to lower

revenue. Increasing R&D expenses also improves the revenue for all companies in the long term. In particular, for low R&D companies, obtaining more patents including biotechnology and non-biotechnology patents has a more significant effect.

Table 6. Revenue Regression Result of Group A and Group B

DV: LnRev 2000-2019	Group A (High R&D) (Fixed Effect)		Group B (Low R&D) (Fixed Effect)	
	ß coefficient	P-value	ß coefficient	P-value
3Y_Patent	0.0008		0.0154	**
Citation	0.0000		0.0001	
3Y_Biopatent	0.0001	*	0.0225	**
BioCitation	0.0001		-0.0008	*
RD	0.0001	***	0.0004	***
Bio_Ratio	0.0012		-0.0153	***
RD x S_Ratio	0.0001	***	0.0002	
R-sq (between)	0.8472		0.8434	
N	11		9	

* P<0.1; ** P<0.05; *** P<0.01.

The regression result in Table 6 reveals for companies that are less financially robust, revenue generated by prestigious biotechnology innovation is lower-than-expected. For companies with limited resources, concentrating on influential biotechnology patents dilutes their resources for product commercialization, marketing, and other revenue-generating activities.

3. Profit Regression Model

Compared to the revenue regression model in Part IV.C.2, the profit regression model demonstrates an important different correlation in the forward citation of biotechnology patent. For high R&D companies, there is a positive correlation between biotechnology patent quality (forward citation) and profit. When high R&D companies receive more forward citations of the biotechnology patent, the profit increases. On the other hand, it might because the high profit allows more R&D expenses to improve the biotechnology patent quality.

For low R&D companies, there is conversely a negative correlation between profit and biotechnology patent citation. When low R&D companies receive more forward citations of the biotechnology patent, the profit decreases in the long term. It could also be that the relatively low profit limits R&D expenses to improve the biotechnology patent quality. We take one Group B company for instance. In 2015, Celgene earned a net profit of $1.602 billion. One more forward citation of the biotechnology correlates to a profit loss of $17,622 (0.0011% of the profit) in the same year. Moreover, for high R&D companies, the marketing and administrative activity efforts boost their revenue, but have no significant effect on profits.

Table 7. Profit Regression Result of Group A and Group B

DV: LnProfit 2000-2019	Group A (High R&D) (Fixed Effect)		Group B (Low R&D) (Fixed Effect)	
	ß coefficient	P-value	ß coefficient	P-value
3Y_Patent	-0.0031		0.0066	
Citation	-0.0001		0.0002	
3Y_Biopatent	0.0109		0.0248	
BioCitation	0.0012	*	-0.0011	*
RD	0.0001		0.0007	***
Bio_Ratio	-0.0082		-0.0044	
RD x S_Ratio	0.0000		0.0002	
R-sq (between)	0.7783		0.8381	
N	11		9	

* P<0.1; ** P<0.05; *** P<0.01.

V. SUMMARY

To summarize the regression result in this study, we list revenue and profit comparisons between high R&D and low R&D company performances in Table 9.

A. The Role of R&D and Innovations for Biopharmaceutical Companies

We find that when a biopharmaceutical company innovates more, its revenue grows more. To be more profitable, those low R&D group companies need to spend more on R&D, while those high R&D groups

need to produce influential patents with higher citations. These large-scale R&D companies utilize high-quality patents to reach a knowledge diffusion effect, which also helps them to positively shape their industrial position and gain profit from competitors.

B. The Patent Portfolio Strategy in Biotechnology Innovation

Biotechnology innovation can increase revenue for both groups of companies, but they should still consider a patent strategy to get greater profit. Large-scale and high R&D companies often have built up a market position with a strong marketing network and tend to be more experienced in product commercialization. Therefore, a prestige and influential biotechnology patent can help them to obtain good profit. In contrast, for low R&D companies, our study suggests pursuing the numbers of biotechnology patents, as focusing just on biotechnology is not a desirable practice. Based on the empirical results, small-scale and low R&D companies should spend more on R&D and diversely invest their innovation into various types of technologies.

C. Marketing Involvement Strengthen Large-Scale R&D Companies in Business Performance

We do observe a significant impact on the revenue from the interaction term between R&D and marketing expenditure for high R&D companies. For high R&D companies, their marketing activities magnify the reward of R&D. In contrast, the interaction term between R&D and marketing expenditure for low R&D companies is not significant. It implies that companies with a limited R&D budget cannot increase sales by marketing if they do not own sufficient and desirable technology.

This situation also reflects historical experience in the California Golden Rush. Compared to surface gold mining, hard rock mining requires more sophisticated tools and skills. It also requires a higher level of capital injection that enables production activities' coordination, transportation system build-up, and more talented people to join the production. When surface gold is exhausted, gold miners without sufficient tools and skills can only walk away.

Biotechnology and pharmaceutical companies need to input a large amount of capital to develop and commercialize the therapeutic protein or small molecule drug.[125] If a company fails to complete the costly process

125. DiMasi & Grabowski, *supra* note 113, at 475.

from drug discovery to product launch, then it would exhaust all investment without rewards. This is just like a gold miner, whereby if he or she lacks the skills or capital to extract the gold deeply encased in rock, then he or she will leave the mining spot when the gold fragments on the ground surface are exhausted.

Table 8. Revenue Performance Comparison

Revenue	Factor	REVENUE		PROFIT	
		High R&D Group	Low R&D Group	High R&D Group	Low R&D Group
Bio-Patent	Quantity	(+)	(+)		
	Quality		(−)	(+)	(−)
All Patent	Quantity		(+)		
	Quality				
Patent portfolio strategy	(BIO-PAT RATIO)		(−)		
R&D		(+)	(+)		(+)
R&D x S_Ratio		(+)			

** The symbol (+) means a positive correlation between the independent and dependent variables, and (−) means a negative correlation. A blank means no significant correlation is found.

Companies with steady and robust R&D expenses are capable of bringing a therapeutic to market from the pipelines. When confronting higher patentability standards of biotechnology innovation, they are more capable of meeting the eligibility, utility, and non-obviousness requirement since they have more R&D personnel and laboratories. They can also develop different types of therapeutics to avoid relying on a single product. When one gene patent is challenged or invalidated by competitors, such a company can turn to other products to secure the economic returns.

Companies spending less money on R&D may less likely develop a variety of marketable products. Without product diversity, they may suffer a loss when the patent is invalidated. This in turn becomes a negative feedback system that is not desirable for companies with lower R&D robustness or for pure biotechnology companies. This may explain why

the gene patent numbers of Myriad and Biogen Inc. (Group B companies) drop significantly as they lack product diversity to recoup profit when their patent is invalidated.

VI. CONCLUSION

Previously in 1995, when prior art taught "a method of gene cloning, together with a reference disclosing a partial amino acid sequence of a protein," a classical biotechnology invention, claiming DNA molecules encoding such protein, was held non-obvious.[126] The court in *Deuel* held "that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the [obviousness] question," and "[a] general incentive does not make obvious a particular result."[127] Twelve years later in 2007, for the same dispute about the obviousness of DNA molecules encoding a known protein, the Federal Circuit cited *KSR* and recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."[128]

There are few pieces of literature emphasizing the market pressures faced by pharmaceutical and biotechnology companies.[129] Biotechnology, which plays a central role in the mainstream small-molecule drug or therapeutic protein, is an unpredictable art. The uncertainty of drug development is huge and costly. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the drug R&D usually takes 10-15 years on average and costs an average of $2.6 billion from discovering the candidate composition to being approved by the U.S. Food and Drug Administration (FDA).[130] Failures are also included in the R&D despite yielding no significant economic returns.[131] Moreover, the FDA approval rate is extremely low.[132] Only one in every five thousand to ten

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126. *In re* Deuel, 51 F.3d 1552, 1557, 1560 (Fed. Cir. 1995).

127. *Id.* at 1559.

128. *In re* Kubin, 561 F.3d 1351, 1359 (Fed. Cir. 2007) (quoting KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)).

129. Oullette, *supra* note 44, at 302-03; Henry Grabowski, *Patents, Innovations, and Access to New Pharmaceuticals*, 5 J. INT'L ECON. L. 849, 850-53 (2002); Allison et al., *supra* note 23, at 1136.

130. *2016 Profile: Biopharmaceutical Research Industry*, PHRMA (Apr. 2016), http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-profile.pdf.

131. *See* Grabowski, *supra* note 129, at 852.

132. *See id.* at 851.

thousand compounds that enter into the pipeline will be approved by the FDA and arrive on the market. In fact, only 16% of medicines that enter phase clinical trials will be approved.

Under the pressure of sunk cost, pharmaceutical and biotechnology companies have every incentive to seek known methods and options within their technical grasp to avoid failure and achieve a marketable drug, despite a tightened patent standard. To satisfy the more stringent standard of non-obviousness and written description, pharmaceutical and biotechnology companies have no option but to conduct more laboratory experiments.

Applying the economic explanation of gold miner behavior during the California Gold Rush, these companies might find themselves in crueler competition than before. When the fence surrounding the surface gold is removed, more gold placers join. The *Myriad* ruling has triggered harsh market competition for cancer test services. Myriad's direct competitors, including private service providers such as Quest Diagnostics as well as numerous academic institutions, immediately announced to begin testing for mutations in the genes BRCA1 and BRCA2 on the same day of the *Myriad* ruling.[133]

Gold encased in hard rock is a proper analogy to small-molecule drugs or therapeutic protein. The stringent patent standard requires companies to spend more laboratory work and talent. Our result suggests that companies with steady and robust R&D expenses enjoy a higher success rate in bringing a therapeutic to market from the pipelines. In contrast, companies expending less or unsteadily on R&D might suffer a low success rate of new drug development.

The finding in this study is consistent with an earlier article by Christopher M. Holman[134] and Kimberly Moore.[135] Holman cast doubt on Jenssen/Murray's study that asserts "20% of human genes are claimed as U.S. IP."[136] The Jessen/Murray study identified Incyte Corporation "as the top gene patent assignee" in the U.S.[137] After examining Incyte's patent, Holman found that only 37 of the 398 surveyed gene patents

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133. Robert Langreth & Shannon Pettypiece, *Myriad Gene Patent Ruling Triggers Race for Cancer Tests*, BLOOMBERG (June 15, 2013, 3:12 PM), http://www.bloomberg.com/news/articles/2013-06-14/myriad-gene-patent-ruling-triggers-race-for-cancer-tests.

134. Holman, *supra* note 13, at 1-16.

135. Kimberly A. Moore, *Worthless Patents*, 20 BERKELEY TECH. L.J. 1521 (2005).

136. Holman, *supra* note 13, at 2 (quoting Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239 (2005)).

137. Holman, *supra* note 13, at 14 (referencing Jensen & Murray, *supra* note 138).

remain active, and the others have all expired due to the failure of paying the maintenance fee.[138] In other words, Incyte maintains less than 10% of its patents and forgoes others. For a company with fewer R&D expenses, this is not an unusual practice, which is consistent with Moore's finding.[139] Gene patent assignees seek to protect their work on the sequence and try to embody the encoded protein in a biology drug that can be approved and reach the market.[140] When the protein encoded in the gene sequence fails to do so, the patent is not worthy to be maintained.[141] Moore finds that chemical, drugs and medical patents are less predictive of commercial value, and "these patents are more like a lottery."[142] Therefore, we anticipate the higher bar of non-obviousness and utility standard of gene patent will encourage true and useful innovation and reduce rent-seeking behavior for patenting a gene sequence that dissipates the social benefit.

One may also keep in mind that low R&D companies often lack sufficient resources to develop their discovery into gaining regulatory approval. Gene patents have a distinct effect on low and high R&D companies, and the distinction comes from the new drug success rate in different companies. Thus, we anticipate that pure biotechnology companies or research-oriented companies are in a disadvantageous position. A negative feedback system may arise that is not desirable for companies with fewer R&D resources and may even expel those relatively small companies out of the competition.

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138. Holman, *supra* note 13, at 14.

139. Moore, *supra* note 135, at 1548-49.

140. Cook-Deegan & Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. GENOMICS & HUM. GENETICS 383, 395-96.

141. Moore, *supra* note 135, at 1544.

142. *Id.* at 1547-48.