4-23-2011

Choice Patents

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CHOICE PATENTS

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ABSTRACT

Empirical contributions to the debate over the commercialization of the life sciences are as rich in detail as they are diverse in approach and conclusions. Citation-based analyses of the genetics literature suggest that patenting undermines knowledge use. Survey research, meanwhile, supports the intuition that university scientists are unhindered day-to-day by patent rights. Material transfer agreements and other forms of intellectual property contracting are, rather, what appear to slow progress. Other qualitative data imply that our understanding of the role that institutional contexts, funding imperatives, professional hierarchies, and norms of scientific competition play is inadequate. The hypothesis motivating many of these investigations is the "tragedy of the anticommons." Combined with the ongoing controversy over gene patents undermining access at the point of patient care, the anticommons hypothesis has prompted litigation against patent-holders, such as Myriad Genetics, Inc., has opened new areas of empirical inquiry, and has begun to reveal the complexity of commercializing scientific pursuits.

In addition to summarizing the strengths and limitations of this evolving body of empirical work, the contribution I make to the debate over commercialization in the life sciences is twofold. First, I theorize a novel tradeoff of academic entrepreneurialism. I term this tradeoff "patent canalization," and posit that, by virtue of participating in the commercialization of their work, academic scientists become more insular in terms of who they collaborate with and more

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[1] Mr. Herder is Assistant Professor at Dalhousie University, Faculties of Medicine and Law. Only through the generous support of the Kauffman Foundation and NYU School of Law was this work possible. I also owe a great deal of thanks to Katherine Strandburg, Rochelle Dreyfuss, Tania Bubela, Fiona Murray, and the members of the Novel Tech Ethics research team at Dalhousie University for struggling through a jumbled, longer version of this work. Your questions were invaluable. The fault is mine alone for problems that remain. Without the expertise of Andrea Smith, Bhaven Sampat, and Jun Yuan, I could not have made sense of the data. Finally, without the assistance of three talented undergraduate NYU students—Milan Sundaresan, Mansi Shah, and especially Eugene Joseph—there would have been little data to make sense of.

entrenched in their chosen line of research inquiry. Patent canalization theory thus draws attention to the potential costs as well as the potential benefits associated with patenting that the anticommons hypothesis does not capture.

Second, I develop a novel methodology to empirically test for patent canalization amongst leading scientists in the field of cancer "epigenetics." Specifically, I track (1) co-authoring relationships and (2) the diversity of lines of research inquiry across each scientist's publication record in order to discern which, if any, intervening patenting "events" account for significant changes in those two types of variables. In a sample of fifty-two academic scientists, there is a modest negative relationship between applying for a patent and four measures of scientific collaboration and research diversity. This pattern is also evident amongst scientists who patent frequently but reverses amongst scientists who patent infrequently. In the year leading up a patent application or a patent grant such scientists enjoy significant increases in scientific collaboration and research diversity. The results thus support and nuance patent canalization theory, motivating a series of questions surrounding intellectual property policy, academic autonomy, and the task of commercializing epigenetic biomarkers currently shared by academic and company labs.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.[2]
—Robert Frost

INTRODUCTION

Virtuous are the roads less travelled—so goes the romantic interpretation of Robert Frost's *The Road Not Taken*.[3] Assuming Frost, thus understood, was on to something, academia might be the last walk of life we would worry about. Relative to most employment contexts, academics enjoy considerable autonomy. They have to teach. They have to publish. Time; funding; resources; technology; and the human capacity to acquire, assimilate, and attack knowledge[4]—all of these factors bound the academic's endeavors. Nevertheless, aside from these general constraints and laws that apply to us all, academics are free to choose what to say, what to study, how to study, and in collaboration with whom. They are, in Frost's words, well placed to choose the lesser traveled of paths for the duration of their academic careers. Or so we might think.

Today, more and more academics are participating directly in efforts to commercialize their work. The means of commercialization vary and there is debate over symptom versus cause. Academic scientists are not, strictly speaking, compelled to try to commercialize their research.[5] However, to encourage

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2 ROBERT FROST, *The Road Not Taken*, *in* MOUNTAIN INTERVAL, 9, 9 (1921).

3 *Id.* This interpretation can be seen as romantic for emphasizing the choice made, not the opportunities foregone. Other interpretations of the poem suggest Frost intended to convey a more cynical message: choosing one road over another has no impact on outcome. *See* WILLIAM H. PRITCHARD, FROST: A LITERARY LIFE RECONSIDERED 127 (1984).

4 *See* Benjamin F. Jones, *The Burden of Knowledge and the "Death of the Renaissance Man": Is Innovation Getting Harder?* 76 REV. ECON. STUD. 283, 283 (2009) (showing that "age at first invention, specialization, and teamwork" have all increased significantly in recent years, and suggesting that innovative activity is becoming more difficult).

5 On its face, legislation now known as the Bayh-Dole Act ("Bayh-Dole") does not place a positive duty upon academic scientists to report findings to their institution. Bayh-Dole Act, Pub. L. No. 96-517, 94 Stat. 3015, 3019–27 (1980) (codified as amended at 35 U.S.C. §§ 200–12, § 202(c)(1) (2009)). However, regulations enacted under Bayh-Dole require recipients of federal funding to, in turn, "require, by written agreement, its [faculty] to disclose promptly in writing to personnel identified as responsible for the administration of patent matters . . . each subject invention" made in connection with those funds. FAR 52.227-

the narrowing of focus thought necessary for knowledge translation, the law, together with university and research funding body policies, and evolving research norms effectively promote licensing the rights to scientific discoveries to the private sector.[6] What's more, academic institutions have learned to take the step of licensing as soon as practicable in order to cover the costs of obtaining those rights from the patent office.[7] This is especially true in the life sciences.

What, then, if the academic scientist-turned-entrepreneur has—wittingly or not—reduced the relatively unconstrained choice he or she heretofore enjoyed, or the choice of his or her fellow scientists?

11(e)(2) (2007); *see* 37 C.F.R. § 401.3(a) – 401.14(c)(1). Moreover, a recent Federal Circuit decision suggests that those in receipt of federal funding risk losing any resulting patent rights if they do not adhere to such disclosure rules. Campbell Plastics Eng'g & Mfg., Inc. v. Brownlee, 389 F.3d 1243, 1249 (Fed. Cir. 2004); *see also* FAR 52.227-11(d) (2007) (providing that the government may obtain title to a patent if the recipient of federal funds fails to disclose the invention within two months after the inventor discloses it in writing to personnel responsible for patent matters). Most, if not all, universities with an active technology transfer office (TTO) thus formally require scientists to disclose findings of potential interest made during the course of their employment, and assign any resulting intellectual property to the university subject to Bayh-Dole's revenue sharing requirements. *See* Martin Kenney & Donald Patten, *Reconsidering the Bayh-Dole Act and the Current University Invention Ownership Model*, 38 RES. POL'Y 1407, 1413 (2009). The enforcement of such disclosure obligations and securing faculty participation in commercialization thereafter are, on the other hand, a continuous source of tension between TTOs and academic scientists and, arguably, considerable inefficiency in the commercialization process. *Id.*, 1413; *see also* Jerry G. Thursby & Sukanya Kemp, *Growth and Productive Efficiency of University Intellectual Property Licensing*, 31 RES. POL'Y 109, 121 (2002) (reporting that TTO managers believe less than 50% of inventions are actually disclosed "though several noted an increasing willingness of faculty (particularly younger faculty) to disclose").

6 Prior to the enactment of Bayh-Dole, many federal government agencies retained ownership of any discoveries resulting from research that they funded. *See* Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663, 1676–79 (1996) (summarizing the rules adhered to by different federal agencies and the evolution of federal policy prior to Bayh-Dole). By delegating ownership and thus the authority to license any intellectual property rights as funding recipients saw fit, Bayh-Dole can be seen as an effective promotion of that particular avenue (or set of avenues) for commercializing publicly funded research.

7 *See* Daniel W. Elfenbein, *Patents, Publications, and the Market for University Inventions*, 63 J. ECON. BEHAV. & ORG. 688, 694 (2007). Experienced technology transfer offices typically enter into licensing arrangements long before a patent application is granted and, if possible, before a patent application is even filed. For example, in a study combining data from Harvard University's Office of Technology and Trademark Licensing and the Office of Technology Licensing and Industry Sponsored Research at Harvard Medical School, Daniel Elfenbein found that "21.4 percent of license agreements are signed before the first patent application, 62.0 percent are agreed upon after the patent application but before the patent grant, and 16.6 percent are agreed upon following the patent grant." *See id.*

On this question, the available empirical evidence is ambiguous. Several economists have shown that patenting correlates positively with publication output[8] and, in one study, seemed to enhance the quality of scientists' work.[9] Sociologists have found that patents per se seldom intervene in an academic scientist's program of research.[10] Yet other legal instruments such as "material transfer agreements" ("MTAs") coupled with increasing norms of secrecy—both byproducts of commercialization—regularly stall laboratory activity.[11] Further, researchers have demonstrated that patenting knowledge appears to precipitate a decrease in the use of that knowledge by others.[12] In addition, another group determined that patenting significantly reduced the number of coauthoring relationships a scientist forms.[13] Two other studies, focusing on intellectual property contracting (as opposed to patenting), illustrated how restrictive licensing practices can reduce the total number of ensuing lines of research in-

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8 Seminal work by Lynne Zucker and Michael Darby demonstrated that academics that patent not only exhibit increased publication output, but also account for firm location, growth, and success during the biotechnology sector's formative years. *See* Lynne G. Zucker & Michael R. Darby, *Star Scientists and Institutional Transformation: Patterns of Invention and Innovation in the Formation of the Biotechnology Industry*, 93 PROC. NATL. ACAD. SCI. 12,709, 12,709–10 (1996); Lynne G. Zucker et al., *Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises*, 88 AM. ECON. REV. 290, 290–91 (1998). This methodology, however, suffers from the fact that Zucker, Darby, and colleagues focus only upon "stars," thus sampling on the dependent variable of publication output. More recent work offers better support for a positive correlation between patenting and publication productivity. *See, e.g.*, Pierre Azoulay et al., *The Impact of Academic Patenting on the Rate, Quality and Direction of (Public) Research Output*, 57 J. INDUS. ECON. 637, 668 (2009); Kira R. Fabrizio & Alberto Di Minin, *Commercializing the Laboratory: Faculty Patenting and the Open Science Environment*, 37 RES. POL'Y 914, 924 (2008); Martin Meyer, *Are Patenting Scientists the Better Scholars? An Exploratory Comparison of Inventor-Authors with Their Non-Inventing Peers in Nano-Science and Technology*, 35 RES. POL'Y 1646, 1648, 1658 (2006).

9 Azoulay et al., *supra* note 8, at 667.

10 John P. Walsh et al., *Where Excludability Matters: Material Versus Intellectual Property in Academic Biomedical Research*, 36 RES. POL'Y 1184, 1185, 1189–91, 1197–99 (2007).

11 *Id.* at 1193–94; Wei Hong & John P. Walsh, *For Money or Glory? Commercialization, Competition, and Secrecy in the Entrepreneurial University*, 50 SOC. Q. 145, 157-158 (2009).

12 *See* Fabrizio & Di Minin, *supra* note 8, at 928; Kenneth G. Huang & Fiona E. Murray, *Does Patent Strategy Shape the Long-Run Supply of Public Knowledge? Evidence from Human Genetics*, 52 ACAD. MGMT. J. 1193, 1193 (2009); Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis*, 63 J. ECON. BEHAV. & ORG. 648, 673 (2007).

13 Tania Bubela et al., *Commercialization and Collaboration: Competing Policies in Publicly Funded Stem Cell Research?*, 7 CELL STEM CELL 25, 29 (2010).

quiry,[14] and the incorporation of early-stage research findings into downstream applications.[15]

Each finding discussed above carries methodological limitations, strong inferences about the social welfare consequences of academic patenting are hard to draw and differ depending on the context. For example, freedom to work on whichever research projects a scientist pleases is generally regarded as a virtue of academic science. In "translational research,"[16] though, the work of translating an initial finding into a robust association might limit the scope of one's work. Thus, where translation is the goal, reductions in the breadth of a scientist's research agenda may theoretically represent an acceptable tradeoff.[17] However, this is so only if the scientist actually does validate his or her findings through repeated study—or if, following the academic's lead, firms undertake the necessary follow-on work. We do not know to what extent that occurs because university-industry deals are not transparent and industry scientists publish less than their academic peers. That, too, though, appears to be changing.[18]

The overarching objectives of this paper are twofold. First, I analyze the strengths and weaknesses of the current empirical literature surrounding patenting in the life sciences. Second, I contribute to that literature by studying changes in patterns of scientific collaboration and research diversity pre and post-participation in commercialization based on the published scientific literature. My contribution is both conceptual and empirical. I theorize a novel tradeoff potentially associated with patenting early-stage research that I term "patent canalization." In short, patent canalization theory posits that, by virtue

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14 Fiona Murray et al., Of Mice and Academics: Examining the Effect of Openness on Innovation 26 (May 1, 2009) (unpublished manuscript) (available at http://www.economics.harvard./faculty/aghion/files/Of%20Mice%20and%20Academics.pdf).

15 Heidi Williams, Intellectual Property Rights and Innovation: Evidence from the Human Genome 23 (Dec. 30, 2009) (unpublished manuscript) (available at http://deugarte.com/gomi/Williams_jmp.pdf).

16 This phrase is used here to refer to "the "bench-to-bedside" enterprise of harnessing knowledge from basic sciences to produce new drugs, devices, and treatment options for patients". *See* Steven H. Woolf, *The Meaning of Translational Research and Why It Matters*, 299 JAMA 211, 211 (2008).

17 This follows as a matter of logic. Translational research requires that scientists replicate and validate their work, and the effort, time, and resources expended to do so must, at some point, take away from other worthwhile projects.

18 Michael Roach & Henry Sauermann, *A Taste for Science? PhD Scientists' Academic Orientation and Self-Selection into Research Careers in Industry*, 39 RES. POL'Y 422, 424 (2010) (noting that "some firms in the biomedical domain explicitly consider publishing and other professional activities in their promotion decisions and there is some evidence that firms that do so tend to be more innovative").

of participating in the commercialization of their work, academic scientists become *more insular* in terms of with whom they collaborate and *more entrenched* in their chosen line of research inquiry. The empirical contribution I make is to develop a novel methodology to test for patent canalization. I track variations in scientific collaboration and research diversity amongst fifty-two (52) leading academic scientists in three sub-fields of "epigenetics"—DNA methylation, histones, and microRNAs ("miRNAs"). Each of these sub-fields hold significant promise as diagnostic, prognostic, and therapeutic "biomarkers" of cancer.[19]

There are four reasons for focusing on this particular scientific realm. First, scientific interest in, and recognition of the importance of, epigenetics generally has increased significantly of late.[20] Second, in contrast to genetics, no one to date has empirically tested the effects of patenting in epigenetics.[21]

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[19] Although epigenetic biomarkers belong to the "molecular" category of biomarkers, Wilson et al. offer a useful summary of all biomarkers:

> Biomarkers are molecular, biological, or physical attributes that characterize a specific underlying (patho)physiological state and that can be objectively measured and evaluated to detect or define disease progression, or predict or quantify therapeutic responses. Classic biomarkers have encompassed surrogate physiological measurements (heart rate, blood pressure), images (chest radiography), and protein molecules (cardiac enzymes). The sequencing of the human genome, in conjunction with advanced analytical technologies, have made possible a new generation of molecular markers, including single-nucleotide polymorphism (SNP) analysis [and] genomic and proteomic profiling, . . . which carry the promise of increased disease-related sensitivity and specificity coupled with higher dimensional complexity to provide greater individualized disease management.

C. Wilson et al., *Biomarker Development, Commercialization, and Regulation: Individualization of Medicine Lost in Translation*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 153, 153 (2007).

[20] Allison Abbott, *Project Set to Map Marks on the Genome*, 463 NATURE 596, 597 (2010); Peter A. Jones et al., *Moving AHEAD with an International Human Epigenome Project*, 454 NATURE 711, 711–13 (2008); Manuel Rodriguez-Paredes & Manel Esteller, *Cancer Epigenetics Reaches Mainstream Oncology*, 17 NATURE MED. 330, 330 (2011).

[21] Epigenetics research was, for instance, outside the formal remit of recent studies conducted by the National Research Council ("NRC") and the Secretary's Advisory Committee on Genetics, Health, and Society ("SACGHS"). *See* DEP'T OF HEALTH & HUMAN SERVS., SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH, & SOCIETY, GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010) [hereinafter SACGHS, PATENTS, AND LICENSING PRACTICES]; NAT'L RESEARCH COUNCIL OF THE NAT'L ACADS., REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH, 1–2 (Stephen A. Merrill & Anne-Marie Mazza, eds., 2006) [hereinafter NRC, REAPING THE BENEFITS]. Some lawyers have, however, begun to map patenting in specific sub-fields of epigenetics such as mi-

Third, as relatively easy-to-test types of cancer biomarkers, epigenetic discoveries are, in principle, commercially attractive[22] and thus constitute prime targets for translational research. Fourth, examining tradeoffs in scientific collaboration and research diversity seems especially relevant to all fields of biomarkers research, including epigenetic biomarkers. Biomarkers, as a whole, proven underwhelming to date, ostensibly due to the complexity of the science[23] combined with poor levels of experimental standardization,[24] replication, validation, and qualification.[25] Several factors seem to have contributed to this state of affairs.[26]

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croRNAs. *See* Bonnie W. McLeod et al., *The 'Real World' Utility of miRNA Patents: Lessons Learned from Expressed Sequence Tags*, 29 NATURE BIOTECH. 129, 132 (2011).

22 Sascha Karberg, *Switching on Epigenetic Therapy*, 139 CELL 1029, 1029 (2009). Only a few "epigenetic drugs" exist at present, however, some contend that scores of new avenues of epigenetic therapeutic intervention are now opening up. *See* George S. Mack, *To Selectivity and Beyond*, 28 NATURE BIOTECH. 1259, 1261–62 (2010).

23 As Doctors Teri A. Manolio and Francis S. Collins, the current director of the National Institutes of Health, explain, the technologies used to examine scan entire genomes for disease associations are, by their very design, likely to turn up scores of false associations:

> Because they test hundreds of thousands of statistical hypotheses—one for each allele or genotype assessed—GWA studies have enormous potential for generating false-positive results due to chance alone. At the usual $p < 0.05$ level of significance, an association study of one million [single nucleotide polymorphisms (SNPs)] will show 50,000 SNPs to be "associated" with disease, almost all spuriously.

Teri A. Manolio & Francis S. Collins, *The HapMap and Genome-Wide Association Studies in Diagnosis and Therapy*, 60 ANN. REV. MED. 443, 448 (2009).

24 *See* George Poste, *Bring on the Biomarkers*, 469 NATURE 156, 156–57 (2011).

25 *See* Joel N. Hirschhorn et al., *A Comprehensive Review of Genetic Association Studies*, 4 GENETIC MED. 45, 46, 50–51 (2002) (demonstrating that of 600 associations between common gene variants and diseases, only 166 had been studied at least three times, and only six had been consistently replicated); Michael V. Holmes et al., *Fulfilling the Promise of Personalized Medicine? Systematic Review and Field Synopsis of Pharmacogenetic Studies*, 4 PLOS ONE e7960 (2009), *available at* http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0007960 (concluding that "the high expectation but limited translation of pharmacogenetic research thus far may be explained by the preponderance of reviews over primary research, small sample sizes, a mainly candidate gene approach, surrogate markers, an excess of nominally positive to truly positive associations and paucity of meta-analyses." *Id.*, at e7960); John P. Ioannidis et al., *A Road Map for Efficient and Reliable Human Genome Epidemiology*, 38 NATURE GENETICS 3, 4 (2006) (finding the prevalence of small, underpowered studies with significant flaws, selective reporting of "positive" results, lack of standardization among studies, poor reporting of results, and difficulties in assessing interactions with environmental risk factors cause the research evidence to be fragmented and hinders the development of the interaction of epidemiological and other biological evidence); T.M. Morgan et al., *Nonvalidation of Reported Genetic Risk Factors for Acute Coronary Syndrome in a Large-Scale Replication Study*, 297 JAMA 1551, 1558 (2007) (showing that

It, therefore, would be helpful to know whether patenting activity, one of many possible forms of "academic entrepreneurialism,"[27] has a mitigating effect.[28]

Following this introduction, the analysis is divided into five parts. Part II begins by mapping the ongoing debate around "gene patenting," and the efforts to diagnose a problem, both conceptually and empirically. The tribulations of biomarkers, both genetic and beyond—one applied offshoot of molecular biology—are then provided, segueing to the remaining two subsections of Part II, which have a predominantly scientific bent. The first subsection describes the historical development of the epigenetics field, while the second provides background about three epigenetic phenomena that are of increasing clinical interest as biomarkers of human disease. Part III introduces the concept of patent canalization by returning to entrepreneurialism at the university-industry interface and explores what it demands of the actors at the heart of the process—individual academic scientists. Inspired by the work of the scientist who conceived of the term "epigenetics," I argue that the concept of patent canalization offers a new window into the potential impact of patenting (and attendant commercialization activity) upon early-stage biomedical research. It is distinct from the two main concerns driving current policy and empirical debates—

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none of the 85 gene variants previously associated with acute coronary syndrome were validated and yet at least six are being used to assess risk of cardiovascular disease); Paolo Vineis et al., *A Field Synopsis on Low-Penetrance Variants in DNA Repair Genes and Cancer Susceptibility*, 101 J. NAT'L CANCER INST. 24, 27, 31 (2009) (finding that of 241 associations between variants in DNA repair genes and cancer, only 31 were found to have nominal statistical significance, and only three of those 31 associations were judged to have strong credibility); Wilson et al., *supra* note 19, at 153–54.

[26] Two governmental bodies have suggested that poor regulation and inadequate reimbursement are contributing factors. *See* DEP'T OF HEALTH & HUMAN SERVS., SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH, & SOCIETY, U.S. SYSTEM OF OVERSIGHT OF GENETIC TESTING: A RESPONSE TO THE CHARGE OF THE SECRETARY OF HEALTH AND HUMAN SERVICES 5–10 (2008) [hereinafter SACGHS, U.S. SYSTEM OF OVERSIGHT], *available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf; PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., PRIORITIES FOR PERSONALIZED MEDICINE 3–5 (2008) [hereinafter PCAST], *available at* http://www.ostp.gov/galleries/PCAST/pcast_report_v2.pdf.

[27] The term "academic entrepreneurialism" could be used to capture any interaction between academics and the private sector, whether rooted in an agreement around intellectual property rights or other arrangements like consulting. Here, my focus is on patenting only.

[28] PCAST, for example, suggested that the issue of intellectual property merited independent study while asserting its integral importance to commercialization. PCAST, *supra* note 26, at 21–22. Another group of authors has argued that further embracing patent rights might be necessary to spur the evaluative research that has been lacking to date. *See* Kathleen Liddell et al., *Patents as Incentives for Translational and Evaluative Research: The Case of Genetic Tests and Their Improved Clinical Performance*, 3 INTELL. PROP. Q. 286, 297 (2008).

access at the "point of patient care" and the "anticommons" tragedy[29]—and may shed light on observed shortcomings in the biomarkers research realm. Part IV sets out the methodology deployed to investigate patent canalization theory. Part V and Part VI present my empirical findings, further analysis, and conclusions.

I. COMMERCIALIZING MOLECULAR BIOLOGY: CONTROVERSIES AND NEW COMPLEXITIES

Molecular biology has progressed remarkably after Doctors Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty, in 1944, published their experimental work demonstrating that DNA, not proteins, constitutes *the* genetic material.[30] Discovery upon discovery in the decades since has helped develop and refine this central dogma of molecular biology.[31] However, until the invention of two foundational tools during the 1970s—recombinant DNA and polymerase chain reaction ("PCR")—which radically improved scientists' ability to manipulate and study DNA, patenting in molecular biology had essentially not begun.[32] Controversy soon surrounded the idea of patenting DNA—no one, critics argued, should "own life"—and continues to this day.[33]

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29 This term was popularized by one article: Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698 (1998).

30 Oswald T. Avery et al., *Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Deoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III*, 79 J. EXPERIMENTAL MED. 137, 155–56 (1944).

31 The dogma is essentially that DNA makes messenger RNA, which makes proteins, which give rise to phenotypic traits. Now, however, we know that the process of genotype to phenotype is far more complex than previously thought. Several elements that are extraneous to DNA regulate mRNA activity, including miRNAs and small interfering RNAs, and various "marks," which can change in real time in response to environmental stimuli, help instruct when and what is to be expressed. *See* Nicholas Wade, *From One Genome, Many Types of Cells. But How?*, N.Y. TIMES, Feb. 24, 2009, at D4.

32 Early in the twentieth century university-based scientists did occasionally patent substances extracted from the human body. T. Brailsford Robertson from the University of California, for example, received a patent in 1917 pertaining to an extract substance called "tethelin" derived from the pituitary gland, which the university hastily championed in a press release as a possible key to growth enhancement and a cure for cancer. Charles Weiner, *Patenting and Academic Research: Historical Case Studies*, 12 SCI. TECH. & HUMAN VALUES 50, 51 (1987). However, tethelin was neither a medical nor a financial success. *Id.* at 51–52.

33 *See* Rebecca S. Eisenberg, *Why the Gene Patenting Controversy Persists*, 77 ACAD. MED. 1381, 1381 (2002); Leon R. Kass, *Patenting Life*, 72 COMMENTARY 45, 49 (1981).

Examples of academic entrepreneurialism long predate the 1970s,[34] but the emergence of "biotech" proved transformative for academic scientists and their parent institutions.[35] More rigorous study of academic entrepreneurialism followed once biotech blossomed. To analyze this entrepreneurialism, researchers have employed both quantitative and qualitative methodologies, at times encompassing whole institutions across substantive fields, in other cases targeting individual actors engaged in select areas of inquiry.[36] In this article, I focus on the literature that speaks specifically to academic entrepreneurialism in the life sciences.

A. A Determined Controversy: "Gene Patenting"

According to one source, approximately one-fifth of the human genome is "owned" at present.[37] A lot of the property was secured some time ago by virtually every entity engaged in genetics research: the government, publicly

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34 Weiner, *supra* note 32, 50–51.

35 JENNIFER WASHBURN, UNIVERSITY, INC.: THE CORPORATE CORRUPTION OF AMERICAN HIGHER EDUCATION, 56–60 (2005); Jeannette A. Colyvas & Walter W. Powell, *From Vulnerable to Venerated: The Institutionalization of Academic Entrepreneurship in the Life Sciences*, 25 RES. SOC. ORGS. 219, 221–23 (2007).

36 According to one meta-analysis of the literature, the field still lacks organization and methodological rigor. Frank T. Rothaermel et al., *University Entrepreneurship: A Taxonomy of the Literature*, 16 INDUST. & CORP. CHANGE 691, 699–703 (2007).

37 Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239, 239 (2005). Scholars will be quick to quibble with this statement since a patent grants the right to exclude others from doing *x*, *y*, and *z*. Having a patent on a gene, in other words, does not mean that the patent-holder owns that gene in a person's body. Suffice it to say, however, that various players own a considerable number of patents that claim exclusive rights in 20% of the human genome. *Id*. There may be reason to doubt that 20% figure, however, because of the methodology used. The authors performed automated searches for sequence identification numbers in patent claims. They did not actually read the claims by hand to verify whether any sequences identified were, in fact, actually claimed as part of the invention or were instead simply mentioned. *See* Kyle Jensen & Fiona Murray, Supporting Online Material for *Intellectual Property Landscape of the Human Genome* (Oct. 14, 2005), http://www.sciencemag.org/cgi/content/full/310/5746/239/DC1. *See also* Christopher M. Holman, *Debunking the myth that whole-genome sequencing infringes thousands of gene patents*, 30 NATURE BIOTECH. 240, 244 (2012) (concluding that whole-genome sequencing would not amount to infringement of many of the gene patents identified by Jensen & Murray, *id.*). Consistent with these reservations about the 20% figure, Professor Isabelle Huys and colleagues find fewer patent claims to block access to genes than anticipated. *See* Isabelle Huys et al., *Legal Uncertainty in the Area of Genetic Diagnostic Testing*, 27 NATURE BIOTECH. 903, 908 (2009).

funded universities, and private firms.[38] Throughout, the practice has garnered criticism.[39] Ongoing litigation[40] over patents owned by Myriad Genetics, Inc. ("*Myriad*")—the University of Utah spinoff made infamous for its decision making regarding two genes associated with breast and ovarian cancers ("BRCA1" and "BRCA2")— may mark the controversy's apogee.[41] Indeed, those and other proceedings[42] may spell lasting change in the doctrine of patentable subject matter. However, the concerns motivating the BRCA1/2 patent challenge are only part of the problem.

Concerns about patients at the point of care appear to be the driving force behind cases like *Myriad* and policy discussions.[43] Refusing to allow other

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38 Jensen & Murray, *supra* note 37, at 239.

39 *E.g.*, Michael Crichton, *Patenting Life*, N.Y. TIMES, Feb. 13, 2007, at A23.

40 Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010), *aff'd in part, rev'd in part* 653 F.3d 1329 (Fed. Cir., 2011), *vacated* 2012 U.S. LEXIS 2356 (U.S., Mar. 26, 2012).

41 *Id.* at 232–37.

42 These proceedings emanate, in part, from the Supreme Court's non-decision in *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006). *See Myriad*, 702 F. Supp. 2d at 221. Although the Supreme Court ultimately denied certiorari in *LabCorp*, in his dissent, Justice Breyer openly questioned the patentability of a "basic science relationship" between bodily protein levels and vitamin B deficiency. *LabCorp*, 548 U.S. at 125–26, 137–38 (Breyer, J., dissenting). That reasoning has subsequently gained a little traction. In *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 2008 WL 878910 (S.D. Cal. Mar. 28, 2008), the District Court found Justice Breyer's reasoning in *LabCorp* persuasive. *Id.* at *8. The District Court found the claims at issue in *Prometheus*, which focused on a method of "optimizing therapeutic efficacy" by first administering a particular drug to a subject and then using the subject's metabolite level to adjust future drug doses, invalid for want of patentable subject matter. *Id.* at *5–7. On appeal, the Court of Appeals for the Federal Circuit reversed the district court. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 581 F.3d 1336, 1350 (Fed. Cir. 2009). However, following the Supreme Court's decision in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), the Supreme Court remanded the case back to the Federal Circuit, Mayo Collaborative Servs. v. Prometheus Labs., Inc., 130 S. Ct. 3543 (2010), which, again, upheld the validity of patent claims, only to be later overturned by the Supreme Court once again. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012), *rev'g*, 628 F.3d 1347, 1359 (Fed. Cir. 2010).

43 This is understandable. There is fairly clear evidence of patent rights being exercised by the patent-holder (or an exclusive licensee) in problematic ways in the clinical setting. One study found that 30% of clinical laboratories reported not developing or abandoning testing for a gene associated with hemochromatosis once the patent issued. Jon F. Merz et al., *Industry Opposes Genomic Legislation*, 20 NATURE BIOTECH. 657 (2002); *cf.* SACGHS, PATENTING AND LICENSING PRACTICES, *supra* note 21, 53–54; Liddell et al., *supra* note 28, at 295–97. Another investigation of over 100 laboratories found that 25% of respondents discontinued testing once they learned that the test in question was the subject of a patent or exclusive license. Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of*

U.S.-based hospitals and firms to perform tests for the cancer-correlated mutations in BRCA1 and BRCA2[44] has generated worry that a certain percentage of patients will not be able to afford BRCA1/2 testing. For those who can afford the testing, the fear is that a certain percentage of false positives and false negatives will go unnoticed.[45] Due to a lack of competition, pricing will remain too high and the "analytic validity" of BRCA1/2 testing services will suffer.[46] This assumes, however, that BRCA1/2 testing possesses "clinical validity"—that is, maps onto clinical outcomes—in the first place.[47] In the case of BRCA1/2, that assumption is sound. The clinical validity of BRCA1/2 mutations has been the subject of repeated investigation by independent researchers notwithstanding Myriad's patent rights.[48]

Clinical Genetic Testing Services, 5 J. MOLECULAR DIAGNOSTICS 3, 4–5 (2003). Myriad's BRCA1/2 test was the most commonly identified test, however, eleven other genetic tests ceased to be offered because of the existence of patent rights. *Id.* at 5, 6 tbl.2 More worrisome, perhaps, is the fact that 53% of respondents in the latter study admitted to halting development of a new clinical test due to a patent or exclusive license. *Id.* at 5. This means that the parties that are arguably in the best position to develop improvements to existing tests—because they have immediate access to clinical data—are deprived the opportunity of doing so. Some instances of healthcare providers continuing to conduct testing have been reported, paralleling academic researchers' claims of being unaware of patents in their midst. However, other healthcare providers, perhaps feeling less "judgment proof" than their (infringing) cousins in academia, have stopped testing outright. *See* NRC, REAPING THE BENEFITS, *supra* note 21, at 68 (citing Michelle R. Henry et al, *DNA Patenting and Licensing*, 297 SCIENCE 1279 (2002); John F. Merz & Margaret K. Cho, *Disease Genes Are Not Patentable: A Rebuttal to McGee*, 7 CAMB. Q. HEALTHCARE ETHICS 425 (1998)); *see also* Aaron S. Kesselheim & Michelle M. Mello, *Medical-Process Patents—Monopolizing the Delivery of Health Care*, 355 NEW ENG. J. MED. 2036, 2036 (2006).

44 Myriad holds nine U.S. patents relating to BRCA1 and BRCA2. *See* E. Richard Gold & Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm*, 12 GENETICS IN MED. S39, at 6 (2010), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3037261/. For a detailed analysis of Myriad's patent rights in the United States and abroad, see Gold & Carbone, *id.*

45 Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181, 206 (S.D.N.Y. 2010).

46 The SACGHS summarizes analytic validity as referring to "a test's ability to measure the analyte or genotype of interest accurately and reliably." SACGHS, U.S. SYSTEM OF OVERSIGHT, *supra* note 26, at 4. Chapter IV of the SACGHS report outlines the concept of analytical validity as well as the concept of clinical validity, and various technical and policy challenges associated with monitoring and improving both, in depth. *See generally id.* at 63–114.

47 "[C]linical validity refers to a test's ability to detect or predict the associated disorder (phenotype)." *Id.* at 4.

48 SACGHS, U.S. SYSTEM OF OVERSIGHT, *supra* note 26, at 88–90 tbl.4-2; Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 JAMA 1379, 1379 (2006).

Few mutations are studied to the same extent as BRCA1/2. In the usual case, fewer academic scientists take up the challenge of investigating and validating a given biomarker.[49] Given that biomarkers are often the subject of a patent application because of their commercial potential, one might wonder how patenting figures in this translational research process. The main focus of empirical investigations to date has been on the relationship between patenting and the scientific field as a whole as opposed to whether patenting encourages the patentee and/or licensee(s) to undertake the necessary evaluative research.

The theory I develop below suggests that, while understanding how patenting, etc., affects knowledge use in academic research as a whole is important, such a frame may not capture commercialization's full impact. In the context of translational research, the process of discovering molecular variations is increasingly automated and cost-effective, yet clinical validation remains a grueling task.[50] As such, the impact of patenting, if any, upon scientists' efforts to establish and verify the clinical validity of a biomarker and to integrate those findings into the etiology of the disease is the prior concern,[51] especially from a healthcare system costs perspective. Three sets of empirical findings—with overlapping focus upon patenting, other legal instruments, and research norms—along with the difficulties of biomarker identification, validation, and qualification foreground that theory.

1. Patent Impact: Sorting Methodology from Claim

The number of patent applications filed by universities and granted by the United States Patent and Trademark Office ("USPTO") has increased expo-

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[49] Poste, in *Bring on the Biomarkers*, notes: "Technologies such as proteomics and DNA microarrays have contributed a voluminous literature of more than 150,000 papers documenting thousands of claimed biomarkers, but fewer than 100 have been validated for routine clinical practice." Poste, *supra* note 24, at 156.

[50] This is because clinical validity is best established by comparing diseased patients with controls and prospective, longitudinal study designs, which are costly and highly time consuming.

[51] My underlying assumption here is that, in a certain percentage of cases, if the scientists responsible for a biomarker discovery do not verify its clinical validity, it is not clear who else will. The published scientific literature seems to support this. Of 10,014 records retrieved when searching MEDLINE for scientific articles relating to DNA methylation research and human cancer, a mere 39 (0.39%) were classified as "validation studies." However, just because it is not being published does not mean that no one is investigating the clinical validity of a biomarker. My assumption therefore presents a problem. I discuss this methodological challenge further below in Part IV as well as its implications for future research in Part V.

nentially since the 1970s.[52] The same is true of licenses executed and MTAs signed over a more condensed timeframe.[53] Unquestionably, then, the number of "commercialization deals" entered into by universities has soared. Whether those deals equate with more commercialization (defined, in absolute terms, as more technologies reaching the market than before) or more of the commercialization that we should want most (more optimal technologies reaching the market than before), remain vexing questions.[54]

Skepticism about the overall benefits of more commercialization deals in the context of biomedical research crystallized around one captivating hypothesis: "the tragedy of the anticommons."[55] In essence, anticommons can emerge when property rights are many and messy.[56] Professor Michael A. Heller coined the concept after observing thriving kiosks in front of scores of empty stores on the streets of post-socialist Russia.[57] The proliferation of private property rights tied to those empty stores was to blame.[58] With the help of Professor Rebecca S. Eisenberg, Heller cautioned that the same tragedy might befall biomedical research in a short article published in *Science* in May 1998.[59] The outcome, the authors warned, may be dire: The abundance of fragmented, overlapping, and ambiguous patent rights in the upstream research space "may lead paradoxically to fewer useful products for improving human health."[60]

It is difficult to overstate the effect that the Heller and Eisenberg anticommons paper has had.[61] Its conceptual elegance resonated with commentators and policy-makers.[62] The authors were careful to note that these may be

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52 *See* David C. Mowery et al., *The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980*, 30 RES. POL'Y 99, 104 (2001).

53 *Id.*; David C. Mowery & Arvids A. Ziedonis, *Academic Patents and Materials Transfer Agreements: Substitutes or Complements?* 32 J. TECH. TRANSFER 157, 158, 160 (2007).

54 Mark A. Lemley, *Are Universities Patent Trolls?*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 611, 622–23 (2008) (arguing that whether the increase in commercialization deals can be equated to an increase in the translation of scientific discoveries into commercial products is contingent upon the "industry in question and the particular nature of the technology").

55 Michael A. Heller, *The Tragedy of the Anticommons: Property in the Transition from Marx to Markets*, 111 HARV. L. REV. 621, 622 (1998).

56 *See id.* at 642–43.

57 *Id.* at 622–24.

58 *Id.* at 633.

59 Heller & Eisenberg, *supra* note 29, at 698.

60 *Id.* at 701.

61 *See* T. Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECH. 1091, 1092–93 (2006).

62 Caulfield et al., *supra* note 61, at 1093–94.

transitional, not tragic, times.[63] Their analysis also contemplated legal devices other than patents that are capable of restricting scientists' freedom to use knowledge, materials, and data.[64] But these important nuances were lost on policy-makers.[65]

Researchers from various disciplinary stripes meanwhile began the painstaking task of generating an evidentiary record to allow more informed decision making. Two research methodologies, two sets of findings, and two conflicting answers to the anticommons hypothesis have followed.[66]

a. Walsh's Opinion Surveys

Commissioned by the National Research Council to do a follow-up study to earlier work,[67] Professor John P. Walsh and colleagues analyzed responses from 507 academic researchers working in genomics and proteomics (414 were randomly sampled from universities, non-profits, or government labs, and the remaining 93 were chosen specifically because their research related to one of three molecular pathways of great commercial and scientific interest).[68] Respondents were asked a series of questions about their reasons for initially choosing a particular research project, whether to continue to pursue a project once chosen, and, to the extent they had difficulty acquiring some research in-

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63 Heller & Eisenberg, *supra* note 29, at 700.

64 *Id.* at 698–99.

65 Caulfield et al., *supra* note 61, at 1093–94.

66 Each methodology has its own limitations. With respect to the opinion surveys, Walsh, Cohen, and Cho note that the modest response (40%) to their survey as well as the limitations of "self-report data," including, presumably, the tendency to provide socially acceptable responses, are reasons to interpret their findings with caution. Walsh et al., *Where Excludability Matters*, *supra* note 10, at 1201. Walsh did, however, take pains to ensure that those who responded to their survey did not differ significantly from those who did not respond in terms of publication and patenting behaviors. *Id.* at 1186 n.6. With respect to Murray's citation-based methodology, the way in which National Center for Biotechnology Information has set up its database, which Murray availed of, is a major potential limitation. The database does not provide a comprehensive list of publications for any particular gene. For that reason, then, and others such as publication bias against studies that simply replicate previous work, a decrease in citations to a paper with a corresponding gene patent does not necessarily mean there was a reduction in actual research involving that gene.

67 *Id.* at 1183; *see* J.P. Walsh et al. *Science and the Law: Working through the Patent Problem*, 299 SCIENCE 1021 (2003).

68 Walsh et al., *Where Excludability Matters*, *supra* note 10, at 1185.

put, why they chose not to manufacture that input in-house, ranking reasons listed by Walsh et al. on a scale of increasing importance from one to five.[69]

Patents proved minimally important overall: Academic scientists instead reported that choice of research project was influenced primarily by scientific importance, interest, feasibility, and access to funding (with 97, 95, 88, and 80% of respondents rating those four reasons, respectively, as highly important).[70] In contrast, whether the results might have commercial potential, whether the results might be patentable, or whether the necessary inputs were patent free were highly important considerations for only 8, 7, and 7% of respondents, respectively.[71] The same essentially held with respect to whether to continue pursuing a project: Respondents judged funding, time available, feasibility, scientific importance, and level of interest as far more important determinants of research project abandonment than patent-related complications or lack of commercial potential.[72] For the sub-populations engaged in "drug discovery" (which Walsh et al. defined broadly as the development of diagnostic tests or therapeutics),[73] or engaged in research around one of the three molecular pathways,[74] this contrast was somewhat attenuated. Roughly 20% of the respondents engaged in drug discovery ranked patentability, commercial potential, and lack of patents on research inputs as important factors to take into account when choosing a research project.[75] Personal income gains and the chance to start a firm—factors that barely registered in the random sample of 414 scientists—were cited as additional reasons to choose or to continue work on a given project, but only amongst 11 and 7% of the 93 scientists working in one of the three molecular pathways.[76]

Thus, patents and related commercial activities represented a minor consideration across the board.[77]

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69 *Id.* at 1188, 1188 n.10–11.

70 *Id.* at 1188, 1188 tbl.2.

71 *Id.* at 1188.

72 The "most pervasively reported reasons why projects are not pursued include lack of funding (62%), a respondent's decision that he was too busy (60%), or judgments that the project was infeasible (46%), not scientifically important (40%) or uninteresting (35%)." *Id.* at 1188.

73 *Id.* at 1186–87.

74 Walsh et al., *Where Excludability Matters*, *supra* note 10, at 1197.

75 *Id.* at 1188.

76 *Id.* at 1188 tbl.2; *id.* at 1189 tbl.3; *id.* at 1198.

77 Not one respondent in the random sample—not even one engaged in drug discovery—admitted to abandoning a line of research. *Id.* at 1190. Only a few (3%) of those scientists working on one of three densely patented molecular pathways reported doing so, and there

Given how widespread patenting has become, Walsh et al. sought to further unpack this main finding. They discovered that many researchers are simply unaware of whether their chosen line of inquiry might infringe upon existing patents. Only 8% of the respondents acknowledged that they had engaged in research during the past two years that they believed was encompassed by a patent held by a third party;[78] 19% did not know one way or the other and the remaining 73% flatly asserted that they did not require permission from any patent-holder to go ahead with their research.[79] Only a scientist's own prior involvement in commercial activity correlated with greater sensitivity to the patent landscape, but that sensitivity remained "modest" relative to industry scientists.[80]

What researchers did have intimate knowledge of were MTAs. The majority of scientists surveyed had acted as both "suppliers" and "consumers" of research materials in the preceding two years. Consistent with the positive social response bias inherent in such surveys, respondents claimed that 18% of their material requests went unheeded by other academic scientists while admitting to failing to deliver materials only 6% of the time.[81] Relying on the former figure, Walsh et al. found that the rate of non-compliance has grown compared to surveys conducted in the late 1990s (up from 10%).[82] Moreover, unlike instances where access to patent rights was theoretically required, MTAs actually intervened, thereby complicating, if not halting, research in real time. Every

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were some reports of project delay (in excess of one month) and modification owing to patent presence. *Id.* at 1190, 1199.

78 Walsh et al., *Where Excludability Matters*, *supra* note 10, at 1189. Walsh, et al., notes the following with respect to this 8% subset of scientists:

> Of the 32 academic respondents who believed that they needed an input covered by someone's patents, 75% (24) contacted the IP owner to receive permission to use the IP. Due to difficulties in obtaining access, four reported having to change research approaches to complete the study, and five delayed completion of the experiment by more than 1 month. No one reported abandoning a line of research. Thus, of the 381 academic scientists – even including the 10% who claimed to be doing drug discovery or related downstream work – none reported having to stop their research due to the existence of third party patents.

Id. at 1190.

79 *Id.* at 1189.

80 *Id.* at 1190.

81 *Id.* at 1191.

82 Walsh et al., *Where Excludability Matters*, *supra* note 10, at 1191–92 (citing Eric G. Campbell et al., *Data Withholding in Academic Genetics: Evidence from a National Survey*, 287 JAMA 473 (2002)).

year, one project per nine researchers is abandoned as a result of unfulfilled material requests. Although noting that MTAs commonly include "reach-through rights" to any future arising inventions, not to mention publication restrictions intended to preserve patent application opportunities,[83] Walsh et al. concluded MTAs were the bigger barrier to research. They also drew attention to the finding that earnest competition and plain busyness explained refusals to share research inputs just as much as scientists' prior forays into the commercial sphere.[84]

b. Murray's Patent-Paper Pairs

The second set of findings regarding the impact of gene patenting—that paints a very different picture—is born from an innovative form of citation analysis developed by Fiona Murray.[85] The methodology takes advantage of the fact that, in the entrepreneurial academic research environment, "the same idea is often inscribed in both a patent and a paper (publication), thus forming a patent-paper pair."[86] Because there is typically a longer lag in time between patent application and patent grant relative to paper submission and publication, tracking forward citations to papers belonging to patent-paper pairs over time essentially provides a natural test of the anticommons hypothesis. Murray and Scott Stern explain:

> if the grant of intellectual property hinders the ability of researchers to build . . . on a given piece of knowledge, and the patent grant itself is *"news"* to the broader scientific community, then the citation rate to the scientific publication disclosing that knowledge . . . should fall after formal property rights are granted.[87]

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83 *Id.* at 1193. This is noteworthy as it runs counter to norms endorsed by the National Institutes of Health. *See* Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources**,** 64 Fed. Reg. 72090, 72094, 79096 (final notice published Dec. 23, 1999).

84 *Id.* at 1197.

85 Fiona Murray, *Innovation as Co-Evolution of Scientific and Technological Networks: Exploring Tissue Engineering*, 31 RES. POL'Y 1389, 1389 (2002). To be precise, Murray first described this methodology in 2002 but substantially refined it from others' prior research for the purpose of testing the anticommons hypothesis in subsequent works. *Id.* at 1392 (citing Philippe Ducor, *Intellectual Property: Co-Authorship and -Inventorship*, 289 SCIENCE 873 (2000)); *see also* Murray & Stern, *supra* note 12 at 650.

86 Murray, *supra* note 87 at 1392.

87 *Id.* (emphasis added).

Murray has, in a series of papers with different co-authors, documented just such an effect. The first drew papers published in *Nature Biotechnology*, a journal committed both to high-quality research and advancing biotechnology applications, and matched them with patents granted by the USPTO to generate 169 patent-paper pairs.[88] Murray and Stern found that the observed boost (20%) in citations to papers with corresponding patents effectively disappears in the years after the patent grant, controlling for a variety of factors such as the impact of each paper, the number of authors on the paper, and institutional affiliations. Using a "differences-in-differences estimate" to control for the time trend in citation levels,[89] the authors showed that the "post-grant decline [in citations to papers belonging to a patent-paper pair] is over 10 percent (and is significant at the 5 percent level)."[90]

Similarly, in a second, much broader study encompassing 1279 human gene patent-paper pairs, Kenneth G. Huang and Murray found that citations decline by 17% following the patent grant and by 5% under a rigorous differences-in-differences estimate.[91] Consistent with the anticommons hypothesis, the complexity of the patent landscape exacerbated this finding: "[O]ver and above the baseline decline in expected citations of 5 percent[,] . . . there is an incremental 7 percent decline . . . in follow-on knowledge production for every unit increase in fragmentation of the patent thicket."[92]

Other factors affected forward citation levels as well. To begin, whether the knowledge embodied in the patent-paper pair was known to be relevant to some form of human cancer heightened the negative effect of the patent grant. Whereas citations to papers related to cancer genes diminished by 11%, citations to non-cancer related genes declined by 4%—a statistically significant 7% difference.[93] Secondly, whether the patent was assigned to a public or private entity mattered: Citations decline 6–9% for privately held patents compared to a 0–3% drop for publicly held patents.[94]

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88 *Id.* at 651.

89 *Id.* at 650. That is, they controlled for the fact that citations may go up or down depending on how old the paper is (its age) and the year in which citations are made (with some areas of research being more "hot" than others from one year to the next). In short, they netted out time as a variable that could explain increase or decrease in citations. *See id.*

90 *Id.* at 670.

91 Kenneth G. Huang & Fiona E. Murray, *Does Patent Strategy Shape the Long-Run Supply of Public Knowledge? Evidence from Human Genetics*, 52 ACAD. MGMT. J. 1193, 1194 (2009).

92 *Id.* at 1211.

93 *Id.* at 1213.

94 *Id.* at 1214.

Comparing the opinion surveys led by Walsh with the citation analyses performed by Murray thus reveals a paradox. If we accept that scientists are generally ignorant of patents, then why do we observe a decrease in citations to papers belonging to patent-paper pairs post-patent grant?[95] Huang and Murray conceded that it is difficult to imagine researchers in general are "so responsive to the details of the patent landscape"[96] as to alter their citation behavior. Nevertheless, they posited that their findings are likely "driven by [aggressive] patent enforcement,"[97] especially by private firms against academic medical centers (which Huang and Murray found are particularly prone to cite papers less frequently post-patent grant).[98]

Others have, meanwhile, sought to make sense of this paradox by examining other legal instruments such as MTAs, which, following Walsh et al., we know to be common to the academic research experience.

2. Other Legal Instruments: Scientists Lost in a Category Mistake Debate?

David Mowery and Arvids Ziedonis investigated whether MTA related transaction costs might account for the decrease in citations reported by Murray and colleagues.[99] They found the opposite: knowledge that was both patented and the subject of an MTA was cited, on average, seven times *more* often than knowledge that was patented only.[100] Importantly, though, Mowery and Ziedonis' methodology differed from Murray's—they tracked citations to patents, not papers—and their data was sampled from only one institution, the University of Michigan.[101]

More robust data supports the broader intuition that intellectual property contracting (if not patents per se) can shape follow-on research. Heidi Williams, for example, queried the impact of Celera Inc.'s decision to protect genomic sequencing data via contract for the two-year period prior to the publicly funded effort's release of sequencing data into the public domain.[102] She found

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95 For this reason, skepticism around why Huang and Murray observe what they observe exists. *See* NRC, REAPING THE BENEFITS, *supra* note 21, at 127–28.

96 Huang & Murray, *supra* note 91, at 1214.

97 *Id.*

98 *Id.*

99 Mowery & Ziedonis, *supra* note 53, at 159.

100 *Id.* at 167.

101 *Id.* at 159.

102 Williams, *supra* note 15, at 1.

that "Celera genes have had 35 percent fewer publications since 2001" and were half as likely to be incorporated into a currently available genetic test.[103] By keeping its data confidential, in other words, Celera undermined rather than catalyzed commercialization, at least at a macro level.

In another study, Murray, Philippe Aghion, Mathias Dewatripont, Julian Kolev, and Scott Stern looked at publications in mouse genetics before and after the NIH reached agreements with DuPont Inc. granting academic researchers access to two types ("Cre-lox" and "Onco") of genetically engineered mice—access which they didn't previously enjoy.[104] Compared to a set of control publications (involving "Knock-out" mice), Murray et al. show that overall citations, citations by new authors, citations by authors at new institutions, use of new key words, and publications in both "basic" as well as "applied" scientific journals all increase significantly in Cre-lox and Onco mice literatures relative to the restrictively licensed Knock-out mice controls.[105]

Together, these findings suggest that less restrictive intellectual property licensing enhances the breadth of a scientific field, facilitating the entry of new scientists and new institutions as well as diversifying lines of research inquiry. While powerful, these findings do not necessarily buttress the conclusions of Murray's prior work with patent-paper pairs. On the contrary, these later studies involving Celera and DuPont beg the question: Would patenting have facilitated access to knowledge relative to intellectual property contracting?[106] At the very least, this underscores the difficulty of pinpointing a problem.

Another approach intentionally blurs the line between intellectual property contracting and patenting.[107] Zhen Lei, Rakhi Juneja, and Brian Wright, for

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103 *Id.* at 2.

104 Murray et al., *supra* note 14, at 1.

105 *Id.* at 22–25.

106 One study of the Canadian stem cell research community does show that patenting creates a statistically significant negative effect on co-authoring relationships: for every one unit increase in patenting, scientists entered into 17% fewer co-authoring relationships, and their overall co-author "neighborhood" (*i.e.*, all co-authors plus each co-authors' fellow co-authors) decreased by 26.5%. *See* Bubela et al., *supra* note 13, at 29.

107 The reason the study's authors offer for doing so derives from what they believe scientists experience in their day-to-day-lives: "How can scientists so unconcerned with infringement see IP rights as an impediment to research? The answer is that they associate problems of IP rights with problems with MTAs." *See* Zhen Lei et al., *Patents Versus Patenting: Implications of Intellectual Property Protection for Biological Research*, 27 NATURE BIOTECH. 36, 38–39 (2009). This view would also seem to underlie Huang and Murray's claim that the observed decline in citations is attributable to patent enforcement issues and other complexities despite the showing that scientists are often unaware of the existence of patent rights. *See* Huang & Murray, *supra* note 91, at 1214.

example, asked academic scientists (engaged in agricultural biology) to rate whether "intellectual property protection"—which they defined broadly to include negotiations pertaining to MTAs—had a positive or negative impact on their work.[108] The answer Lei et al. received was decidedly negative, leading the authors to conclude that the "patent-MTA dichotomy" suggested by the title of Walsh et al.'s paper is "false," at least amongst agricultural biologists.[109] Other commentators, responding in turn, argue that Lei et al. are guilty of making a category mistake.[110]

Arguments in support of either position can be made. Patents and MTAs are intimately intertwined in practice.[111] Yet clear evidence of patent-mediated problems in the upstream research environment is currently lacking compared to other forms of intellectual property contracting. My worry is that this category debate risks shifting our attention away from the individuals who, depending on which set of empirical findings deserves more weight, experience transaction costs first-hand—academic scientists—or are affected by commercialization in ways that may escape the conceptual frame of the anticommons.

3. Academic Research Norms: Unpacking the Social Welfare Consequences

Losing sight of the academic scientist distances the analysis from how science works in the real world.[112] In the context of large-scale genomics re-

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108 Lei et al., *supra* note 107, at 38.

109 *Id.* at 39.

110 *See, e.g.*, Kevin E. Noonan, *Conflating MTAs and Patents*, 27 NATURE BIOTECH. 504, 505 (2009); Zhen Lei & Brian D. Wright, *Reply*, 27 NATURE BIOTECH. 505, 506 (2009).

111 Sean O'Connor explains this with reference to seminal patents on stem cell technology held by the Wisconsin Alumni Research Foundation. *See* Sean O'Connor, *The Use of MTAs to Control Commercialization of Stem Cell Diagnostics and Therapeutics*, 21 BERKELEY TECH. L.J. 1017, 1017–18 (2006).

112 For instance, David Adelman has rebuked anticommons theory by noting that the scope of scientific research is, in principle, "unbounded." *See* David E. Adelman & Kathryn L. DeAngelis, *Patent Metrics: The Mismeasure of Innovation in the Biotech Patent Debate*, 85 TEX. L. REV. 1677, 1699 (2007); David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 BERKELEY TECH. L.J. 985, 985–86 (2005). Adelman forgets, however, that science often proceeds in clusters. Dan Burk and Mark Lemley make this point colorfully:

> Adelman's explanation for the lack of an anticommons is that the number of potential drug targets is so large that human pharmaceutical research is effectively "unbounded" and "uncongested." We think he confuses the average case with individual ones. Adelman's argument is essentially equivalent to claiming that New York and San Francisco will not become congested or experience soaring property values because of all the open space available in

search, data access, storage, and integrity are often more immediate concerns.[113] We have also known for a long time that competition for credit can limit collegiality, if not fuel secrecy, in scientific circles.[114]

Qualitative studies suggest that we are giving undue attention to formal barriers to information sharing and collaboration.[115] Steven Vallas and Daniel Kleinman reported that while academic scientists claim to have complete control over their scientific affairs, "shifting reward structures, changing funding imperatives and normative pressures emerging among scientists themselves" limit, "in subtle yet important ways, the choices" that they make.[116] Walsh's opinion surveys failed to capture this level of nuance but his more recent work with Wei Hong supports the claim that secrecy has increased compared to the past.[117]

Given the challenges of teasing apart these intersecting facets of commercialization practiced in the lived academic world, there is room to draw radically different inferences about whether all or some commercialization activities impose social welfare costs.

Consider again some of the figures produced by the Walsh and Murray-led analyses. Walsh et al. found that one in nine researchers abandoned one

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> Montana and the Dakotas. But while it is true that the less congested spaces may at the margins absorb some uses from more congested areas, powerful incentives persist for remaining in Manhattan or near the Bay . . . .

See DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 152 (2009).

113 Dawn Field et al., *'Omics Data Sharing*, 326 SCIENCE 234 (2009); Ewan Birney et al., *Prepublication Data Sharing*, 461 NATURE 168 (2009); Paul N. Schofield et al., *Post-publication Sharing of Data and Tools*, 461 NATURE 171, 173 (2009).

114 Robert K. Merton, *Priorities in Scientific Discovery*, 22 AM. SOC. REV. 635, 659 (1957).

115 Steven Vallas and Daniel Kleinman stated:

> [I]mpediments [to sharing and collaboration amongst academic scientists] do not hinge on such formal, institutional arrangements as patent rights, licensing constraints or direct ties to industry (predominant concerns in the literature). Indeed, such arrangements were only episodically reported among the academic scientists we studied. Rather, *it is the normative orientation that has taken root in many departments and disciplines, based in status competition, which impedes the sharing of knowledge and other resources among professional scientists.*

Steven Peter Vallas & Daniel Lee Kleinman, *Contradiction, Convergence and the Knowledge Economy: The Confluence of Academic and Commercial Biotechnology*, 6 SOCIO-ECON. REV. 283, 302–03 (2008) (emphasis in original).

116 *Id.* at 291.

117 *See* Hong & Walsh, *supra* note 11, at 157–58.

research project every two years. Huang and Murray showed that "genetic researchers forego about one in ten research projects (or, more precisely, research publications) through the causal negative impact of a gene patent grant."[118] Yet these broadly similar figures gave rise to a worry about how patenting limits knowledge flows on one hand and the suggestion that patent-related transaction costs are overblown on the other.

These conflicting claims betray different intuitions about the status quo. Pushing the patent-paper pair methodology further in the future to track the quality of the subsequent citations will enable stronger inferences about the social welfare consequences associated with increased patenting, etc. As I explain next, in the context of early-stage biomarkers research, I think that more closely examining tradeoffs between scientific collaboration and research diversity is critically important.

4. The Trouble with Biomarkers

Quality concerns abound genetic testing as well as various other applications predicated upon observable changes at the molecular level—changes in gene regulation, protein expression, and metabolic pathways—all of which can be classified as modern biomarkers.[119] Genetic tests have garnered the most attention, in significant part, because over 1,000 DNA variants associated with diseases and traits have been identified and are supporting a new wave of "direct-to-consumer" (DTC) companies the likes of "23andMe" and "Navigenics."[120] The "(bio)pharmaceutical" industry,[121] in the midst of rebranding and merging with biotech, is—out of necessity—showing increasing interest in exploiting biomarkers, genetic or otherwise, to improve therapeutic penetrance or rescue products removed from the market by regulators.[122] We should applaud this in principle because the inadequacy of most (small molecule) drugs

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118 Huang & Murray, *supra* note 91, at 1214.

119 Wilson et al., *supra* note 19, at 153.

120 Pauline C. Ng et al., *An Agenda for Personalized Medicine*, 461 NATURE 724, 724 (2009).

121 *See* Ronald A. Rader, *(Re)defining Biopharmaceutical*, 26 NATURE BIOTECH. 743, 747 (2008).

122 Genentech, for example, hopes to re-obtain market approval for Avastin in metastatic breast cancer by stratifying patients with a new biomarker. *See* Karen Carey, *Avastin Loses Breast Cancer Indication*, 30(1) NATURE BIOTECH. 6 (2012); *see also, e.g.*, Giora Z. Feuerstein & Juan Chavez, *Translational Medicine for Stroke Drug Discovery: The Pharmaceutical Industry Perspective*, 40 STROKE S121, S121 (2009).

is plain. Studies have shown that many patients do not respond to such drugs[123] or, worse, suffer harm.[124] As a means to stratify patient populations between responders and non-responders, better responders versus worse, and so forth, biomarkers are harbingers of more personalized medicines.

The trouble is that we essentially do not yet know what most biomarkers really tell us. Thus the resistance to clinical uptake: more misinformation leads to more misdiagnosis and more mistreatment. To explain this quality of care quagmire it is useful to elaborate upon two concepts from above—analytic validity and clinical validity—plus introduce a third, clinical utility.[125]

Analytic validity refers to the quality of the testing service.[126] Is the laboratory performing the service able to get the right answer as to whether a particular DNA variant is present, most, if not all, of the time? *Clinical validity* relates to the quality of the information that the test, accurately performed, provides.[127] Does the DNA variant correlate with the progression of a specific disease? Finally, *clinical utility* situates the test in terms of overall patient treatment quality.[128] Does the knowledge about the DNA variant facilitate clinical decision-making, in turn, improving clinical outcomes?

The available evidence suggests that many, if not most, biomarker-based applications lack all three markers of quality. Few laboratories are required to demonstrate the analytic validity of their testing services.[129] Clinical validity is likewise seldom shown and clinical utility represents a complete unknown.[130] According to an independent expert panel, the Evaluation of Ge-

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123 Brian B. Spear et al., *Clinical Application of Pharmacogenetics*, 7 TRENDS IN MOLECULAR MED. 201, 201 (2001).

124 Jason Lazarou et al., *Incidence of Adverse Drug Reactions of Hospitalized Patients*, 279 JAMA 1200, 1204 (1998); *see also* Daniel S. Budnitz et al., *National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events*, 296 JAMA 1858, 1860 (2006) (estimating that more than 700,000 people per year are treated in a hospital emergency room because of a drug-related adverse event); Munir Pirmohamed et al., *Adverse Drug Reactions as Cause of Admission to Hospital: Prospective Analysis of 18820 Patients*, 329 BRIT. MED. J. 15, 17 (2004).

125 SACGHS, U.S. SYSTEM OF OVERSIGHT, *supra* note 26, at 67–72, 85–91, 115–38 (explaining each concept in depth).

126 *Id.* at 67.

127 *Id.* at 85.

128 *Id.* at 115.

129 *See, e.g.*, *id.* at 73–77.

130 Stuart Hogarth et al., *The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues*, 9 ANN. REV. OF GENOMICS AND HUMAN GENETICS 161, 169–70 (2008).

nomic Applications in Practice and Prevention Working Group, the reason is as follows: "Test applications are being proposed and marketed based on descriptive evidence and patho-physiologic reasoning, often lacking well-designed clinical trials or observational studies to establish validity and utility, but advocated by industry and patient interest groups."[131] Most studies to date are also simply "underpowered," that is, employ small sample sizes studied for short periods of time.[132] Further, experimental standardization is lacking and current levels of experimental replication are exceedingly low insofar as biomarker-disease associations are concerned.[133] Upon re-investigation by independent scientific teams, several biomarker-disease associations have proven spurious.[134]

The reason why better evidence of clinical validity isn't forthcoming has multiple, intersecting dimensions.

The first dimension to this evidentiary problem is regulatory. The Centers for Medicaid & Medicare Services (CMS) and the FDA, the two governmental agencies with jurisdiction over those purporting to provide testing services, have exercised their discretion in counterproductive ways. Under the *Clinical Laboratory Improvement Amendments of 1988*, any lab in receipt of human biological materials must be CMS-certified.[135] Because genetic testing was still in its infancy at the time the CMS issued its standards for certification, no "specialty area" was created within the CMS to enforce personnel and proficiency testing requirements against genetic testing labs.[136] Despite being subse-

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131 Steven M. Teutsch et al., *The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group*, 11 GENETICS IN MED., no. 1, Jan. 2009, at 3.

132 *See, e.g.*, Peter W. Laird, *The Power and the Promise of DNA Methylation Markers*, 3 NAT. REV. CANCER 253, 256 (2003); Wilson et al., *supra* note 19, at 153.

133 *See* Hirschhorn et al., *supra* note 25, at 60.

134 *See* Morgan et al., *supra* note 25, at 1559; Vineis et al., *supra* note 25, at 24.

135 42 C.F.R. § 493.1 (2011).

136 Specialty areas are essentially a bureaucratic structure or mechanism used by CMS as a way of implementing and enforcing compliance by clinical laboratories engaged in a particular kind of testing with more specific (and stringent) requirements. *See At Home DNA Tests: Marketing Scam or Medical Breakthrough: Hearing Before the S. Spec. Comm. on Aging*, 109th Cong. 4–5 (2006) [hereinafter Hudson Testimony] (written testimony of Kathy Hudson, Director, Genetics and Public Policy Center & Associate Professor, Berman Bioethics Institute, Institute of Genetic Medicine & Department of Pediatrics, Johns Hopkins University), *available at* http://www.dnapolicy.org/resources/Testimony_of_Kathy_Hudson_Senate_Aging_7-27-06.pdf..

quently re-classified as a highly complex form of testing, no specialty area has been created for genetic testing to this day.[137]

Arguably, because of CMS' inaction, the analytic validity of many genetic tests continues to suffer.[138] Clinical validity, on the other hand, is the province of the FDA.[139] Like CMS, though, the FDA has chosen to exercise its discretion in a problematic fashion. Unless a test is sold as a "test kit"—and precious few are given the predominant business model of in-house testing[140]—or test results cannot be interpreted without the aid of complex (often proprietary) mathematical algorithms executed by a computer,[141] the FDA does not require a prior demonstration of clinical validity.[142] Consecutive attempts to legislate FDA review for clinical validity have failed.[143]

Secondly, the lack of better evidence around biomarkers has a significant cost-reimbursement dimension.[144] Payers (whether private insurance or government) decide whether, and how much, to reimburse a healthcare provider for a service depending on the clinical utility of that service. But, as noted above, that information is altogether absent because the clinical validity of the

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137 In contrast, CMS has created specialty areas for other types of testing that have received the highly complex designation, including Microbiology, Diagnostic Immunology, and Chemistry. *See id.* at 4.

138 At the very least, CMS' inaction places the burden upon consumers to distinguish between labs that are able to reliably perform genetic testing and those that are not able to do so. *See id.* at 6; *see also* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-06-977T, NUTRIGENETIC TESTING: TESTS PURCHASED FROM FOUR WEB SITES MISLEAD CONSUMERS 1–2 (2006), *available at* http://www.gao.gov/new.items/d06977t.pdf.

139 Seemingly, the FDA considers "in vitro diagnostic" tests to constitute medical devices. *See* Medical Device Amendments of 1976, sec. 2, § 321(h), Pub. L. No. 94-295, 90 Stat. 539, 575 (1976).

140 One source reports that, at the time of writing, the FDA had reviewed eight test kits. *See* Gail Javitt, *In Search of a Coherent Framework: Options for Coherent Oversight of Genetic Tests*, 62 FOOD & DRUG L. J. 617, 624, 629 (2007).

141 *See* DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF: IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS, 72 FED. REG. 41,081 (July 27, 2007), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079148.htm.

142 PCAST, *supra* note 28, at 38.

143 The *Genomics and Personalized Medicine Act of 2007* was introduced by then-Senator Barack Obama on Mar. 23, 2007. A modified version of the legislation, the *Genomics and Personalized Medicine Act of 2008*, was subsequently introduced by Rep. Patrick Kennedy on July 15, 2008. Neither bill passed. *See generally* Genomics and Personalized Medicine Act of 2007, S. 976, 110th Cong. (2007); Genomics and Personalized Medicine Act of 2008, H.R. 6498, 110th Cong. (2008).

144 *See* PCAST, *supra* note 28, at 48.

biomarker is still in question, the analytic validity of the corresponding test is moderate to poor, or both, creating a near-perfect Catch-22.[145] Without evidence of clinical validity, payers decline to pay. Without payment, such evidence is challenging to build.

The last and likely most important dimension to the evidentiary problem confronting biomarkers is the sheer complexity of the science itself. Consider cystic fibrosis, a "single gene disorder." When the gene was identified in 1989, scientists believed that correcting the genetic anomaly was readily attainable, at least relative to disorders known to involve multiple genes and molecular interactions.[146] Twenty years on research has revealed over 1,500 different types of mutations in that same CFTR gene, and therapeutic intervention remains in the distance.[147] Or, consider breast cancer, a more complex disease that has mobilized an incredible amount of resources over a similar timeframe. Genetic testing based on the discovery of "myriad" mutations in the BRCA1/2 genes has reduced but not removed uncertainty about whether to undergo prophylactic surgery.[148] But the genetic complexity of the disease itself is far from unraveled. The first reported "next generation" or "deep" sequencing of a breast cancer tumor—taken from a single patient—showed that nineteen of thirty-two mutations detected in the tumor were not present nine years before when the tumor was removed.[149] Breast cancer tumors, thus, exhibit remarkable genetic heterogeneity over time.

The complexity of the science intersects with the above regulatory and reimbursement issues. Evidentiary standards of analytic validity and clinical validity remain elusive, in large part, because we do not know enough about the biological mechanism of disease. To draw an analogy to Murray's patent-paper pair citation analysis, we do not know what the decrease in citations is a marker of.

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145 As Rena Conti and colleagues note: "The current reimbursement system for diagnostic tests is cost-based rather than value-based." *See* Rena Conti et al., *Personalized Medicine and Genomics: Challenges and Opportunities in Assessing Effectiveness, Cost-effectiveness, and Future Research Priorities*, Med. Decision Making 1, 6, 9 (2009); *cf.* Chul-So Moon et al., *Slow Development Impedes the Uptake of Diagnostics*, 451 NATURE 16, 16 (2008) ("[t]he the "problem lies not with physician uptake and reimbursement, but with the slow development and validation of accurate tests providing useful information for early detection and treatment.").

146 Helen Pearson, *One Gene, Twenty Years*, 460 NATURE 165, 165 (2009).

147 *Id.*, at 167–68.

148 *See* SACGHS, U.S. SYSTEM OF OVERSIGHT, *supra* note 26, at 88–90.

149 Sohrab P. Shah et al., *Mutational Evolution in a Lobular Breast Tumour Profiled at Single Nucleotide Resolution*, 461 NATURE 809, 809 (2009).

The trouble with biomarkers appears, then, to be almost everything. Understanding how efforts expended upon commercialization by academic scientists in concert with his or her academic institution affect this is, therefore, important. I focus the inquiry around biomarkers from the realm of cancer epigenetics.

B. Added Layers of Complexity: Epigenetics

With profile comes controversy. The Human Genome Project galvanized the genetics research community through the 1990s as they raced against Craig Venter's company, Celera, and its efforts to appropriate the human DNA sequence.[150] In the process, attention was focused on the issue of gene patenting, a practice that began before and has continued since despite the Project's efforts to disseminate sequencing information into the public domain. Now, as evidence mounts regarding the complexity of gene expression, scientists interested in the field of epigenetics are moving forward with a project of their own: the International Human Epigenome Consortium (IHEC).[151] Those governing the IHEC intend to adopt a policy of open access to research data. However, patenting in the field, especially epigenetic findings relevant to various forms of cancer, is well underway.[152]

The following two sub-sections introduce the field's origins and describe three streams of epigenetic research that are currently generating interest as potential cancer biomarkers.

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150 Robert Cook-Deegan, *The Science Commons in Health Research: Structure Function and Value*, 32 J. OF TECH. TRANSFER 133, 140 (2007).

151 A "Human Epigenome Project" has already begun; however, it is focused solely on DNA methylation, rather than the full range of epigenetic phenomena. Presumably, the IHEC initiative will encompass other areas of epigenetics research. *See* Jones et al., *supra* note 20, at 712. The stated aim of the IHEC Consortium is to map 1000 reference epigenomes from normal tissue over the course of the next decade at an estimated cost of $130 million. Notably, making data "freely available" is intended to be a condition of participation. However, decisions about how to implement such an open-access policy have yet to be made. Abbott, *supra* note 20, at 596–97.

152 For example, one recent article calls attention to the current "miRNA patent rush." *See* Bonnie W. McLeod et al., *The "Real World" Utility of miRNA Patents: Lessons Learned from Expressed Sequence Tags*, 29(2) NATURE BIOTECH. 129 (2011).

1. Waddington's Invention: An Incomplete History of the Concept of Epigenetics

Conrad Hal Waddington, a scientist formally trained in paleontology with an extensive publication record spanning the fields of embryology, developmental genetics, population genetics, and theoretical biology,[153] is credited with coining the term epigenetics. To understand what he meant by the word and related terminology that he developed—terminology that I use for both conceptual and empirical purposes throughout the remainder of the paper—versus the field of epigenetics today, it is helpful to provide some further background about Waddington the person and debates in biology at the time.

Born in England in 1905, Waddington was an eccentric scientist.[154] While at Cambridge University Waddington read more philosophy than science, in particular, the works of Alfred North Whitehead, a mathematician turned philosopher who lectured at Cambridge in the early 1900s.[155] He later claimed that these extracurricular readings had a lasting influence on his scientific thinking.[156] Some suggest that his interdisciplinary focus—unusual at the time—limited his career.[157] Regardless, it does seem to account for the epigenetic lexicon that Waddington later developed.[158]

In the 1930s, even though the DNA structure was unknown, genetics (what we now call "classical," not molecular, genetics) had already assumed a dominant mantle within the "evo-devo" sphere of biology.[159] Questions about

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153 Jonathan M.W. Slack, *Conrad Hal Waddington: The Last Renaissance Biologist?* 3 NATURE REVIEWS GENETICS 889, 889–90 (2002) ("[b]y modern standards, [Waddington] . . . irretrievably blotted his copybook by not finishing his Ph.D. thesis (although this would have been quite common at the time) and he remained 'Mr. Waddington' until 1938, when he received a doctorate for his published work.").

154 *Id.* at 890.

155 *Id.*

156 *Id.*

157 Scott F. Gilbert, *Epigenetic Landscaping: Waddington's Use of Cell Fate Bifurcation Diagrams*, 6 BIOLOGY AND PHILOSOPHY 135, 137 (1991). Owing, perhaps, to his wide-ranging interests, Waddington was only able to secure temporary fellowships (first at Strangeways Laboratories in Cambridge in 1929, then in Berlin through the mid-1930s, and at Caltech in 1939) prior to becoming the Director of the Institute of Genetics at the University of Edinburgh in 1944 where he remained until his death in 1975.

158 Slack notes: "This conception of the [epigenetic] landscape seems to derive from the philosophical heritage of Whitehead, as Waddington describes the action of many genes as forming a 'concresence,' a typical Whiteheadian concept." Slack, *supra* note 153, at 892.

159 "Evo-devo" is today used as a short-hand for the interface of evolutionary and developmental biology.

how organisms developed by observing morphological changes in the embryo had, on the other hand, been marginalized by Thomas Hunt Morgan's demonstration in 1926 that "particular genes resided on specific chromosomes and that these genes determined the phenotype of the adult fruit fly."[160] Although Morgan self-identified as an embryologist, genetics claimed the title of a "newer and higher embryology."[161]

Waddington was not satisfied with this view of heredity and development. To assume that genes and "characters" (traits) were absolutely paired was to him a threatening new form of dualism.[162] The terms "genotype" and "phenotype" only captured "differences between whole organisms . . . [and were] not adequate or appropriate for the consideration of differences *within* a single organism."[163] Waddington recognized that genetic variation had an effect on phenotypic variation. But he was equally, if not more, intrigued by instances where genetic variation did *not* lead to phenotypic variation.[164] A richer, more holistic paradigm was, in his view, needed.[165]

This philosophical intuition appears to be grounded in experimental work Waddington conducted with Joseph Needham, Dorothy Needham, and Jean Brachet in the mid-1930s.[166] While studying development in amphibian embryos, Waddington and his colleagues observed something surprising. Contrary to preliminary studies, the group found that any number of substances could be used to induce neural cells to form from the embryo's ectoderm layer, which, in turn, inspired the following line of reasoning:

Since many [substances] could act as inducers, the specificity of the developmental reaction wasn't in the inducer but in the competent tissue. The inducer, [Waddington] wrote . . . was only the push. It was the *competence* that was genetically controlled and which was responsible for the details of the de-

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160 Gilbert, *supra* note 157, at 139.

161 *Id.* This amounted, in essence, to a modern kind of "preformationism"—the notion that organism development is wholly attributable to some form of internal program, in this case genes, rather than an internal program in concert with external factors. *See* STANFORD ENCYCLOPEDIA OF PHILOSOPHY, EPIGENESIS AND PREFORMATIONISM (Oct. 11, 2005), *available online*, http://plato.stanford.edu/entries/epigenesis/ [hereinafter STANFORD, EPIGENESIS].

162 D. Haig, *The (Dual) Origin of Epigenetics*, 69 COLD SPRING HARB SYMP QUANT BIOL. 67, 67 (2004).

163 CONRAD H. WADDINGTON, AN INTRODUCTION TO MODERN GENETICS 156 (1939).

164 Eva Jablonka & Marion J. Lamb, *The Changing Concept of Epigenetics*, 981 ANN. N.Y. ACAD. SCI. 82, 85 (2002).

165 Gilbert, *supra* note 157, at 138.

166 Gilbert described Needham as a scientist who, like Waddington, was "working in the 'no man's land' between two more orthodox disciplines." *Id.* at 140.

velopment. Not all cells could [form] neural tubes; only the competent ectoderm could. Thus, the genes of this tissue were seen as having a different activity than genes in other tissues. This led Waddington to propose that this competence was due to the existence of genetically controlled pathways. If the developmental pathway is advantageous to the organism, that path from one state to another (say, from ectoderm to neural tube) became *canalyzed* by natural selection. Canalization meant that the pathway was "buffered" such that it would be difficult to get out of the channel once into it. Once the pathway had been entered, cell fate was rigidly fixed if the pathway were sufficiently canalyzed. Competent tissues were tissues in which such pathways were present. All that the inducer did was shove a cell into such a path.[167]

Borrowing from Aristotle's notion of "epigenesis,"[168] Waddington postulated on the basis of these experiments with the Needhams and Brachet that the adult form of an organism emerges gradually over time, subject to external influences.[169] He sketched the "epigenetic landscape," Figure 1, as a symbolic representation of this idea of canalization.[170] The ball represents a cell in an embryo, the valley as a whole represents a "cluster of similar trajectories through state space," which, absent a significant "external or internal perturbation will not affect the pathway,"[171] *i.e.*, disturb the cell's fate.

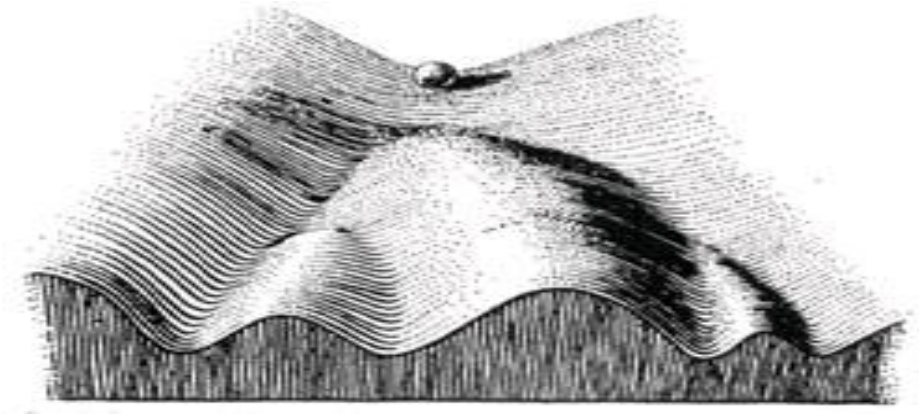

Figure 1. The epigenetic landscape.

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167 *Id.* at 140–41 (emphasis in original).

168 Aristotle's notion of epigenesis stands in direct contrast to preformationism. *But see* STANFORD, EPIGENESIS, *supra* note 161.

169 Gilbert, *supra* note 157, at 140–41.

170 Slack, *supra* note 153, at 891.

171 *Id.* at 892–93.

Waddington insisted on this theory in a series of publications dating back to 1939.[172] The amphibian embryo experiments only demonstrated that something beyond genes is capable of mediating tissue differentiation. They said nothing of the mechanisms that brought such differentiation about. For that reason, perhaps, some have questioned the value of the epigenetic landscape as a theoretical model.[173] It may also explain why Waddington's conception of epigenetics rested in obscurity for decades.[174] In recent years, however, his notions of canalization and an epigenetic landscape have begun to resonate.[175]

2. Epigenetic Events: Marker or Mechanism?

Epigenetics, in the contemporary sense, is used to refer to the study of the various chemical modifications made to a cell's "chromatin," the material—essentially a collection of proteins—encasing the DNA sequence of each cell comprised in an organism.[176] DNA methylation is the most studied chemical

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172 WADDINGTON *supra* note 162; CONRAD H. WADDINGTON, ORGANISERS AND GENES 45 (1940); Conrad H. Waddington, *Canalization of Development and the Inheritance of Acquired Characters*, 150 NATURE 563, 564 (1941); Conrad H. Waddington, *The Epigenotype*, 1 ENDEAVOUR 18, 18–19 (1942).

173 For example, it's not clear what Waddington intended the surface of the landscape to represent. Slack, *supra* note 153, at 892; *see also* Gilbert, *supra* note 140, at 151.

174 Jablonka & Lamb, *supra* note 164, at 86–87. *But see* J. Huxley, *Epigenetics*, 177 Nature 807, 807 (1956); J. Huxley, *Cancer Biology: Viral and Epigenetic*, 32 BIOLOGY REV. 1, 14 (1957); D.L. Nanney, *Epigenetic Control Systems*, 44 PROC. NAT'L. ACAD. SCI. 712 (1958); D.L. Nanney, *Epigenetic Factors Affecting Mating Type Expression in Certain Ciliates*, 23 COLD SPRING HARBOR SYMP. QUANTITATIVE BIOLOGY 327, 330 (1959); S. LØVTRUP, EPIGENETICS. A TREATISE ON THEORETICAL BIOLOGY 14–15 (1972).

175 For example, Shinya Yamanaka's elegant experiment—first published in 2006—demonstrating how to induce adult stem cells into a pluripotent state through the manipulation of the cells' transcription factors quickly calls to mind Waddington's epigenetic landscape and notion of canalization. *See* K. Takahashi & S. Yamanaka, *Induction of Pluripotent Stem Cells from Mouse and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663, 663 (2006); K. Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors*, 131 CELL 861, 861 (2007). Coincidentally, Yamanaka recently adapted Waddington's epigenetic landscape in order to illustrate a stochastic model of induced pluripotent stem cell generation. *See* Shinya Yamanaka, *Elite and Stochastic Models for Induced Pluripotent Stem Cell Generation*, 460 NATURE 49, 50 (2009).

176 Put differently, epigenetics is used to refer to "the study of mitotically or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence." *See* Gary Felsenfeld, *A Brief History of Epigenetics*, *in* EPIGENETICS 16 (C. David Allis et al. eds. 2007); C.T. Wu & J.R. Morris, *Genes, Genetics, and Epigenetics: A Correspondence*, 293 SCIENCE 1103, 1104 (2001). However, this is not meant to suggest that every cell in an organism has one uniform epigenome. On the contrary, each cell has multiple epigenomes,

modification.[177] But epigenetics also encompasses modifications to other elements extraneous to DNA, including modifications to the special-purpose proteins known as "histones" whose tails essentially mark up the DNA sequence, as well as various small, "noncoding RNA" molecules (most of which are now referred to as "microRNAs").[178] Together with what are known as "chromatin regulators" and "transcription factors," these diverse epigenetic phenomena are thought to regulate what genes are expressed within a cell, when, and in response to what.[179]

Although epigenetic phenomena have been correlated with various biological processes from development to disease[180] and death, we do not fully understand what triggers what.[181] There is support for the hypothesis that epigenetic phenomena play a causal role in some forms of cancer,[182] but in others it's unclear whether they are simply signs of some other change in the molecular environment. Improvements to technology that allow more reliable and cost-effective study of epigenetic variations provide reason for optimism.[183] But, to

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which may vary one cell to the next, and change in response to environmental stimuli as well as internal processes to do with aging and disease. For a useful review of the epigenetics literature, which contrasts the modern field with Waddington's conception of epigenetics, and ties together various epigenetic phenomena, see Aaron D. Goldberg et al., *Epigenetics: A Landscape Takes Shape*, 128 CELL 635 (2007).

177 Goldberg et al., *id.* at 636.

178 *Id.* at 636–37.

179 For this reason, epigenetic phenomena may help explain why the most powerful study design genetics researchers have at their disposal—genome-wide association studies—have "generally identified variants that account for only a fraction of the heritability of a particular disease." *See* Louisa Flintoff, *Adding Epigenetics to the Mix*, 11 NATURE REVIEWS GENETICS 94, 94 (2010) (referring to a study by A. Kong et al., *Parental Origin of Sequence Variants Associated with Complex Diseases*, 462 NATURE 868 (2009)).

180 *E.g.*, Mehregan Movassagh et al., *Differential DNA Methylation Correlates with Differential Expression of Angiogenic Factors in Human Heart Failure*, 5(1) PLOS ONE e8564 (2010) (reporting differences in DNA methylation in hearts from a small number of people with end-stage cardiomyopathy who were undergoing heart transplantation and the healthy hearts of age-matched victims of road traffic accidents).

181 Goldberg et al., *supra* note 176, at 637–38.

182 *See* Andrew P. Feinberg & Benjamin Tycko, *The History of Cancer Epigenetics*, 4 NATURE REVIEWS CANCER 143, 148–49 (2004).

183 According to some of leading researchers, we are on the cusp of a "golden age of human methylomics." *See* Benjamin P. Berman et al., *Locking in on the Human Methylome*, 27(4) NATURE BIOTECH. 341, 342 (2009) (citing Jie Deng et al., *Targeted Bisulfite Sequencing Reveals Changes in DNA Methylation Associated with Nuclear Programming*, 27(4) NATURE BIOTECH. 353 (2009)); Madeleine P. Ball et al., *Targeted and Genome-scale Strategies Reveal Gene-body Methylation Signatures in Human Cells*, 27(4) NATURE BIOTECH. 361, 366

refine how we manage patients in view of epigenetic biomarkers we must also resolve fundamental questions about the mechanisms behind these diverse phenomena, how they inter-relate, and to what extent they account for the onset, and onslaught, of diseases such as cancer.[184] Part of the question I frame next is whether a relationship exists between academic entrepreneurialism and the poor depth we have seen in much of biomarkers research thus far, including methylation[185] and miRNA biomarkers.[186]

II. THEORY-BUILDING: PATENT CANALIZATION

Citation-based methodologies such as Murray's studies of patent-paper pairs can tell us something about the extent to which published knowledge *appears* to be used before and after it is patented. Murray and colleagues did not examine the extent to which scientists responsible for generating (and patenting) that knowledge engage in "self-citation."[187] As such, patent-paper pair methodology tells us nothing particular to those individuals beyond the fact that they are named inventors on a patent. Walsh et al.'s survey methodology, in contrast, does tell us something about the impact (or lack thereof) of patenting on individual academic scientists. But Walsh's data is derived solely from scientists' own perceptions. We might take solace in scientists' perceptions that patents held by others need not interfere with their own work. However, we should be cautious about relying on scientists' self-assessment of the impact patenting by his- or herself, on his- or herself. The lengths to which the scientist's mind will go to avoid the conclusion that financial incentives might influence his or her decision-making,[188] put an asterisk on Walsh's finding that scien-

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(2009); *see also* Meng Li et al., *Sensitive Digital Quantification of DNA Methylation in Clinical Samples*, 27(9) NATURE BIOTECH. 858, 862 (2009).

184 Laird *supra* note 132, at 254.

185 *Id.* at 256, 260.

186 *See* Scott A. Waldman & Andre Terzic, *Translating MicroRNA Discovery into Clinical Biomarkers in Cancer*, 297(17) JAMA 1923 (2007).

187 Self-citation, by individual authors to their own work and the work of others who share their institutional home, is a well-documented phenomenon. *See* Ken Hyland, *Self-citation and Self-Reference: Credibility and Promotion in Academic Publication*, 54(3) J. AM. SOC'Y INFO. SCI. & TECH. 251, 252 (2003); Dean Hendrix, *Institutional Self-citation Rates: A Three Year Study of Universities in the United States*, 81(2) SCIENTOMETRICS 321 (2009).

188 A number of findings from social psychology provide support for this. *See, e.g.*, M.A. Steinman et al., *Of Principles and Pens: Attitudes and Practices of Medicine House Staff Toward Pharmaceutical Industry Promotions*, 110(7) AM. J. MED. 551, 556 (2001) (showing that physicians are more likely to believe that their colleagues are influenced by pharmaceutical sales-persons than themselves). In another amazing study researchers demonstrated that

tists' choice of research project is seldom motivated by the prospect of patenting.[189]

Given the prevalence of academic patenting today, it is the impact of patenting on the scientific self that I am principally interested in. What we think we know about these individuals vis-à-vis commercialization follows, which I summarize to set up a new conceptual framework to investigate what commercialization, and participating therein, means for the academic scientist.

A. Along the Beaten Path: Findings from the Technology Transfer Laboratory

Commercialization is hard stuff.[190] Steps in the process—from disclosure of an "invention" to the university's technology transfer office (TTO),[191] to filing a (provisional) patent application and licensing the technology—can vary in detail and in sequence,[192] rest on questionable market assumptions, consume years of time, or seldom generate significant financial returns.[193]

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disclosure of a financial incentive led to worse advice (from the party with a financial incentive to give inaccurate advice) and greater reliance on that same advice (by another party with knowledge of the financial incentive in play). Daylian M. Cain et al., *The Dirt on Coming Clean: Perverse Effects of Disclosing Conflicts of Interest*, 34 J. LEGAL STUDIES 1, 5–6 (2005).

189 According to Walsh's survey results, only 7% of respondents indicated that their ability to obtain a patent would favor one research project over another. WALSH, *supra* note 10, at 1188.

190 It is important to note that most academic entrepreneurialism occurs in the absence of intellectual property. In the life sciences—the context of greatest interest here—that is less true, however. *See* Riccardo Fini et al., *Inside or Outside the IP System? Business Creation in Academia*, 39(8) RES. POL'Y 1060, 1060 (2010).

191 The term invention disclosure is somewhat of a misnomer as the disclosed information may or may not comprise a patentable invention. *See* Richard A. Jensen et al., *Disclosure and Licensing of University Inventions: 'The Best We Can Do With the S**t We Get to Work With'*, 21(9) INTERNATIONAL J. OF INDUSTRIAL ORG. 1271, 1272 (2003).

192 In a significant number of cases, the license is executed before a patent application, provisional or otherwise, is filed. In others, a license will only be struck after the patent grant, the prosecution of which can consume upwards of five years but averages closer to three. In still other instances, no licensee comes forward and, assuming the TTO continues to believe in the invention's commercial merits, a start-up company is founded with an exclusive license, if not outright assignment of the technology in hand. *See* Elfenbein, *supra* note 7, at 693–94.

193 In fiscal year 2004, the average licensing agreement at the University of California at San Francisco—one of the leading performers in commercializing biotechnologies—generated somewhere around $60,000. *See* Office of the President, University of California Technology Transfer Program, Annual Report, Fiscal Year 2004 (2004), http://www.ucop.edu/ott/ars/ann04/ar04.pdf.

Involving the would-be academic inventor in this process, however it unfolds, is the key to success according to many.[194] A number of studies have thus explored how TTOs can counteract "moral hazard" amongst faculty participating in commercialization.[195] A more radical proposal (seemingly with some momentum of late) is to vest ownership in academic scientists instead of their parent institutions.[196]

Each strategy assumes that the faculty member desires to participate in the process whereas faculty attitudes toward commercialization are, in fact, still mixed.[197] For some, patenting is anathema. Others have either acquiesced in or accepted the presence of TTOs on campus, and have learned how to participate—at least strategically—in the commercialization process.[198] To the extent participation remains personally troubling, academic scientists adopt complicated strategies to reconcile their behavior and underlying belief system.[199]

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194 Ajay Agrawal, *Engaging the Inventor: Exploring Licensing Strategies for University Inventions and the Role of Latent Knowledge*, 27 STRATEGIC MANAGEMENT JOURNAL 63 (2006).

195 *See* Richard A. Jensen & Marie C. Thursby, *Proofs and Prototypes for Sale: The Licensing of University Inventions*, 91 AM. ECON. REV. 240, 255; *cf.* Nicola Lacetera, *Academic Entrepreneurship*, 30 MANAGERIAL & DECISION ECON. 443, 452 (2009) (suggesting that while involving academics in start-ups may be critical to company survival initially, their continued participation may impede company maturation).

196 This view, advanced by the Ewing Marion Kauffman Foundation, was highlighted by the *Harvard Business Review* as one of the top breakthrough ideas for 2010. *See The HBR List: Breakthrough Ideas for 2010*, HARV. BUS. REV., Jan.–Feb. 2010, at 41, 52–53; *Kauffman Foundation Experts' Solution for University Technology Licensing Reform Named to List of 'Ten Breakthrough Ideas for 2010' by Harvard Business Review*, EWING MARION KAUFFMAN FOUNDATION (Dec. 17, 2009), http://www.kauffman.org/newsroom/kauffman-foundation-experts-solution-named-to_list-of-ten-breakthrough-ideas-for_2010-by-harvard-business-review.aspx; *see also* Dov Greenbaum & Christopher Scott, *Hochschullehrerprivileg—A Modern Incarnation of the Professor's Privilege to Promote University to Industry Technology Transfer*, 15 SCI., TECH. & SOC'Y 55, 71 (2010); Kenney & Patton, *supra* note 5, at 1414.

197 Even amongst those who ostensibly participate, attitudes are heterogeneous. Henry Etzkowitz has documented three types of participation: "(1) hands off, leave the matter entirely to the transfer office; (2) knowledgeable participant, aware of the potential commercial value of research and willing to play a significant role in arranging its transfer to industry; and (3) seamless web, integration of campus research group and research program of a firm." *See* Henry Etzkowitz, *The Norms of Entrepreneurial Science: Cognitive Effects of the New University-Industry Linkages*, 27 RES. POL'Y 823, 830 (1998).

198 This is not meant to suggest that the researchers participating in commercialization (in one form or another) outnumber those who have no interest in doing so. Etzkowitz, for example, notes that many faculty are not involved at all. *Id.* at 830–31.

199 Sanjay Jain and colleagues document scientists' tendency to preserve the primacy of their academic selves through considerable "identity work," "delegating" certain tasks such as interfacing with the TTO to more junior members of their lab, and "buffering" themselves from the commercialization process, for instance, by giving explicit priority to basic, as opposed to

A substantial body of sociological research therefore aims to decipher the factors that shape attitudes toward commercialization amongst the university researcher population. Imprinting during their graduate student and postdoctoral experiences is often a factor. Holding a degree from Stanford University, an early mover toward norms of academic entrepreneurialism, is a strong predictor of researcher willingness to commercialize.[200] The tendency of a postdoctoral fellow's supervisor to patent (or not) appears to cause a fellow to patent (or not) later in his or her career.[201] But present-day context also has an effect.[202] Scientists modify their behavior to minimize social dissonance. They learn to forbear from, or express enthusiasm for, patenting after discovering their new departmental home's receptivity to the same notwithstanding previously established patterns of behavior to the contrary.[203] Finally, status can matter, especially in decades past. "Star scientists" were the ones who led the transition to the entrepreneurial world,[204] and they tended to do so during the later stages of their careers.[205] Today, though, the ubiquity of technology transfer infrastructure suggests that commercialization is an increasingly normalized aspect of academia.[206] As Toby Stuart and Waverly Ding note, the transition to entrepreneurialism has become increasingly "democratic"—more and more attempted by the rank and file, not just the scientific elite.[207]

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applied, research. *See* Sanjay Jain et al., *Academics or Entrepreneurs? Investigating Role Identity Modification of University Scientists Involved in Commercialization Activity*, 38 RES. POL'Y 922, 923 (2009).

200 Janet Bercovitz & Maryann Feldman, *Academic Entrepreneurs: Organizational Change at the Individual Level*, 19 ORG. SCI. 69, 81 (2008) ("Holding a Stanford degree increases the probability of engaging in technology transfer by 27%, all other things being equal.").

201 Pierre Azoulay et al., Abstract, *Social Influence Given (Partially) Deliberate Matching: Career Imprints in the Creation of Academic Entrepreneurs* (Harvard Bus. Sch. Entrepreneurial Mgmt., Working Paper No. 09-136, 2009), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1410816.

202 Jason Owen-Smith & Walter W. Powell, *To Patent or Not: Faculty Decision and Institutional Success at Technology Transfer*, 26 J. TECH. TRANSFER 99, 113 (2001).

203 Bercovitz & Feldman, *supra* note 200, at 86.

204 *See* Pierre Azoulay et al., *The Determinants of Faculty Patenting Behavior*, 63 J. ECON. BEH'R & ORG. 599, 603 (2007).

205 Lacetera, *supra* note 195, at 450 (citing D.B. Audretsch, *The Role of Small Firms in U.S. Biotechnology Clusters*, 17 SMALL BUS. ECON. 3 (2001)).

206 For example, Fini et al., *supra* note 190, at 1063, found that 97% of their survey respondents had a TTO.

207 Toby E. Stuart & Waverly Ding, *When Do Scientists Become Entrepreneurs? The Social Structural Antecedents of Commercial Activity in the Academic Life Sciences*, 112 AM. J. SOC. 97, 124 (2006).

B. Choices in Academic Science

Stuart and Ding's work, like findings about rising patent filings, licensing revenues, and numbers of start-up companies formed, support the view that the level of commercialization witnessed in academia today is unprecedented. Intuitions about the consequences of this state of affairs differ. Some contend it represents an unprecedented threat to academia[208] notwithstanding that (a) the university and those in its employ have, for centuries, struggled to negotiate the expectations of student bodies, surrounding communities and businesses, government agencies, and legislatures; and, (b) the expectations held by funding sources may best account for why commercialization has entered the academic scene to this extent. Whether new in genus or in species, these commentators believe current commercialization imperatives compromise the university's mission of disinterested, fundamental, and critical inquiry. Others caution that the tradeoffs wrought by commercialization, or evidence thereof, is uncertain.[209] I am doubtful of a resolution to this sort of meta-debate given disagreement over what the university was, is, or ought to be.

Here, I focus solely on the choices that academic scientists make, in terms of who to work with and what to work on, in the time that they have. We know that having choice is critically important to academic science and, in turn, to society.[210] But my impression is that academic scientists are dubious of claims that commercialization threatens their choice as such.[211] They might see just the opposite. Academics who patent more, for example, tend to publish

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208 JENNIFER WASHBURN, UNIVERSITY, INC.: THE CORPORATE CORRUPTION OF HIGHER EDUCATION, at xii (2005).

209 DEREK BOK, UNIVERSITIES IN THE MARKETPLACE: THE COMMERCIALIZATION OF HIGHER EDUCATION 118 (2003).

210 Economists have developed models to illustrate this very point. *See* Philippe Aghion et al., *Academic Freedom, Private-Sector Focus, and the Process of Innovation*, 39 RAND J. ECON. 617, 634 (2008) ("[I]n a world where ideas can be sold to the private sector at all stages of the research process, academia—by virtue of its commitment to leaving control in the hands of scientists—can play a valuable role in fostering research projects that would not be viable entirely in the private sector. Moreover, we have shown that it is possible for ideas to be privatized sooner than is socially optimal, with negative consequences for the overall rate of innovation.").

211 This is where the duality exhibited by academic scientists in Vallas and Kleinmann's qualitative study becomes particularly interesting. In their study, scientists claimed absolute dominion over the direction of their work and its execution while at the same being beholden to institutional and funder expectations as well as shifting norms within their own research communities. *See* Vallas & Kleinmann, *supra* note 115, at 291.

with more industry-affiliated co-authors.[212] Given current funding imperatives perhaps having more links to scientists in the private sector is seen as a way of improving one's chances of getting a grant. Maybe patenting, as an entrée to private funding, is seen as a way of avoiding writing yet another grant proposal. Or maybe the private sector scientists are simply better equipped for the project they have in mind. The intention here, then, is to provide more information about what happens to some dimensions of academic choice when scientists exercise whatever agency they have in entrepreneurial ways,[213] and then to consider how that bears upon the development of epigenetic biomarkers.

C. Conceptual Distinction

Like Waddington, who used the term canalization to elucidate how a cell's fate becomes increasingly entrenched during development, patent canalization theory posits that the academic scientist turned entrepreneur becomes increasingly insular and entrenched in his or her program of research as it—and the commercialization thereof—unfolds. Specifically, I expect that the academic scientist turned entrepreneur is apt to become less open and flexible in terms of who he or she works with; I expect him or her to limit the number of lines of research inquiry she is actively engaged in; and, I expect these tradeoffs in scientific collaboration and research diversity to occur in real time.[214]

Canalization could occur regardless of whether a researcher condones commercialization of his or her work. Acceptance of a government grant carries an obligation to see the research project through, possibly, at the expense of other worthwhile projects. My theory, however, is that the process of commercialization (from disclosure of the invention to filing a provisional patent application, executing one or more licensing agreements, prosecuting the patent until

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212 Azoulay et al., *supra* note 8, at 638.

213 Views differ about what might happen if we enhance scientists' entrepreneurial agency. *Compare* Kenney & Patton, *supra* note 5, at 1419 (arguing that inventor ownership is preferable to TTO management), *with* Heller & Eisenberg, *supra* note 29, at 701 (suggesting scientists' tendency to over-value their contribution may cause bargaining breakdowns). A fascinating experiment by Christopher Buccafusco and Christopher Sprigman, showing that individuals who create a work of art tend to dramatically over-value that work, adds credence to the latter view. *See* Christopher Buccafusco & Christopher Sprigman, *The Creativity Effect*, 78 UNIV. CHICAGO L. REV. 31, 45, 46 (2011).

214 Thomas Hellmann contends that when a patent is actually granted the power dynamics change in the scientist's favor, which makes intuitive sense: her reward now guaranteed should a financial profit ever be turned, the scientist qua inventor is more motivated to assist in licensing and commercial development. *See* Thomas Hellmann, *The Role of Patents in Bridging the Science to Market Gap*, 63 J. ECON. BEH'R & ORG. 624, 626, 627 (2007).

it is issued, and attempting to generate new sources of revenue), whether realized in whole or in part, will exacerbate the level of canalization that we would otherwise see—assuming the researcher has some real time awareness of commercialization's dénouement.

The available evidence indicates that academics aren't aware of efforts to commercialize by others,[215] but there is support for academic scientists responding in real time to their own commercialization workload. Jerry Thursby and Marie Thursby found, for example, that researchers' publications drop in years when an invention disclosure is made.[216] Further, Stuart and Ding found that coauthor networks contract after an academic scientist transitions to an entrepreneurial environment, whether by founding a firm or serving on an executive board.[217]

These findings help ground the first of three features that distinguish patent canalization from the current discourse and empirical findings to date; namely, that patent canalization theory targets something different from anticommons theory. The principal object of the inquiry, the scientist qua entrepreneur, is different from that of transaction cost theory, the scientist qua knowledge user.[218]

Nor, secondly, does patent canalization theory evoke the same concerns as path dependency.[219] In the economics literature, a few scholars have detailed how less than ideal technologies can become *the* standard due to path depend-

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215 *See* Walsh et al., *supra* note 10, at 1189.

216 Jerry G. Thursby & Marie C. Thursby, *University Licensing*, 23 OXFORD REV. ECON. POL'Y 620, 636 (2007) [hereinafter Thursby, *University Licensing*]. However, the same authors have also shown that while invention disclosures increased by tenfold between 1983 and 1999, the proportion of research published in so-called "basic" science journals has remained constant during that period. *See* Jerry G. Thursby & Marie C. Thursby, *Patterns of Research and Licensing Activity of Science and Engineering Faculty*, *in* SCIENCE AND THE UNIVERSITY 77, 92 (Paula E. Stephan & Ronald G. Ehrenberg eds., 2007) [hereinafter Thursby, *Patterns of Research*].

217 Stuart & Ding, *supra* note 207, at 133, 136.

218 This is not to say that anticommons theory and patent canalization theory are mutually exclusive.

219 Some scholars in the technology transfer debate have hinted that path dependence is a potential concern. Brett Frischmann, for instance, has noted that because knowledge spillovers are often undervalued, research may tend to become biased towards short term, more predictable goals—a change that may be hard to counteract down the road due to strategic behavior by market incumbents and due to "the costs of changing directions once a path has been taken." Brett Frischmann, *Commercializing University Research Systems in Economic Perspective: A View from the Demand Side*, *in* UNIVERSITY ENTREPRENEURSHIP AND TECHNOLOGY TRANSFER: PROCESS, DESIGN, AND INTELLECTUAL PROPERTY 155, 177 (Gary D. Libecap ed., 2005); *see also* Thursby, *University Licensing*, *supra* note 216, at 637–38.

ence.[220] Patent canalization, in contrast, tries to set the stage for judging whether maintaining a particular research path—with a parallel reduction in scientific collaboration —represents an acceptable tradeoff if gains in research depth (*i.e.*, a decrease in research diversity) are also observed. In this way patent canalization tries to develop a more refined account of the costs and benefits of commercializing academic science, for the scientist individually, and for those who might be advantaged by his or her work. In short, path dependence—not in the pejorative sense—might be exactly what we want to cultivate in particular kinds of research.

Thirdly, patent canalization theory may only have purchase in the context of research that is contingent upon significant follow-up, validation research like biomarkers. For other fields, where reductions in research diversity amongst academic scientists represent a net cost, other lenses, including the anticommons, may be more useful organizers of methodology.

III. THEORY-TESTING: A NEW METHODOLOGY

To test for relationships amongst scientific collaboration, research diversity, and patenting, I rely exclusively on academic scientists' published work and information obtained from a patent database. This strategy carries two major limitations. First, there are a number of other factors that may limit collaboration and research diversity, including access to funding, new technology, available human resources, and access to clinical information. Controlling for these factors is simply beyond the scope of this work. Second, relying solely on the published literature does not provide a comprehensive picture of collaboration or changes in research diversity. Research agreements between an academic institution and a private firm are seldom transparent and there is no searchable database for university-industry licensing. Therefore, simply identifying firms that might be engaged in follow-up research, let alone determining whether they are actually doing so, is highly problematic. For their part, academic scientists may also keep validation data confidential because of an agreement with a

[220] Paul David's work regarding how one sub-optimal technology (the "QWERTY" letter arrangement along the type writer keyboard's top row) became the industry standard is particularly interesting, however. *See* Paul A. David, *Understanding the Economics of QWERTY: The Necessity of History*, *in* ECONOMIC HISTORY AND THE MODERN ECONOMIST 30, 39–46 (William N. Parker ed., 1986); Paul A. David, *Clio and the Economics of QWERTY*, 75 AM. ECON. REV. 332, 334–36 (1985).

firm,[221] a desire to add more value to the work, or the inability to find a suitable publication venue.[222] I cannot discount these possibilities.

Nevertheless, given the growing interest amongst, incentives and support for, academic scientists to engage in biomarkers discovery and translation into diagnostic and therapeutic products,[223] the published literature harbors a wealth of information about the role of patenting in those commercial endeavors.

A. Data Set Construction

1. Sampling

To identify the academic scientists publishing the most in three streams of epigenetics—DNA methylation, histones, and microRNAs—and human oncology, a search was performed on the MEDLINE database using each of the three epigenetic terms in the "topic" search field along with humans and oncology for the "subject heading," and "subject area" search fields, respectively. The top 100 names were then culled from each of the resulting three scientific literatures. The total pool of scientists was far smaller for three reasons.

First, many scientists appeared more than once in each of the three top-100 lists (because they inconsistently used their initials when publishing and thus appeared as different names), and/or appeared on two or all three of the lists (because the three streams of epigenetics research are closely intertwined). Second, several of the authors have names that proved extremely difficult to disambiguate. Because there was more than one scientist in the world with the same name and common initials, searching for publications authored, for example, by "Brown, R*" yields thousands, if not tens of thousands, of hits. I therefore included only scientists with names that have 500 or fewer publications—a

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221 It is important to note that firm practices may be shifting, if not more open, than many currently believe. Vallas and Kleinman found that private sector scientists enjoyed "zones of autonomy" and that at least some firms encourage publication. *See* Vallas & Kleinman, *supra* note 115, at 295, 300.

222 There are several forms of publication bias. Perhaps the most damaging to translational research is the trend against publishing negative results from animal studies. *See* Janelle Weaver, *Animal Studies Paint Misleading Picture*, NATURE (Mar. 30, 2010), http://www.nature.com/news/2010/100330/full/news.2010.158.html.

223 Of particular note, the current director of the National Institutes of Health is advocating in favor of creating a "National Center for Advancing Translational Sciences." *See* Meredith Wadman, *The Bridge Between Lab and Clinic*, 468 NATURE 877, 877 (2010). Others contest that strategy. *See* Michael M. Crow, *Time to Rethink the NIH*, 471 NATURE 569, 569–70 (2011).

more manageable but still taxing number to verify by hand—associated with them. Third, although scientists from around the world were included, preference was given to scientists based at U.S. institutions because it was generally easier to verify biographical information for those individuals. In the end, I compiled data for fifty-two scientists.

2. Data Collection

Data collection involved two main steps. The first step was to identify each scientist's published experimental work. Including scientists' entire body of published experimental work—not just the work relating, for example, to DNA methylation—was important because that work also speaks to collaboration and research diversity. No database is perfect, thus there is a risk that works produced by a scientist will be omitted. Although scientists may positively contribute to a scientific field in many ways, for instance, by highlighting funding shortfalls in a newspaper editorial, variations in a scientist's experimental work are of primary interest here. Therefore publications that did not include original research findings were excluded. I sequenced the publications according to the date of submission[224] on the theory that variations in scientific collaboration and research diversity would be best observed in real time, as potential responses to patenting activity. Lags between submission and publication might obscure any relation amongst these variables.

The first step of data collection was therefore broken down as follows for each of the fifty-two scientists identified,

1. Conduct a search of the PubMed Central database (which encompasses, but is broader than MEDLINE) by author name (last name plus first initial);
2. Conduct a search of the ISI Web of Science (which encompasses, but is broader than MEDLINE) by author name (last name plus first initial);
3. Cross-check the two publication lists to produce a list of all publications belonging to the scientist in question;
4. Exclude all publications that are not original research articles such as meeting abstracts, reviews, editorials, commentaries, and proceedings papers (assuming they do not contain original experimental data); and,
5. Verify the precise date of submission for each original research article, ordering them chronologically.

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[224] Because some journals do not provide submission dates, in some cases, the next available earliest date was used (*e.g.*, the date of revisions, the date of acceptance, the date of electronic publication, or, if no other date is available, the date of publication).

For pragmatic reasons, the sequence of publications was limited to a seventeen-year period, 1991-2008.

The second step of data collection involved searching the Delphion database for all patent applications filed or granted for each scientist, which I describe further below. The result of data collection was a panel data set with fifty-two scientists and seventeen years of observation. A number of independent and dependent variables were abstracted from the panel data set.

B. Variables

To reiterate, patent canalization predicts that an academic scientist's participation in the commercialization of his or her work will limit scientific collaboration and the diversity of his or her subsequent research. To make this hypothesis testable, it was necessary to define what I mean by "participation in commercialization," "scientific collaboration," and "research diversity," as well as attempt to control for potentially significant differences between the scientists under scrutiny.

1. Independent Variables

a. Scientist Attributes and Other Extrinsic Factors

Academic scientists with an entrepreneurial bent may simply be, for reasons that are otherwise unintelligible, different from those lacking in overt entrepreneurialism. Similarly, there may be a two-way, or endogenous, relationship between entrepreneurial behavior and scientific behavior (*i.e.*, scientific activity shapes whether a scientist participates in commercialization, and vice versa). Therefore, following Azoulay et al.,[225] I attempt to mitigate the potential for confounding by examining a number of attributes and extrinsic factors related to each scientist, including the sex of each scientist; years of experience since graduation; the ranking of the TTO at his or her current university; and, whether the scientist holds a medical degree, a PhD, or both.

I also tabulated the number of publications each scientist produced per year of observation, and over the 1991-2008 timeframe. I used this publication output information to create three variables of publication output—a "within" or "same year" publication output variable, a one-year before the year of interest variable, and a two-year before the year of interest variable—in order to exam-

[225] Azoulay et al., *supra* note 8, at 653–54.

ine the relationship between publication output and the dependent variables over time.

Biographical, publication output, and other information relevant to the present study are included in the Appendix.

b. Participating in Commercialization

I used two variables to track a scientist's participation in commercialization: patent applications and patent grants. Both types of patent documents were identified by searching the Delphion database for all patent applications filed or granted in the United States, Europe, and patent abstracts from Japan, in which the scientist's name appeared in the inventor field.

Determining the number of different patenting "events" for each scientist is not straightforward due to the intricacies of the patent prosecution process. For example, one patent application may result in multiple patent grants. Because my focus is on the individual academic scientist, I attempted to distinguish between patenting events that were likely to directly involve the scientist from events attributable to other actors like lawyers. Whereas patent applications with the same priority date were typically counted only once,[226] patent grants stemming from the same application were counted multiple times if they had multiple grant dates on the theory that each grant date corresponds to a different potential market and thus a bigger reward or incentive for the scientist in question.

Each of these events was placed within the sequence of published papers (again, ordered according to date of submission) using the priority date, filing date, or date of the patent grant. As with publication output, I created within year, one-year lag, and two-year lag variables for both patent applications and patent grants.

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[226] A patent application may have a priority date in common with one or more other patent applications, but possess a unique "date of filing." In such instances, I chose to "count" that date of filing, in effect, like a new priority date—even though the two are distinct for the purposes of patent law—on the assumption that the scientist under scrutiny was likely consulted and to some degree involved in supplying new information for the purpose of that new filing. Again, the idea is that that involvement might somehow impact the scientist and was therefore important to count as a patenting event.

2. Dependent Variables

a. Scientific Collaboration

The first of two sets of dependent variables related to scientific collaboration, specifically, interpersonal collaboration. I measured the total number of new co-author relationships that a scientist formed over time. For every publication, using a Microsoft Excel macro, I distinguished between new co-authors that are "absolutely new" versus co-authors that are "relatively new," that is, between co-authors that are new in view of a scientist's entire body of previously work versus co-authors that are new relative to the article that immediately preceded the article in question.[227]

b. Research Diversity

The second set of dependent variables utilized information from the ISI Web of Science database "KeyWords Plus" field associated with every research article produced by each scientist in the pool. Phrases and words appearing in the KeyWords Plus field were, like the interpersonal co-author data, categorized as either "absolutely new" or "relatively new" in view of the scientist's prior publication record. In rare cases where a publication was missing from ISI Web of Science but appeared in PubMed, the first ten "MeSH terms" from the PubMed record were manually input as keywords.[228]

Both MeSH terms and KeyWordsPlus terms speak to the range of a scientist's published body of work but they are based on different things.[229] Despite this incongruity in the research diversity data, I elected to strive for comprehensive coverage of a scientist's published work, and include papers even if only MeSH terms were available.

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[227] A scientist must have at least three publications before I can draw this distinction; that is, by the second publication, any new co-authors will be both absolutely new and relatively new. Due to the limitations of the software, publications with forty or more co-authors were excluded from the analysis. Such publications were rare, however.

[228] Often PubMed records had more than ten MeSH terms. However, due to the limits of the macros, no more than ten terms could be analyzed per publication. I simply took the first ten MeSH terms, in alphabetical order.

[229] Whereas MeSH terms place a paper within a scientific nomenclature (devised by the architects of MEDLINE), KeyWordsPlus terms are generated through an algorithm that places a paper within a scientific literature (as derived from the references cited by the authors of that particular paper).

IV. ANALYSIS

Patent canalization theory predicts that patenting will encourage scientists to become more insular in their research (reflected as less new co-authoring relationships) and more entrenched in their lines of research inquiry (reflected as less new keywords associated with each publication). As described in detail below, various analyses of the data I compiled provide support for patent canalization, with important nuances depending on how frequently scientists patent.

A. Findings

1. Descriptive Statistics

Despite all being top publishing scientists in one or more streams of cancer epigenetics, the fifty-two scientists (six women and forty-six men) in the sample differed in several ways. Most notably, the scientists varied widely in their level of experience, ranging from five to forty-seven years of experience since graduating from their last degree program (the mean years of experience by 2008 was 22.83). Accordingly, scientists also differed considerably in terms of total publication output during the 1991-2008 time frame. Whereas the scientist with only five years experience by 2008 published twenty-two papers, the most prolific scientist, producing 391 publications, had thirty-nine years of experience at that time. However, when grouped together depending on patenting activity, the scientists in the sample show broad similarities in terms of average years of experience, total publication output, educational backgrounds, etc. (see Table 1).

	0 Patents	**>5 Patents**	**≤5 Patents**	**Total Sample**
Gender (female)	2 (15.38%)	3 (16.67%)	1 (4.76%)	6 (6.92%)
Years of Experience	20.38 (9.82)	23.95 (11.46)	23.52 (8.18)	22.83 (9.46)
Total publication output by 2008	110.77 (62.14)	133.21 (95.08)	155.19 (84.51)	133.60 (83.89)
MD	7 (53.85%)	9 (50.00%)	8 (38.10%)	22 (42.31%)
PhD	8 (61.54%)	8 (44.44%)	9 (42.86%)	22 (42.31%)

MD & PhD	1 (7.69%)	1 (5.56%)	4 (19.05%)	6 (6.92%)
Other	1 (7.69%)	1 (5.56%)	0	2 (3.85%)
Patent applications	0	2.53 (1.54)	12.71 (10.38)	6.06 (8.64)
Patent grants	0.17 (0.55)	0.95 (1.13)	5.24 (5.88)	2.46 (4.41)
N	13	18	21	52

Table 1. Descriptive Statistics By Patent Group.

Notes: (1) "Patents" refers to both patent applications and patent grants. (2) Reported results are means (standard deviations) for continuous variables and n (%) for categorical variables.

In terms of education, the vast majority held a PhD (twenty-two) or MD (twenty-two) although a few attained both an MD and PhD (six), and two held some other combination of degrees. . Many attended top ranked institutions as students, held appointments at such an institution presently, or both.

Only four of the fifty-two scientists had filed for a patent application prior to 1991. All others continued to abstain from, or began patenting, within the time frame under study. Specifically, 13 of the 52 scientists in the sample did not file for a patent application, nor receive a patent grant, between 1991 and 2008; 18 scientists held between one and five patent applications or grants, which I liberally categorized as "Non-Repeat Players;" and, the remaining 21 scientists ("Repeat Players") held five or more patent applications and grants. The mean number of patent applications (6.06) and patent grants (2.46) are higher than previous studies. Given that I selected for scientists engaged in research connected to an "applied" field of study, biomarkers of human oncology, higher patenting activity is perhaps to be expected.

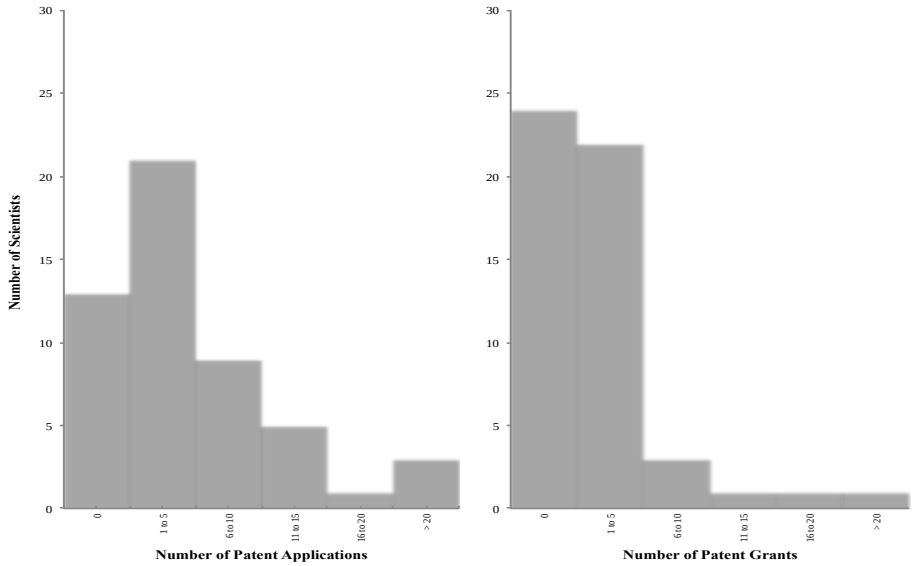

Figure 2. Distribution of Patent Applications and Patent Grants for All Scientists, 1991-2008.

2. Regression Results

I tested a number of different regression models for each of the dependent variables of interest (which I refer to hereafter as *Abs.Co-Authors*, *Rel.Co-Authors*, *Abs.KeyWords*, and *Rel.KeyWords*). Given the high proportion of zeros in the dependent variables and their skewed nature, I chose to treat the dependent variables as count variables and applied a Poisson distribution. Due to the panel structure of my data I used generalized estimating equations to account for the correlation of observations within individuals over time. I used an exchangeable correlation structure because an autoregressive structure, though theoretically ideal, was too data intensive.

Hausman tests, a statistical technique used to determine whether random effects versus fixed effects models best fit the data, favored the latter for all dependent variables. Thus, apart from the following exception, I estimated a time invariant individual effect using the xtpoisson, fixed effect procedures with Stata 11 software. Because Stata excluded three of the independent variables (gender; degree(s); TTO ranking) due to co-linearity when fixed effects models were selected, random effects models (not reported here) were used to discern the relationships between these three independent variables and the co-authoring

and keyword measures.[230] These relationships remained constant across all regressions described below except for minor exceptions. Gender and having a TTO ranked in the top 50 bore no relationship to the dependent variables. However, holding an MD as well as a PhD, an attribute of only five scientists in the sample, was associated with tremendous increases in *Abs.Co-Authors* (>122%) and *Rel.Co-Authors* (>114%) as well as *Abs.KeyWords* (>33%) and *Rel.KeyWords* (>39%) amongst the 52 scientists. In contrast, holding a PhD only was associated with a significant decrease in both types of new co-authoring (by 27-29%) but showed no relationship with research diversity in the full sample.[231]

Two sets of fixed effects regressions were ultimately run: a set of regressions including the full sample of scientists, and a set of regressions in which scientists are grouped into one of two groups dependent on their patenting activity. The results are reported in terms of incidence rate ratios ("IRRs"), which, holding all other variables constant, show increases (above 1) and decreases (below 1) in a given dependent variable.[232] After accounting for individual scientists' experience in both the full sample and patent group regressions I assessed the relationship between the remaining independent variables and *Abs.Co-Authors*, *Rel.Co-Authors*, *Abs.KeyWords*, and *Rel.KeyWords* at select points in time. With respect to patent events, I assessed: the relationships between patent applications and grants occurring in the year prior to the year in which the dependent variables are measured (*i.e.*, "T-1"); the relationships between patent applications and grants occurring the same year in which the dependent variables are measured (*i.e.*, "T"); and, the relationships between patent

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230 Interestingly, despite the fact that Hausman tests favored fixed effects for all dependent variables, the relationships between the remaining independent variables (experience, publications, patent applications, and patent grants) and the dependent variables are essentially exactly the same when the random effects models are used. That is, the size and direction (positive versus negative), or lack thereof, is the same for every variable regardless of which models are used.

231 When scientists were segregated into two groups based on their participation in patenting, the positive effect of holding both MD and PhD degrees disappeared amongst scientists who patented less frequently. This likely results from the fact that only one scientists in that group had that attribute. Also, the negative effect of holding a PhD only shown in the full sample regressions was not present amongst either frequent or infrequent patentees in the group regressions.

232 In a Poisson regression model, the IRRs represent the percentage change in the dependent variable in question. For example, in Table 1, the IRR for the dependent variable *Abs.Co-Authors* and the independent variable of experience is ~1.05. This means that every one unit increase in experience is associated with a 5% increase in *Abs.Co-Authors*, holding everything else constant.

applications and grants occurring in the year after the year in which the dependent variables are measured (*i.e.*, "T+1"). In contrast, the relationship between publications and the dependent variables was examined at T, T-1, and T-2.

Full Sample

	Abs. Co-Authors	*Rel. Co-Authors*	*Abs. Key Words*	*Rel. Key Words*
Experience	IRR: 1.051222***	IRR: 1 .055927***	IRR: 1. .017062***	IRR: 1 .032762***
	SE: 0.0024594	SE: 0.0017398	SE: 0.0020262	SE: 0.0014898
Publications				
Year T	IRR: 1.065501*** SE: 0.0016911	IRR: 1.072277*** SE: 0.001176	IRR: 1.080395*** SE: 0.0014918	IRR: 1.077787*** SE: 0.001079
Year T-1	IRR: 0.9957505* SE: 0.0017618	IRR: 1.003981** SE: 0.0011791	IRR: 0.992686*** SE: 0.0015507	IRR: 1.001199 SE: 0.0010901
Year T-2	IRR: 0.9944929** SE: 0.0017737	IRR: 1.000349 SE: 0.0011808	IRR: 0.992154*** SE: 0.001556	IRR: 0.9989747 SE: 0.0010955
Apps				
Year T-1	IRR: 0.9731966** SE: 0.0097201	IRR: 0.976398*** SE: 0.0066503	IRR: 0.9837798 SE: 0.0090412	IRR: 0.9789754** SE: 0.0063236
Year T	IRR: 0.963206*** SE: 0.0080081	IRR: 0.951840*** SE: 0.0053176	IRR: 0.945898*** SE: 0.0072462	IRR: 0.94704*** SE: 0.0050009
Year T+1	IRR: 0.9928822 SE: 0.0082797	IRR: 1.001217 SE: 0.0055317	IRR: 1.004759 SE: 0.0075671	IRR: 1.006818 SE: 0.0052368

Grants				
Year T-1	IRR: 1.022394 SE: 0.0162998	IRR: 1.002257 SE: 0.0109764	IRR: 1.01822 SE: 0.0147839	IRR: 1.026317* SE: 0.0103005
Year T	IRR: 0.9879718 SE: 0.0159535	IRR: 0.951725*** SE: 0.0106027	IRR: 1.007677 SE: 0.0145654	IRR: 0.9961972 SE: 0.0100719
Year T+1	IRR: 1.007123 SE: 0.0129496	IRR: 1.025774** SE: 0.0087046	IRR: 0.9924519 SE: 0.0116537	IRR: 1.026023** SE: 0.0080809
Number of obs	702	702	702	702
Number of groups	52	52	52	52
Log likelihood	-3169.3825	-3737.7732	-3031.55	-3626.05

Notes
Significant at the 0.001 level
Significant at the 0.01 level
Significant at the 0.05 level

Table 2. Effect of Patenting on Scientific Collaboration and Research Diversity Across Scientists: Fixed Effects Poisson Models.

Notes: (1) Number of observations = 702; number of scientists = 52. (2) *significant at $p < 0.05$; **significant at $p < 0.01$; ***significant at $p < 0.001$. (3) IRR = incidence rate ratio; SE = standard error.

a. Across All Scientists

Table 2 presents the results from the first set of regressions using data from all fifty-two scientists with 702 waves of observations. Several patterns emerge. First, consistent with intuition, across all measures, scientific collaboration and research diversity tend to grow with experience and publication productivity. Second, the direction of the relationship between publication output and the dependent variables reversed with time. Increases in publication output tend to predict decreases in absolutely new co-author and keywords

measures, however, these negative effects were both less than a single percentage point. Third, patent applications at T-1 and T had a consistently negative effect on nearly all of the dependent variables in the range of 3-5%. Fourth, and finally, fewer grant variables had a significant relationship with the dependent variables; interestingly however, three of the four significant relationships were positive in contrast to the generally negative effect of applications.

b. Patent Count Groups

As reflected in Table 3, for a second set of regressions I segregated the fifty-two scientists based on patent application and patent grant counts during 1991-2008. As noted above, those who did not apply for or receive a patent during that timeframe were excluded from this second regression. The remaining scientists were classified as either Non-Repeat Players if they applied for and obtained less than five patents (n=18), or as "Repeat Players" if they who filed for or received more than five patents (n=21).

Consistent with the full sample regression, the relationship between experience as well as publication output (at T and T-1) and the dependent variables remains positive for both Non-Repeat Players ("Non-RPs") and Repeat Players ("RPs"). The relationships between patenting activity and the dependent variables differ markedly by patent group, however. Amongst Non-RPs, an increase in patenting at T-1 has a positive effect upon the *Rel.Co-Authors* (~7%), *Abs.KeyWords* (~8%), and *Rel.KeyWords* (~9%) one year later. Within the same year these relationships are not present. But when the dependent variables are measured one year prior to a patent application, we see 18-19% and 9-11% gains in the co-authoring and keyword variables, respectively, amongst Non-RPs. No such gains in the dependent variables occur in the lead up to a patent application amongst RPs. Instead, increases in patenting at T-1 or T have a 2-4% negative effect on co-authoring and keywords.

The effect of grants also differs depending on whether a scientist falls into the Non-RP or RP category. Amongst the former, grants predict a significant increase (~12-15%) in research diversity one year later. With respect to collaboration, for Non-RPs grants have a strong and positive association with *Abs.Co-Authors* (~18%) and *Rel.Co-Authors* (~17%) when measured in the year leading up to an increase in grants. For RPs, few significant relationships with grants exist; only a 4% increase in *Abs.Co-Authors* at T-1 and a 6% decrease in *Rel.Co-Authors* at T is observed.

	Non RPs			
	Abs. Co-Authors	*Rel. Co-Authors*	*Abs. Key Words*	*Rel. Key Words*
Experience	IRR: 1.054944***	IRR: 1.050637***	IRR: 1.011982***	IRR: 1.026536***
	SE: 0.0041012	SE: 0.0028306	SE: 0.0033455	SE: 0.0024254
Publica-tions				
Year T	IRR: 1.062239*** SE: 0.0031349	IRR: 1.075372*** SE: 0.0021141	IRR: 1.087846*** SE: 0.0027092	IRR: 1.082821*** SE: 0.001933
Year T-1	IRR: 0.9939281 SE: 0.0031399	IRR: 1.000652 SE: 0.0020411	IRR: 0.9925768** SE: 0.002654	IRR: 1.000194 SE: 0.0018836
Year T-2	IRR: 0.9991475 SE: 0.0028613	IRR: 1.005977** SE: 0.0018146	IRR: 0.9954964 SE: 0.0023964	IRR: 1.002769 SE: 0.001675
Apps				
Year T-1	IRR: 1.04489 SE: 0.0335161	IRR: 1.071496** SE: 0.0245822	IRR: 1.078634** SE: 0.0304542	IRR: 1.08702*** SE: 0.022687
Year T	IRR: 0.9969844 SE: 0.0338496	IRR: 1.037914 SE: 0.0248522	IRR: 0.9566153 SE: 0.0289504	IRR: 1.029135 SE: 0.0225786
Year T+1	IRR: 1.19992*** SE: 0.0375603	IRR: 1.186059*** SE: 0.0266843	IRR: 1.085845** SE: 0.0306191	IRR: 1.114315*** SE: 0.0231377
Grants				
Year T-1	IRR: 0.9958735 SE: 0.041651	IRR: 1.042827 SE: 0.0302385	IRR: 1.147628*** SE: 0.0423125	IRR: 1.117262*** SE: 0.0295469

Year T	IRR: 1.080629 SE: 0.0462335	IRR: 1.07862* SE: 0.0327515	IRR: 1.085155* SE: 0.0425762	IRR: 1.09799** SE: 0.0307523
Year T+1	IRR: 1.17711*** SE: 0.0458538	IRR: 1.165055*** SE: 0.0326367	IRR: 1.031381 SE: 0.0390186	IRR: 1.095558** SE: 0.0292688
Number of obs	237	237	237	237
Number of groups	18	18	18	18
Log likeli-hood	-1042.5997	-1269.52	-1091.79	-1272.46

	RPs			
	Abs. Co-Authors	***Rel. Co-Authors***	***Abs. Key Words***	***Rel. Key Words***
Experience	IRR: 1.03485***	IRR: 1.053853***	IRR: 1.015765***	IRR: 1.031913***
Publica-tions	SE: 0.0039775	SE: 0.0028719	SE: 0.0034359	SE: 0.0025462
Year T	IRR: 1.066699*** SE: 0.0023965	IRR: 1.068635*** SE: 0.0017337	IRR: 1.07315*** SE: 0.0022142	IRR: 1.071704*** SE: 0.0016359
Year T-1	IRR: 0.9969954 SE: 0.0025489	IRR: 1.006509*** SE: 0.001752	IRR: 0.9954357 SE: 0.0023491	IRR: 1.004183* SE: 0.001657
Year T-2	IRR: 0.9950732 SE: 0.0026648	IRR: 1.000747 SE: 0.0018389	IRR: 0.9946539* SE: 0.0024511	IRR: 1.000191 SE: 0.0017463
Apps				

Year T-1	IRR: 0.9755281* SE: 0.0107241	IRR: 0.970605*** SE: 0.0072431	IRR: 0.959272*** SE: 0.0079739	IRR: 0.972798*** SE: 0.0068875
Year T	IRR: 0.9788652* SE: 0.0088901	IRR: 0.960538*** SE: 0.0058941	IRR: 0.9768044* SE: 0.0098749	IRR: 0.955671*** SE: 0.0055272
Year T+1	IRR: 0.9908309 SE: 0.0088656	IRR: 0.9975193 SE: 0.0058878	IRR: 1.003637 SE: 0.0080918	IRR: 1.006278 SE: 0.0055933
Grants				
Year T-1	IRR: 1.043107* SE: 0.0185063	IRR: 1.005338 SE: 0.0122341	IRR: 0.9968974 SE: 0.0158963	IRR: 1.017998 SE: 0.0113484
Year T	IRR: 0.9832742 SE: 0.017595	IRR: 0.94420*** SE: 0.0115952	IRR: 1.001495 SE: 0.0161557	IRR: 0.9884622 SE: 0.0110129
Year T+1	IRR: 1.005026 SE: 0.0139282	IRR: 1.017264 SE: 0.0092099	IRR: 0.9902206 SE: 0.0124235	IRR: 1.020196* SE: 0.0085649
Number of obs	290	290	290	290
Number of groups	21	21	21	21
Log likeli-hood	-1330.471	-1525.27	-1108.96	-1364.87

Notes
Significant at the 0.001 level
Significant at the 0.01 level
Significant at the 0.05 level

Table 3. Effect of Patenting on Scientific Collaboration and Research Diversity by Patent Count

Group: Fixed Effects Poisson Models.
Notes: (1) *significant at $p < 0.05$; **significant at $p < 0.01$; ***significant at $p < 0.001$.

B. Limitations and Implications

The present study carries three limitations. First, co-authoring and key words data are imperfect proxies of scientific collaboration and research diversity. Much co-authoring within the life sciences is the product of the norms of authorship. The norm is to name all, or nearly all, of the members of a lab on each paper; all who are named are understood to have contributed to the experimental findings, but not necessarily the conception of the project or in writing up of the results—the standards used for determining inventorship in patent law[233] and authorship in other academic disciplines like the humanities. Co-authoring data might for this reason be considered an inflated measure of true collaboration. Similarly, key words, which in the case of ISI's KeyWordsPlus, are generated by an algorithm that takes into account the title of the work in question and the literature it references. They cannot fully capture the similarities and differences between one experiment and those that preceded it, nor speak to the full breadth of a scientist's ongoing work. Second, patenting's association with decreases in the dependent variables might be temporal rather than causal. Other factors that I did not track such as changes in funding or resources remain possible causes of canalization. Third, the foregoing findings are based on a small, non-random sample of academic scientists.

The study design nevertheless has unique strengths compared to previous empirical work. First, because I verified that each publication was, in fact, a publication produced by the scientist in question, the data set is not contaminated by publication "false positives."[234] Second, in limiting the data set to publications containing original experimental findings, my findings are in theory more germane to problems in biomarkers discovery and development. Observed changes in research diversity are not confounded by the inclusion of other types of important, but different, work that scientists engage in, including professional activities (writing practice guidelines), education (summarizing the state of the art in review articles), and advocacy (calling attention to a problem in editorials). Third, by sequencing the publications according to the date of submission, the relations between patenting and collaboration and research diversity are not confounded by lags in publication.

The findings reported here are broadly consistent with patent canalization theory. In the full sample of 52 scientists, there is a negative relationship between applying for a patent and all of the measures of scientific collaboration and research diversity. While these relationships are modest, they approach in size the positive relationship observed between experience and publication output and these measures, especially *Abs.KeyWords* and *Rel.KeyWords*.

The findings also add considerable nuance to patent canalization theory. The first nuance concerns time. Patent canalization theory predicts that a scientist's investment in working up a

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[233] For a detailed discussion of the law of inventorship and challenges to determining inventorship in the academic context, see Sean B. Seymore, *My Patent, Your Patent, Our Patent? Inventorship Disputes within Academic Research Groups*, 16 ALB. L.J. SCI. & TECH. 125, 135–36 (2006).

[234] Data sets created through automated searches using author names are not free from such contamination.

patent application would translate into decreases in collaboration and diversity. Here, however, such negative effects were only observed in the full sample of scientists in the year in which a patent application is filed (*i.e.*, at T), or the year after filing (*i.e.*, at T-1). The second nuance relates to the type of patenting activity. Patent canalization theory predicts that applications are more likely to influence levels of collaboration and diversity than patent grants because applications are more likely labor-intensive for the scientist. The regression results support this insofar as there is seldom a significant relationship between grants and the four dependent variables except in the case of scientists who engaged in patenting on fewer than five occasions (the Non-RPs). And therein lies the third nuance to patent canalization theory: the frequency with which scientists participate in patenting. As depicted in Table 3, the relationships between patent applications, grants, and the dependent variables differ markedly in the case of Non-RPs whereas RPs show relationships that are essentially the same as those observed in the full sample. For example, in the year leading up to a patent application or a patent grant (*i.e.*, at T+1), Non-RPs tend to increase their levels of scientific collaboration and research diversity by ~10-20%. The present study thus suggests that engaging in limited amount—not a lot—of patenting is associated with increased scientific collaboration and research diversity.

How, then, do these findings fit with the existing empirical literature around patenting in the life sciences? On one hand, it is broadly consistent with some previous studies employing different methodologies. Network-based analyses by Bubela et al.[235] as well as Stuart and Ding[236] show that co-authoring relationships can be limited by patenting or other forms of entrepreneurialism. In terms of scientists becoming more entrenched in their lines of research inquiry, Murray et al.'s finding that the removal of intellectual property-related restrictions help to diversify a given field provides indirect support for the key words-related findings documented here.

On the other hand, some thinkers have postulated that patenting would *add* co-authoring opportunities and *diversify* research agendas—the exact opposite of patent canalization. Although Azoulay et al. did not directly test those hypotheses,[237] they do provide two related accounts of why we might expect such results. First, they note that "scientists who choose to patent and thereby shift into the commercialist camp will begin to allocate their research time across a wider set of research questions than they had done when they were [not patenting]."[238] Second, through interactions with industry, academic scientists "gain exposure to new (relative to their previous work) areas of commercially useful scientific inquiry."[239] The first account is a story about increases in overall diversity, one project to the next. The second account underscores the fresh supply of research questions that the private sector may hold, which, may or may not, translate into an increase in overall research diversity.[240] Azoulay et al.'s logic could be equally applied to co-authorship: industry supplies a fresh source of collaborators, project to project as well as overall.

However, with the important exception of Non-RPs, my results generally run counter to these predictions, painting a different picture of what industry—if we assume that's what patenting will attract—brings to the table in collaborations with academic researchers. Azoulay et al., in effect, suggest that industry brings a lot to the collaboration: new collaborators and new re-

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235 Bubela et al., *supra* note 13, at 29.

236 Stuart & Ding, *supra* note 207, at 137.

237 In documenting a trend of increased co-authoring with members of industry after patenting, Azoulay et al. provide some indirect support for these ideas. *See* Azoulay et al., *supra* note 8, at 638.

238 *Id.* at 642.

239 *Id.* at 643.

240 Using my methodology as a lens, we might think the first story Azoulay et al. offer up might be evidenced through increases my "relatively new" key words measure and the second story through increases in "absolutely new" key words. *See id.* at 642–43.

search questions. The present findings, in contrast, suggest that industry's presence, which typically begins post patent application but prior to a patent grant,[241] results in net losses in co-authoring relationships and diversity of scientific inquiry, which I interpret as evidence of patent canalization. While Non-RPs do enjoy the kinds of increases that Azoulay et al. imagine, it seems implausible that those gains are sourced from industry given that Non-RPs are—by virtue of their infrequent participation patenting—less apt to have established relationships with industry.

In sum, coupled with the existing literature the present empirical findings set the stage for more refined thinking about the social welfare consequences of patenting activity within academia, and within particular areas of academic science. I close by examining three potential consequences.

3. Three Social Welfare Consequences, Queries for Future Empirical Work, and Intellectual Property Policy

The first social welfare consequence concerns the future retinue of academic scientists. Although university norms are shifting, publishing remains critical to building a career in academic science. And as scientists publish papers, gain experience, build their own lab, receive grants, etc., they serve as a hub for junior scientists set on pursuing a similar path. Therefore, while we do not presently know whether a decrease in new co-authoring relationships marks a decrease in lasting, peer-to-peer collaboration, it does mean that patenting scientists become more tight-knit hubs of publishing activity than, it seems, they otherwise would. Over time this may reduce the overall pool of junior scientists able to pursue academic careers for want of demonstrated publishing capacity[242]—careers, which, we estimate deliver significant social good.[243] We have evidence that patenting increases publication output,[244] but we do not know whether trading more publication output for co-authoring insularity, on balance, translates into more scientific collaboration. To assess the impact of patenting on the long-term supply of scientists able to pursue academic careers, future work should take both effects of patenting into account.

The second potential social welfare tradeoff is tied to academic choice or autonomy. Combined with previous work indicating that patenting correlates with subtle forms of shaping—from co-authoring with more industry-affiliated scientists, publishing in journals with higher proportions of industry-affiliated scientists, to pursuing more patentable research—the present study shows that new co-authoring relationships (regardless of affiliation) and new lines of research inquiry (regardless of patentability) tend to diminish with patent application. The distinction between "absolutely new" and "relatively new" co-authors and key words was intended to capture two different types of academic autonomy: in the case of the former, a continuing *openness* to choose new persons to work with or new projects to work on, and in the latter, day-to-day *flexibility* to shift between multiple groups of researchers or multiple research projects. In the sample of fifty-two scientists examined here, applying for a patent appears to limit both. In the regressions comparing Non-RPs, though, applying for a patent or receiving a patent grant might enhance a scientist's choices. Therefore, as patenting continues to be normalized and routinized within the academy as a whole, scientists of different disciplines should evaluate whether such reductions in

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241 *See* Elfenbein, *supra* note 7, at 693–94. That university-to-industry licensing most often occurs before a patent is granted is important, in this regard, because the findings above tend to show a positive relationship between patent grants and new co-authoring relationships and key words.

242 For a discussion of the importance of publishing to building a career in academic science, see Seymore, *supra* note **Error! Bookmark not defined.**, at 131–32.

243 Aghion et al., *supra* note 210, at 634.

244 Azoulay et al., *supra* note 8, at 638.

scientific collaboration and research diversity—to the extent the findings here generalize—compromise their autonomy.[245] Paradoxically, it may be important to set limits upon how often scientists participate in the practice of patenting in order to preserve other choices.

The third and final potential consequence of patent canalization has to do with tradeoffs in the breadth and depth of scientists' experimental work. Many attest to the social and economic gains that free academic inquiry affords.[246] However, unlike other areas of academic inquiry, reductions in research diversity may be welcome in the context of translational biomarkers research. Recall that biomarkers research has, to date, underwhelmed due to a lack of experimental standardization, replication, and validation, as well as the complexity of the science itself.[247] If we are to rely on academic science to make sense of that complexity and address shortfalls in standardization, replication, and validation, one might assume that reductions in the breadth of academic research agendas can service those goals—assuming that is, in fact, what diminishing levels of absolutely and relatively new key words means. Perhaps patenting can facilitate knowledge translation, not just in terms of bringing actors with different expertise and resources together, but by motivating scientists to drill further down on a given research problem.[248] It is premature to say that patenting is adding this sort of promise to the three streams of cancer epigenetics studied here given how young those fields of inquiry are. We can, however, discern relationships between patenting and the apparent diversity of their experimental work of the scientists leading those three fields, which, in time, might help make sense of any progress in cancer epigenetics.

V. CONCLUSION

In summary, in a sample of fifty-two academic scientists I found negative relationships between applying for a patent and four measures of scientific collaboration and research diversity. These negative relationships were also evident amongst scientists that engaged in patenting on five or more occasions during 1991-2008. However, for those who participated less frequently, patenting was associated with significant increases in scientific collaboration and diversity.

This study thus adds to a growing body of empirical knowledge about the apparent impact of patenting within the life sciences. The decreases in co-authoring relationships and key words diversity observed in the published experimental work of academic scientists engaged in cancer epigenetics research, described conceptually as patent canalization, are a counterweight to past studies showing that patenting bolsters publication output;[249] an asterisk on the view that patenting seldom influences research direction and choices about whom to work with and what to

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245 Of course, a prior question to ask is whether the phenomenon observed here is to be found in other areas of academic science.

246 Perhaps the most famous statement to this effect was made to President Truman in a report by Vannevar Bush, Director of the Office of Scientific Research and Development, during World War II. *See* VANNEVAR BUSH, SCIENCE—THE ENDLESS FRONTIER 12 (1945). http://www.nsf.gov/od/lpa/nsf50/vbush1945.htm. For a contemporary, economics-based argument to this effect, see Aghion et al. *supra* note 210, at 618.

247 Other dimensions of this problem highlighted above are poor regulatory oversight and inadequate reimbursement from health care providers. *See supra* text accompanying notes 115–17.

248 This raises questions of intellectual property theory, which I plan to examine in future work. Using patents to attract private sector research partners has been the dominant justification invoked for the creation of the Bayh-Dole Act. The notion that patents can serve as an a priori motivation for academic scientists to generate new knowledge—a notion that borrows from the classic "public goods" justification for intellectual property rights generally—has been dismissed because of the other incentives for knowledge production that exist in the academic context (*e.g.*, government grants; the need to publish to receive tenure). In view of the findings presented here, the dismissal of that view merits reconsideration.

249 Azoulay et al., *supra* note 8, at 638.

work on;[250] and, a qualification to proofs that patenting undermines knowledge use[251] and knowledge translation.[252] In view of this complicated body of empirical evidence, academic institutions, academic scientists, and policy makers must consider whether the limitations seemingly occasioned by patenting upon academic autonomy should be tolerated in the name of *choice* translational research. As with epigenetic markers of cancer, there is much we still do not know about commercialization practiced with academia. However, to let complexity arrest efforts to develop institutional, personal, and policy answers to the questions of commercialization is to read Robert Frost's *The Road Not Taken* cynically, to say that the influence of patenting upon outcomes isn't knowable, a stance antithetical to the project of science.

Scientist	**Degree(s)**	**Year (Experience)**	**Current Institution**	***h*-index[234]**	**# Pubs**	**# Apps**
Baylin, Stephen B.	MD	1968 (40)	Johns Hopkins University	92	185	19
Belinsky, Steven A.	PhD	1984 (24)	Lovelace Respiratory Research Institute	30	82	6
Biegel, Jaclyn A.	PhD	1981 (27)	University of Pennsylvania	39	106	0
Bloomfield, Clara	MD	1969 (39)	Ohio State University Medical Center	62	156	0
Byrd, John C	MD	1991 (17)	Ohio State University Medical Center	55	154	6
Calin, George A	MD/PhD	2000 (8)	University of Texas MD Anderson Cancer Center	41	77	13
Carducci, Michael	MD	1988 (20)	Johns Hopkins University	37	87	0
Coukos, George	MD/PhD	1990 (18)	University of Pennsylvania	33	75	4
Croce, Carlo M	MD	1969 (39)	Ohio State University	98	391	43
Dahiya, Rajvir	PhD	1982 (26)	University of California at San Francisco	48	191	5
Dashwood, Roderick	PhD	1986 (22)	Oregon State University	32	75	0
Davidson, Nan-	MD	1979 (29)	University of	61	114	4

250 Walsh et al., *supra* note 10, at 1199.

251 Huang & Murray, *supra* note 12, at 2009; Murray & Stern, *supra* note 12, at 683.

252 Williams, *supra* note 15, at 27.

cy E			Pittsburgh			
Dent, Paul	PhD	1991 (17)	Virginia Commonwealth University	56	228	6
Domann, Frederick	PhD	1991 (17)	University of Iowa	25	83	0
Esteller, Manel	MD/PhD	1996 (12)	University of Barcelona	63	165	8
Fackler, Mary Jo	PhD	1988 (20)	Johns Hopkins University	17	23	4
Feinberg, Andrew P	MD/MP	1981 (27)	Johns Hopkins University	49	79	14
Fuchs, Charles S	MD/MP	1993 (15)	Dana-Farber/Harvard Cancer Center	57	203	0
Futscher, Bernard	PhD	1990 (18)	University of Arizona Cancer Center	28	60	0
Garcia-Manero, Guillermo	MD	1991 (17)	University of Texas MD Anderson Cancer Center	46	166	1
Gazdar, Adi F	MB	1961 (47)	University of Texas Southwestern Medical Center at Dallas	88	315	1
Goggins, Michael	MD	1988 (20)	Johns Hopkins University	47	137	6
Goodfellow, Paul J	PhD	1985 (23)	Washington University in St. Louis	30	99	1
Hamilton, Stanley R	MD	1973 (35)	University of Texas MD Anderson Cancer Center	83	205	2
Hecht, Stephen S	PhD	1968 (40)	University of Minnesota	53	239	0
Herman, James G	MD	1989 (19)	Johns Hopkins University	84	175	11
Hoon, Dave SB	PhD	1983 (25)	John Wayne Cancer Institute	41	147	25
Isaacs, William B	PhD	1984 (24)	Johns Hopkins University	62	197	8
Issa, Jean-Pierre	MD	1987 (21)	University of Texas MD Anderson	62	145	6

			Cancer Center			
Jass, Jeremy R	MD	1983 (25)	Imperial College London	52	156	0
Jones, Peter A	PhD	1973 (35)	University of Southern California	61	111	8
Judkins, Alexander R	MD	1996 (12)	University of Pennsylvania	17	42	0
Karpf, Adam R	PhD	1997 (11)	Roswell Park Cancer Institute	16	27	1
Kelsey, Karl T	MD/MP	1987 (21)	Brown University	48	203	1
Laird, Peter W	PhD	1988 (20)	University of Southern California	36	73	14
Marcucci, Guido	MD	1986 (22)	Ohio State University	36	102	1
Meltzer, Stephen J	MD	1979 (29)	Johns Hopkins University	54	140	5
Mendell, Joshua T	MD	2003 (5)	Johns Hopkins University	14	22	4
Minna, John D	MD	1967 (41)	University of Texas Southwestern Medical Center at Dallas	87	281	4
Munster, Pamela N	MD	1992 (16)	University of California at San Francisco Cancer Center	19	43	4
Nelson, William G	MD/PhD	1987 (21)	Johns Hopkins University	46	82	8
Nephew, Kenneth	PhD	1991 (17)	Indiana University	28	64	0
Ogino, Shuji	MD/PhD	2001 (7)	Dana-Farber/Harvard Cancer Center	23	68	0
Pfeifer, Gerd P	PhD	1984 (24)	City of Hope National Medical Center	53	134	4
Pili, Roberto	MD	1989 (19)	Roswell Park Cancer Institute	25	57	0
Plass, Christoph	PhD	1993 (15)	German Cancer Research Center	39	111	4
Schmittgen, Thomas D	PhD	1992 (16)	Ohio State University	24	36	1

Sidransky, David	MD	1984 (24)	Johns Hopkins University	88	340	36
Slack, Frank J	PhD	1993 (15)	Yale University	23	80	5
Sukumar, Saraswati	PhD	1977 (31)	Johns Hopkins University	38	80	15
Stein, Gary	PhD	1969 (39)	University of Massachusetts Medical School	67	276	3
Widschwendter, Martin	MRCOG	1992 (16)	University College London	27	60	4