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Matthew Herder

*Dalhousie University*, [matthew.herder@dal.ca](mailto:matthew.herder@dal.ca)

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# Patents & The Progress of Personalized Medicine: Biomarkers Research as Lens

*Matthew Herder*\*

## I. INTRODUCTION

“Personalized medicine” has enormous capital at the moment. It is the promise that start-up biotech firms and mainstay pharmaceutical companies alike claim they will deliver,<sup>1</sup> the cornerstone of proposals for healthcare reform,<sup>2</sup> the subject of the penultimate report by former President George Bush’s Advisory Council on Science and Technology,<sup>3</sup> and the object of legislation once introduced by newly elected President Barack Obama.<sup>4</sup> With industry, policy-makers, and politicians all seemingly on board, there appears to be great interest in removing any barriers to realizing

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\* Matthew Herder, B.Sc. (hons), L.L.B., L.L.M., J.S.M., Visiting Professor, Loyola University Chicago School of Law, 2008-2009. This article is based on a presentation given at Loyola University Chicago School of Law’s Second Annual Beazley Symposium on Access to Health Care, “Perspectives on Patents Versus Patients: Can they Co-Exist?” in November 2008. The author would like to thank Professor Cynthia Ho for helpful feedback early in the writing process as well as the editorial staff of the *Annals of Health Law* for their tremendous efforts translating this article into its final form.

1. See generally Biotechnology Industry Organization, Targeting Disease Through Pharmacogenomics & Personalized Medicine, <http://www.bio.org/healthcare/personalized/> (last visited Feb. 10, 2009).

2. See BRUCE QUINN, CROSSING THE THREE CHASMS: COMPLEX MOLECULAR TESTING AND MEDICARE REGULATIONS 2 (2008), <http://www.foleyhoag.com/~media/Files/Publications/Generic/2008%20Foley%20Hoag%20Crossing%20Chasms%20Molec%20Med.ashx>.

3. See generally PRESIDENT’S COUNCIL OF ADVISORS ON SCI. & TECH., PRIORITIES FOR PERSONALIZED MEDICINE (2008), [http://www.ostp.gov/galleries/PCAST/pcast\\_report\\_v2.pdf](http://www.ostp.gov/galleries/PCAST/pcast_report_v2.pdf) [hereinafter PCAST].

4. 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, but the specifics of the latter bill will be discussed *infra* Part II.A. 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).

personalized medicine's full potential.

The most immediate barrier concerns the poor quality of the technologies that have been developed to date. This is, in significant part, attributable to the complexity of the science. The human genome warrants greater humility than we perhaps imagined.<sup>5</sup> However, it is also partly attributable to deficiencies in the present regulatory framework, including unclear criteria for evaluating product risk, ambiguous standards of study design, and redundant requirements from different regulatory authorities.<sup>6</sup> Because of these deficiencies, or perhaps in spite of them, much of the relevant research and commercial activity has escaped regulatory oversight. And the clinical utility of most developed technologies appears to have suffered as a result.

However, this quality barrier is also a problem of coordination. The President's Council of Advisors on Science and Technology (PCAST) explains, with reference to genomics-based molecular diagnostics, the technology that it foresees as having the "greatest potential to accelerate progress in personalized medicine."<sup>7</sup>

Despite the promise of genomics-based molecular diagnostics to advance personalized medicine, significant challenges remain in validating the genomic/clinical correlations required to advance these products into clinical use. While an increasing number of candidate genetic markers are being discovered, clinical validation of these markers has proceeded at a slow pace. To correct this imbalance between discovery and validation, public and private sector research will need to be coordinated and prioritized more effectively, and the tools required for validation studies will need to be strengthened.<sup>8</sup>

To address this coordination failure, PCAST recommends that the federal government (through the auspices of the National Institutes of Health) make critical investments in three enabling tools, specifically: (1) "collections of high quality biological specimens accompanied by comprehensive disease annotation;" (2) "study designs addressing biomarker standardization and incorporating the sophisticated statistical methods necessary for demonstrating the clinical validity and utility of genomic profiles;" and, (3)

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5. Recent calls for a large-scale effort to map the human "epigenome"—a "layer of information . . . embedded in the special proteins that package the DNA," that is highly variable between different cells in the body, over time, and in response to environmental stimuli, yet still inheritable—only underscore the point. Nicholas Wade, *From One Genome, Many Types of Cells. But How?*, N.Y. TIMES, Feb. 24, 2009, at D4; see also Peter A. Jones et al., *Moving AHEAD with an International Human Epigenome Project*, 454 NATURE 711 (2008).

6. PCAST *supra* note 3, at 3.

7. *Id.* at 1.

8. *Id.* at 2.

“large population cohorts for longitudinal health and disease studies.”<sup>9</sup>

Each of these tools is indeed critical to future generations of technologies befitting of the name personalized medicine. What the PCAST report and other accounts of personalized medicine’s shortcomings fail to contemplate, however, is the role played by intellectual property rights (especially patents) in this problem of coordination. In fact, PCAST explicitly carved off intellectual property issues for separate study,<sup>10</sup> painting intellectual property as a kind of incentives problem (noting that recent events have “threatened the stability of intellectual property protection in the biosciences” that is “essential for pharmaceutical and biotechnology companies”)<sup>11</sup> as opposed to a factor contributing to the problem of coordination amongst scientists, research institutions, healthcare providers, and commercial actors.

The hypothesis advanced in this paper is exactly the opposite. Contrary to what PCAST suggests, intellectual property issues cannot be easily disentangled from other barriers facing personalized medicine, particularly the deficiencies of the present regulatory framework. Nor can they be cast primarily as a problem of industry incentives. Rather, understanding these intellectual property issues is critical to understanding the paucity of relationships and data sharing between researchers, healthcare providers, and private firms, which, in turn, help to explain why the quality of research expected to feed into personalized medicine has so far suffered. Unless these issues are addressed, progress toward the goal of personalized medicine will be impeded significantly, and no substantial gains will be made from creating large-scale biospecimen repositories.

The bulk of this paper aims to substantiate this hypothesis and underlying claims, devising a set of future research questions to gauge how deep this barrier to personalized medicine is, and what corrective measures may be more or less effective. As a secondary objective, the paper explores why these intellectual property issues have received minimal attention to date and concludes that the way the current discourse around the impact of intellectual property rights upon early stage scientific research has been framed may be partially to blame. Before beginning this two-fold task, it is useful to place some boundaries on the analysis and explain why some visions of personalized medicine appear more worthy of pursuit than others.

#### A. *Personalized Medicine & Population Health*

The meaning of the phrase “personalized medicine” varies depending upon the scientific context in which it is used. In one subset of stem cell

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9. *Id.* at 2-3.

10. *Id.* at 22.

11. PCAST, *supra* note 3, at 21.

research that involves cloning embryonic stem cells, the idea is to develop stem cell based therapies that are uniquely suited to individual persons. Personalized stem cell medicine, if realized, will be literally personal. Outside cloning-based embryonic stem cell research, the personal becomes aspirational. Research into genes, proteins, metabolic pathways, and the dynamic interactions amongst those biological elements, as well as the impact of and the environmental and social factors upon those elements/interactions—what some now group under the heading “biomarkers” research<sup>12</sup>—is ultimately intended to stratify patient populations, for example, in terms of how well they will respond to a particular course of drug therapy. However, no one intends that biomarkers research will culminate in drugs for a population of one.

Interest in developing patient-specific stem cell lines (and subsequent therapies) via cloning stems from the nature of the human immune system. Any transplantation of cells, tissues, or organs from one human body to another carries the risk of immune rejection.<sup>13</sup> Generating cells, tissues, or organs through cloning technology theoretically negates this risk.<sup>14</sup> But while this line of research would appear well-intentioned for future individual recipients, others argue—convincingly—that the pursuit of cloning-based embryonic stem cell research is antithetical to overall population health in the present. Cloning technology is horribly inefficient. Producing two cloned nonhuman primate embryonic stem cell lines required 304 eggs from 14 rhesus macaques—an efficiency of 0.7%.<sup>15</sup> In

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12. See discussion *infra* Part II. for a detailed overview of this area of research. Wilson and colleagues offer the following summary:

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, 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).

13. See Rudolph Jaenisch, *The Biology of Nuclear Cloning and the Potential of Embryonic Stem Cells for Transplantation Therapy*, in *PRESIDENT'S COUNCIL ON BIOETHICS, MONITORING STEM CELL RESEARCH* app. N, at 387-417 (2004), [http://bioethicsprint.bioethics.gov/reports/stemcell/pcbe\\_final\\_version\\_monitoring\\_stem\\_cell\\_research.pdf](http://bioethicsprint.bioethics.gov/reports/stemcell/pcbe_final_version_monitoring_stem_cell_research.pdf).

14. *Id.*

15. J.A. Byrne et al., *Producing Primate Embryonic Stem Cells by Somatic Cell Nuclear*

humans, hundreds of thousands of eggs would seem to be needed to create a single cloned embryonic stem cell line.<sup>16</sup> Given this, the cost of any therapy resulting from a personalized stem cell line would be prohibitive perhaps even for the most wealthy of society.<sup>17</sup> Additionally, the physical and psychological harms likely visited upon women—especially young women of lower socioeconomic status—if demand for eggs in support of this avenue of research continues will undermine population health directly.<sup>18</sup>

On the other hand, visions of personalized medicine in the context of biomarkers research carry a legitimate promise to radically improve overall population health. At present, only about half of patients actually respond positively to prescription medications.<sup>19</sup> For the remainder, the drug is either ineffective or toxic.<sup>20</sup> Adverse drug reactions are reportedly the fourth leading cause of death in America.<sup>21</sup> Biomarkers (or the various fields of scientific inquiry and corresponding technologies grouped under that heading and described below)<sup>22</sup> are intended to enable healthcare providers to make more informed decisions about how a patient should be treated. In marked contrast to the inefficiencies of cloning-based stem cell research and the clear-cut social welfare tradeoffs it carries, the efficiencies to be gained from biomarkers research in terms of drug development costs, times, and attrition rates are potentially tremendous. One study suggests that twelve years of drug development time could shorten to three, and that total cost reductions could approach 90% (from \$800 million to \$90 million).<sup>23</sup>

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*Transfer*, 450 NATURE 497, 497 (2007).

16. Stephen Minger, *Interspecies SCNT-Derived Human Embryos - A New Way Forward for Regenerative Medicine*, 2 REGENERATIVE MED. 103, 104 (2007).

17. See JESSE REYNOLDS ET AL., CENTER FOR GENETICS & SOC'Y, THE CALIFORNIA STEM CELL PROGRAM AT ONE YEAR: A PROGRESS REPORT 11 (2006); Mita Giacomini, Francoise Baylis & Jason Robert, *Banking on It: Public Policy and the Ethics of Stem Cell Research and Development*, 65 SOC. SCI. & MED. 1490, 1494-95 (2007).

18. F. Baylis & C. McLeod, *The Stem Cell Debate Continues: The Buying and Selling of Eggs for Research*, 33 J. MED. ETHICS 726, 730 (2007).

19. Brian B. Spear, Margo Heath-Chiozzi & Jeffrey Huff, *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR MED. 201, 201-02 (2001).

20. *Id.* at 201, 203.

21. See CTR. FOR DRUG EVAL. & RES., PREVENTABLE DRUG ADVERSE REACTIONS: A FOCUS ON DRUG INTERACTIONS, <http://www.fda.gov/cder/drug/drugReactions/default.htm> (citing J. Lazarou, B. Pomeranz & P.N. Corey, *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies*, 279 JAMA 1200, 1200-05 (1998)).

22. See *infra* Part I.

23. JOHN A. VERNON & W. KEENER HUGHEN, NAT'L BUREAU OF ECON. RESEARCH (NBER), WORKING PAPER NO. W11875, THE FUTURE OF DRUG DEVELOPMENT: THE ECONOMICS OF PHARMACOGENOMICS 14, 19-20 (2005), available at <http://www.nber.org/papers/w11875>. Others predict more modest, but nonetheless significant savings. Geoffrey S. Ginsburg et al., *Implications of Pharmacogenomics for Drug Development and Clinical*

It is this more promising avenue of scientific inquiry and vision of molecular personalized medicine that will be under scrutiny here, although stem cells will play the role of interloper, as will empirical observations about the impact of intellectual property upon that scientific field.<sup>24</sup> Part II of the paper provides a detailed background of biomarkers research, the regulatory picture, and the field's perceived shortcomings. Part III presents: (a) the intellectual property dimension of biomarkers as it has been cast thus far; (b) the contours of the broader debate around patenting "upstream" research generally; (c) the data that we do possess about the impact such patenting has upon research and development, and; (d) the data that we lack, and why. Part IV aims to make the various claims put forth in Parts II and III more concrete by examining a new initiative in the realm of cancer research—a field in which the study of biomarkers and stem cells converge—called the "Cancer Stem Cell Consortium" while also critiquing one possible policy option, the proposed *Genomics and Personalized Medicine Act of 2008*. Finally, Part V concludes by setting out a series of questions for future research.

## II. BIOMARKERS RESEARCH: CURRENT STATUS

Terminology is important not only for reasons of clarity, but also as a measure of market dynamics. Researchers and firms operating within the broad realm of biomarkers research may center their efforts around molecular variations at the genomic, proteomic, or metabolic levels, or, more ideally, the relationships between all three. But these same researchers and firms often also participate in efforts to redefine lines of scientific inquiry and re-brand business models to enhance investor interest and generate goodwill. Pharmacogenomics has been supplanted by biomarkers.<sup>25</sup> Pharmaceutical companies are now "biopharmaceutical" companies.<sup>26</sup> While these efforts are not necessarily disingenuous—they may reflect real shifts in research agendas and business strategies—the

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*Practice*, 165 ARCH. INTERN. MED. 2331, 2333 (2005) (noting that cost reductions could amount up to \$500 million per drug marketed); see also Monya Baker, *In Biomarkers We Trust?*, 23 NATURE BIOTECHNOLOGY 297, 298 (2005) (citing a report predicting savings of forty-five percent by 2008 for projects favorably affected by biomarker technology). *But cf.* David F. Horrobin, *Realism in Drug Discovery—Could Cassandra be Right?*, 19 NATURE BIOTECHNOLOGY 1099 (2001); Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469 (2007).

24. To be precise, this paper will incorporate findings from the field of stem cell research as a whole.

25. These two terms overlap, although the term "biomarkers" is broader in scope and more en vogue currently.

26. Ronald A. Rader, *(Re)defining Biopharmaceutical*, 26 NATURE BIOTECHNOLOGY 743, 748 (2008).

shifting terminology does reveal the utter uncertainty in the market at present. Companies are jockeying for position in anticipation of a potential reallocation of value between diagnostic and therapeutic interventions.<sup>27</sup> As elucidated below, this uncertainty coupled with a deficient regulatory framework has not helped to develop promising biomarkers, save for a few notable exceptions.

#### A. *Biology, Language, & Markets*

Biomarkers are the new cool kids on the block.<sup>28</sup> The high degree of interest that biomarkers presently command signals a positive move away from the “one mutation/one function model” that has misguided molecular biology research for some time<sup>29</sup> and fueled much of the hype surrounding the Human Genome Project.<sup>30</sup> Fundamentally understood, however, biomarkers are not new. Simple physiological measurements (e.g. blood pressure), imaging techniques (e.g. chest radiography), or laboratory analytes (e.g. cholesterol) could be considered “classic” biomarkers.<sup>31</sup> But while these classic indicators fit within the scope of the basic definition of a biomarker, the term has risen to prominence in connection with efforts to study the mechanism of diseases/disorders at the genetic, proteomic, and metabolomic levels, and the impact of therapeutic interventions upon the same.<sup>32</sup>

Within this broad realm of biomarkers new and old, different typologies

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27. See Rebecca S. Eisenberg, *Will Pharmacogenomics Alter the Role of Patents in Drug Development?*, 5 PHARMACOGENOMICS 571, 571-72 (2002) (“[T]here are limits to the foresight and control of firms over how this technology will unfold and where its commercial benefits will fall.”).

28. See Baker, *supra* note 23, at 297 (describing biomarkers as the “sexy new word for basic tools to probe biology”). Baker concludes by positing that “[t]he ultimate success of biomarkers may only be realized when the focus shifts from finding them to understanding their physiological relevance. . . . [o]nly when the word biomarker loses its buzz can it be trusted.” *Id.* at 304.

29. John H. Barton, *Emerging Patent Issues in Genomic Diagnostics*, 24 NATURE BIOTECHNOLOGY 939, 940 (2006) (citing NAT’L RESEARCH COUNCIL OF THE NAT’L ACADEMIES, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH 134 (2006)).

30. See Timothy Caulfield, *Popular Media, Biotechnology, and the “Cycle of Hype,”* 5 HOUS. J. HEALTH L. & POL’Y 213 (2005), available at [http://www.law.uh.edu/hjhlp/Issues%5CVol\\_52%5CCaulfield.pdf](http://www.law.uh.edu/hjhlp/Issues%5CVol_52%5CCaulfield.pdf).

31. Baker, *supra* note 23, at 297; Wilson et al., *supra* note 12, at 153.

32. Consistent with this, the proposed *Genomics and Personalized Medicine Act of 2008* (See discussion *infra* Part III.) employs the following definition: “The term ‘biomarker’ means an analyte found in or derived from a patient specimen that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” H.R. 6498, 110th Cong. § 3(2) (2008). Associated definitions, for instance, of a “pharmacogenetic test,” and other provisions of the bill evince a clear focus on molecular biology research. See H.R. 6498, § 3(7) *passim*.



have emerged. In the name of personalized medicine (or, “individualized medicine”), Wilson and colleagues distinguish amongst the following types of biomarkers:

The practice of preemptive individualized medicine is predicated on the discovery, development, and application of biomarkers in specific clinical domains. *Preventive* biomarkers prospectively identify individuals at increased risk for developing disease. *Diagnostic* biomarkers identify the presence of disease at the earliest stage, before clinical manifestation. *Prognostic* biomarkers stratify risk of disease progression in patients undergoing definitive therapy. *Predictive* biomarkers identify patients most likely to respond to specific interventions. *Therapeutic* biomarkers provide a quantifiable measure of response to therapy in patients undergoing treatment. Finally, biomarkers can be used to identify patients at risk for developing adverse reactions to individual therapeutics.<sup>33</sup>

This last type identified by Wilson et al. would be referred to as “toxicity biomarkers” according to other typologies.<sup>34</sup> Suffice it to say that the biomarkers research field has many layers, and thus many different potential pathways to commercial services and products.

Some products depend upon integration of several different types of biomarkers whereas others do not, or do so only to a lesser extent. Different business models or categories of companies and their corresponding products can be branded along these lines. At one end of the spectrum, there are firms whose business model is based entirely or primarily upon “genetic testing” services.<sup>35</sup> These so-called “diagnostics” (or “Dx”) companies can go to market as soon<sup>36</sup> as they have phenotype-gene association information and the necessary genetic sequencing equipment in hand.<sup>37</sup>

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33. Wilson et al., *supra* note 12, at 154 (emphasis added).

34. Baker, *supra* note 23, at 297 tbl.1 (offering another typology, comprised of disease biomarkers, surrogate endpoints, efficacy or outcome biomarkers, mechanism biomarkers, pharmacodynamic biomarkers, target biomarkers, toxicity biomarkers, and bridging or translational biomarkers).

35. According to the *Genomics and Personalized Medicine Act of 2008*, the “term ‘genetic test’ means an analysis of human DNA, RNA, chromosomes, or metabolites, that detects genotypes, mutations, or chromosomal changes.” H.R. 6498 § 3(5).

36. There are certain regulatory requirements that laboratories performing genetic testing services must, in theory, observe. Whether they actually do so will be discussed briefly in Part I.C, *infra*, along with other deficiencies in the present regulatory framework.

37. The most (in)famous company in this mold is Myriad Genetics Inc. based in Salt Lake City, Utah. As discussed in Part II, *infra*, Myriad holds nine United States patents relating to two genes known as “BRCA1” and “BRCA2” that are associated with breast and ovarian cancers. See E. RICHARD GOLD & JULIA CARBONE, INT’L EXPERT GROUP ON BIOTECHNOLOGY, INNOVATION, & INTELLECTUAL PROP., MYRIAD GENETICS: IN THE EYE OF THE POLICY STORM 9 (2008), <http://www.theinnovationpartnership.org/data/ieg/documents/>

A second brand of product or business model is described alternately as “pharmacogenomics” or “pharmacogenetics,” (depending on the scale of the gene sequencing) although both have been colloquially dubbed “PGx.” Great fanfare has surrounded the notion of PGx products for years now for precisely the same reason that has fueled the current excitement over *neo*-biomarkers: the prospect of (more) personalized medicine. PGx research is, in this sense, the father frame of biomarkers research and a slew of pharmaceutical (or “Rx”) corporations continue to claim to be actively pursuing the area. Stratifying patient populations for the purpose of drug therapy in the case of PGx, though, typically only seeks to incorporate genetic information. In other words, PGx essentially “aims to identify the genetic basis of variability in drug efficacy and safety.”<sup>38</sup> Other types of biomarkers, be they related to gene transcription, protein expression, or metabolic pathways, are generally left out of the equation.<sup>39</sup>

The third brand, theragnostics (or “Tx”), purports to go further. “In contrast to pharmacogenomics,” Vural Ozdemir et al. explain, “theragnostic tests focus not on a singular market set, such as genetic polymorphisms, but rather on the integration of information from a diverse set of biomarkers (e.g. genomic, proteomic, metabolomic).”<sup>40</sup> In other words, Tx technologies have the potential to harness significantly greater amounts of biomarker information to the direct therapeutic benefit of patients.

None of these technologies, brands, or business models need be considered mutually exclusive.<sup>41</sup> Indeed, the few success stories to emerge from the burgeoning biomarkers field have involved partnerships between Dx and Rx, companies culminating in what have become known as

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cases/TIP\_Myriad\_Report.pdf [hereinafter MYRIAD GENETICS]; see also discussion *infra* Part III.

38. Vural Ozdemir et al., *Shifting Emphasis from Pharmacogenomics to Theragnostics*, 24 NATURE BIOTECHNOLOGY 942, 942 (2006), available at <http://www.genethics.ca/personal/Theragnostics.NBT.pdf>.

39. Admittedly, however, as betrayed by the definition of a “genetic test” used in the *Genomics and Personalized Medicine Act of 2008*, genetic variations of interest can in some cases be deduced using other kinds of information from the molecular environment, such as enzyme metabolites. See H.R. 6498, § 3(5).

40. Ozdemir et al., *supra* note 38, at 942.

41. Indeed, the potential for overlap is strong as shown once again by the definition of “pharmacogenetic test” included in the *Genomics and Personalized Medicine Act of 2008*:

The term “pharmacogenetic test” means a genetic test intended to identify individual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics), including polymorphic variation in the genes that encode the functions of transporters, receptors, metabolizing enzymes, and other proteins, or other genomic variations, including rearrangements, insertions, and deletions, or alterations in gene expression or inactivation, that may be correlated with pharmacological function and therapeutic response.

See H.R. 6498 § 3(7)(A).

“companion diagnostics” (or “Dx/Rx”).<sup>42</sup> None of these collaborative ventures have escaped controversy or setback, however.

Perhaps the best known is Roche’s Herceptin, a monoclonal antibody used to treat a subcategory of breast cancer patients shown to over-express a protein associated with the oncogene “ERBB2.”<sup>43</sup> For the 25 to 30% of women with metastatic breast cancer falling into that category, Herceptin is a highly effective treatment with annual sales for the biologic surpassing \$200 million. Yet concerns about the accuracy of different types of ERBB2 testing are emerging.<sup>44</sup> A second prominent example, Gleevec,<sup>45</sup> works by inhibiting a specific type of enzyme (a type of tyrosine kinase enzyme known as “BCR-ABL”) involved in causing chronic myelogenous leukemia.<sup>46</sup> Despite receiving regulatory approval, uptake in foreign markets has been complicated by allegations of exorbitant pricing in South Korea,<sup>47</sup> as well as a Court decision finding one of Novartis’ Gleevec patents invalid due to a lack of efficacy in India.<sup>48</sup> Third, Amgen’s Vectibix, a colon cancer drug, received approval from the United States’ Food and Drug Administration (FDA) only to be turned down by European regulators.<sup>49</sup> When Amgen submitted new data demonstrating higher

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42. H.R. 6498 § 2 (listing several of these success stories as preamble findings).

43. This gene is sometimes referred to as HER2/neu instead of ERBB2. Compare Malorye Allison, *Is Personalized Medicine Finally Arriving?* 26 NATURE BIOTECHNOLOGY 509, 516 (2008) [hereinafter Allison] with Barton, *supra* note 29, at 940 (2006).

44. The Food and Drug Administration has approved both an immunohisto-chemical test and an *in situ* hybridization test to determine the status of HER2. Some clinical laboratories are reportedly using genetic sequencing (quantitative “polymerase chain reaction” (“PCR”)) as an alternative. See Allison, *supra* note 43, at 516.

45. Novartis markets this drug as “Glivec” outside of the United States.

46. See Barton, *supra* note 29, at 940.

47. Limb Jae-un, *Glivec Debate Poses Vital Issues*, JOONGANG ILBO (Seoul), May 18, 2002, at 6, available at [http://joongangdaily.joins.com/\\_data/pdf/2002/05/18/2002051806.pdf](http://joongangdaily.joins.com/_data/pdf/2002/05/18/2002051806.pdf).

48. Section 3(d) of the 2005 Indian *Patents (Amendment) Act* excludes from patentable subject matter mere “new form[s] of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.” The Patents (Amendment) Act, 2005, No. 15, Acts of Parliament, 2005; see also USAIC, Patent Law Synopsis, <http://www.usaindiachamber.org/images/Patent-law-synopsys.pdf>. The Indian Patent Office invoked this provision to deny Novartis’ patent application for a beta-crystal form of Gleevec. On August 6, 2007, the Chennai (Madras) High Court dismissed Novartis’s suit, upholding the Patent Office’s rejection of the patent claim under section 3(d), and deferring any assessment of the section’s (in)consistency with respect to TRIPs to the WTO. *Novartis AG v. Union of India*, Writ Petition Nos. 24759 & 24760 of 2006, 4 Madras L.J. 1153 (2007), available at <http://judis.nic.in>; see also ICTSD, *Bridges Weekly Trade News Digest*, vol. 11, no. 29, Sept. 5, 2007, “Novartis Patent Challenge Dismissed in India,” available at <http://www.ictsd.org/weekly/07-09-05/story3.htm>.

49. Editorial, *Looking Forward, Looking Back*, 26 NATURE BIOTECHNOLOGY 475

efficacy for patients for whom chemotherapy failed, and who also tested positive for epidermal growth factor receptor (EGFR), European officials reversed their decision.<sup>50</sup> But then the FDA responded in kind, withdrawing its previous approval of the biologic.<sup>51</sup>

With so much uncertainty related to the scientific, intellectual property, and regulatory aspects of biomarkers, neither the market's current volatility nor the tenuous nature of the relationships amongst various players in the field should be surprising.

*B. Market Dynamics: Rx → (Dx) → PGx/Tx → ?*

There is no consensus as to what business model or pathway works best for commercializing technologies that incorporate biomarkers. Some products, like Herceptin, are the result of coordinated development amongst multiple actors.<sup>52</sup> First, the University of California, Los Angeles (“UCLA”) secured a patent on the use of the oncogene ERBB2 to determine whether patients over-expressed certain proteins. The large biotech firm Genentech subsequently in-licensed the technology from the University. Genentech then entered into several partnerships with other firms to develop a set of diagnostic tests. Meanwhile, Roche, a member of “big pharma,” developed Herceptin, and bundled it together for sale with a companion diagnostic.

In other instances, cooperation is lacking at the outset. Instead of working with pharmaceutical companies, smaller diagnostic firms work independently to identify biomarkers that can help assess when pharmaceuticals that are already on the market will be more or less useful to a group of patients. Once the firm finds the biomarker(s), it tries to sell the technology to the drug-maker; in a sense, poaching a share of the pharmaceuticals' original market. This is essentially what took place with the cancer treatment, Gleevec. Genzyme, a large biotechnology firm, obtained a license from UCLA over the BCR-ABL mutation, developed a test that predicted resistance to Gleevec based upon that mutation, and then sold the test to Novartis even though Gleevec had already received FDA approval.<sup>53</sup>

On paper, the cooperative Dx/Rx model would appear to make the most sense. Drug firms typically have more financial resources, and thus have superior access to expensive clinical trial data. Diagnostic companies have

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(2008).

50. *Id.*

51. *Id.*

52. Barton, *supra* note 29, at 940 (describing this sequence of events and also suggesting that another success story, ImClone's Erbitux, followed a pathway similar to Herceptin).

53. *Id.*

greater expertise in developing diagnostics. Therefore, both parties have assets that should be attractive to share. Why not make arrangements *a priori* to do so? The reality is that Herceptin-esque Dx/Rx partnerships remain “extremely rare.”<sup>54</sup> This bare fact is at the heart of the problem framed in this paper. And the answer as to why non-cooperative models of development are likely to persist under current conditions—yet fail more often than not to result in a product like Gleevec—appears to be essentially twofold. The first half of the answer is developed in the remaining sections of Part II, whereas the second half is the focus of Part III.

To begin, distrust amongst market players works against greater collaboration. Skepticism remains as to how receptive pharmaceutical firms are to biomarkers.<sup>55</sup> After all, the principal benefit that biomarkers (and pharmacogenomics more specifically) offer—improved drug penetration through patient segmentation—will reduce drug market size.<sup>56</sup> Some have suggested that large pharmaceutical company participation in the NIH’s single nucleotide polymorphism (SNP) consortium was less a gesture of corporate goodwill, and more an attempt to sabotage pharmacogenomics as a field because of its potential to undermine blockbuster drugs.<sup>57</sup> On the other hand, many within the pharmaceutical industry have explicitly acknowledged that the end of blockbuster drugs is clear.<sup>58</sup> Because biomarkers can “rescue a product by providing a basis for statistically significant benefits for a subcategory of patients in a clinical trial,”<sup>59</sup> many pharmaceutical firms are at least open to using biomarkers as a back-pocket plan.<sup>60</sup> This would still seem less than ideal, though, not to mention shortsighted assuming certain economic forecasts of remarkable research and development savings through pharmacogenomics prove to be accurate.<sup>61</sup>

For their part, many smaller biotech companies engaged in diagnostic or other forms of biomarker-related development are content to go it alone until they are in a position to approach a willing partner, as Genzyme—a larger biotech company to which many smaller firms aspire—seemingly did with Novartis. That this is a viable business strategy is the combined result

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54. Allison, *supra* note 43, at 516.

55. See Bryn Williams-Jones & Vural Ozdemir, *Challenges for Corporate Ethics in Marketing Genetic Tests*, 77 J. BUS. ETHICS 33, 40-41 (2008) (noting it is not the case that big pharma is “uniformly enthusiastic about pharmacogenomics”).

56. Ozdemir et al., *supra* note 38, at 944.

57. Eisenberg, *supra* note 27, at 572.

58. See Rader, *supra* note 26, at 749 (distinguishing industry terminology and describing recent challenges of the pharmaceutical industry).

59. Barton, *supra* note 29, at 940.

60. Allison, *supra* note 43, at 513; Ginsburg et al., *supra* note 23, at 2332.

61. Vernon & Huguen, *supra* note 23, at 17-20; and, Ginsburg et al., *supra* note 23, at 2333.

of a) the current regulatory framework and b) the intellectual property dimension of biomarkers research. The problem framed throughout is that the quality of the research inevitably suffers.

*C. The Regulatory Dimension: In Brief*<sup>62</sup>

As noted above, the regulatory framework as it applies to biomarker technologies is highly uncertain at present. One or two regulatory bodies—the FDA, the Centers for Medicare and Medicaid Services (CMS), or both—could have jurisdiction over a given laboratory or firm depending on the type of technology to be marketed as well as each regulatory body’s (evolving) understanding of its mandate. The simplest way to explain this is to first focus upon entities providing genetic testing (or Dx) services and to differentiate between the “analytic validity” and the “clinical validity” of a genetic test. Kathy Hudson explains:

For a genetic test to be of high quality, it must be both analytically and clinically valid. Analytic validity refers to a laboratory’s ability to get the correct answer reliably over time, for example, to detect a genetic variation when it is present and *not* detect it when it is absent. Clinical validity refers to whether a particular genetic variation is associated with an individual’s current or future health status.<sup>63</sup>

Under the *Clinical Laboratory Improvement Amendments of 1988* (CLIA), a clinical laboratory<sup>64</sup> is prohibited from receiving human specimens whether for genetic testing or any other kind of testing unless it has been issued a certificate of compliance by CMS or another body acting on its behalf.<sup>65</sup> In this way, CMS ensures the analytic validity of all testing in clinical laboratories, although there are different levels of oversight imposed upon clinical laboratories depending upon the complexity of the test(s) being provided.<sup>66</sup>

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62. A full analysis of the current regulatory picture in relation to biomarkers research is beyond the scope of this paper.

63. *At Home DNA Tests: Marketing Scam or Medical Breakthrough: Hearing Before the S. Spec. Comm. on Aging*, 109th Cong. 34 (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) (emphasis in original), available at [http://www.dnapolicy.org/resources/Testimony\\_of\\_Kathy\\_Hudson\\_Senate\\_Aging\\_7-27-06.pdf](http://www.dnapolicy.org/resources/Testimony_of_Kathy_Hudson_Senate_Aging_7-27-06.pdf).

64. CLIA defines a clinical laboratory as a “facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.” 42 U.S.C. § 263a(a).

65. 42 C.F.R. § 493.1.

66. See 42 C.F.R. § 493.17(a) (describing the categorization of testing according to

Therein lies the problem with respect to ensuring the analytic validity of clinical laboratories performing genetic testing. Unlike other types of testing that have been deemed highly complex,<sup>67</sup> CMS has not sought to create a “specialty area”<sup>68</sup> in respect of genetic testing laboratories to monitor the qualifications of laboratory personnel and/or require enrollment in proficiency testing programs (i.e. “a method of externally validating the level of a laboratory’s performance”).<sup>69</sup> Some laboratories have voluntarily enrolled in programs for proficiency testing. Many do not, however, making it “difficult for health care providers or patients to distinguish between those laboratories that are qualified to perform genetic testing and those that are not.”<sup>70</sup> Yet despite clear evidence of errors and misleading statements by those purporting to provide genetic testing services,<sup>71</sup> CMS has explicitly refused to create a specialty area and/or mandate proficiency testing.<sup>72</sup>

To complicate matters, ambiguity exists as to which regulatory body carries the responsibility of ensuring that a genetic test is clinically valid in the first place.<sup>73</sup> Apparently, the FDA considers in vitro diagnostic tests to be medical devices and thus subject to its jurisdiction.<sup>74</sup> However, unless such tests are sold to laboratories as “test kits”—in which case the manufacturers must demonstrate the safety and efficacy of the kit—the FDA has chosen to exercise its discretion and not enforce its regulatory authority with respect to in vitro diagnostics.<sup>75</sup> This stance has effectively pushed the vast majority of clinical laboratories to utilize so-called “home brew” tests, i.e. tests developed in-house for which no FDA review is sought or required.<sup>76</sup>

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complexity).

67. CMS has created specialty areas for many types of tests, including Microbiology, Diagnostic Immunology, and Chemistry. Hudson Testimony, *supra* note 63, at 35.

68. 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 Hudson Testimony, *supra* note 63, at 35.

69. *Id.* at 35-36.

70. *Id.* at 36.

71. U.S. GOV’T ACCOUNTABILITY OFFICE, NUTRIGENETIC TESTING: TESTS PURCHASED FROM FOUR WEB SITES MISLEAD CONSUMERS 5-7 (July 27, 2006), <http://www.gao.gov/new.items/d06977t.pdf>.

72. See Letter from Dennis G. Smith, Dir., Ctr. for Medicare & Medicaid Servs., to Kathy Hudson (Aug. 15, 2007, <http://www.dnapolicy.org/resources/CMSresponse8.15.07.pdf>).

73. Hudson Testimony, *supra* note 63, at 37.

74. See Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539, 575 (1976).

75. PCAST, *supra* note 3, at 37.

76. Wilson et al., *supra* note 12, at 153; see also PCAST, *supra* note 3, at 39 (“Based on the FDA’s longstanding decision to exercise enforcement discretion with respect to [home-

The administrative decisions adhered to by CMS to not mandate proficiency testing to better ensure analytic validity and the FDA to exercise its discretion not to review home-brew tests have, in turn, significantly altered the commercial landscape. Historically, for example, firms with diagnostic technologies followed a business model that sought FDA approval in any event, exploiting the FDA's seal of approval to market "test kits" to clinical laboratories.<sup>77</sup> Now a new paradigm exists. Many firms have laboratories of their own. In select cases, firms will seek CLIA certification from CMS for their laboratory facilities for the same reason that they formerly sought FDA approval: to enhance credibility and thus value of their product in the marketplace. But, in most cases, firms forgo CLIA certification as well as FDA approval in order to save money and attempt to commercialize technology faster.<sup>78</sup> Indeed, almost all of the 1,000 plus genetic tests that are commercially available are marketed as home-brews.<sup>79</sup>

Of course, this picture is subject to change or becomes more complex when other technologies are paired with diagnostics. For example, the FDA appears to be planning to expand its authority "to a subset of home-brew molecular tests termed *in vitro* diagnostic multivariate index assays (IVDMIA), which measure multiple analytes analyzed with algorithms or software programs."<sup>80</sup> The reason for this proposed oversight is that the algorithms used in IVDMIA are "often proprietary, resulting in an inability of physicians to interpret the results directly."<sup>81</sup> On the other hand, pharmacogenomic technologies (at least those that involve drugs to be marketed with a companion diagnostic) presumably fit within the existing definition of a "drug" or a "device" in the *Food, Drug and Cosmetic Act*,<sup>82</sup> and are thus subject to FDA review both pre- and post-market entry. In fact, the FDA has spelled out its approach to pharmacogenomic data during the regulatory process,<sup>83</sup> and produced a draft concept paper on drug-

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brew tests], many developers have already launched or have planned to implement new IVDMIA diagnostic tests as [home-brew tests] rather than as manufactured kits. Thus, a number of business plans were based on a path to market via laboratory-based implementation and CLIA regulation, rather than the path of a PMA submission to the FDA, which is perceived to be riskier and more costly.").

77. Wilson et al., *supra* note 12, at 155.

78. *Id.* at 155.

79. *Id.* at 153.

80. *Id.* at 154. FDA, DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF: IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (2007), <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>.

81. Wilson et al., *supra* note 12, at 154.

82. *See, respectively*, 21 U.S.C. § 321(g)-(h) (2006).

83. FDA, GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS (2005), available at <http://www.fda.gov/cber/gdlns/pharmdtasub.pdf>.



diagnostic co-development.<sup>84</sup>

Even if the FDA extends its jurisdiction to IVDMIAs, a change that some would presumably welcome while others suggest would be misguided unless potential overlap with CLIA requirements and other ambiguities are first resolved,<sup>85</sup> a fundamental problem remains. The majority of biomarkers-related research that presently exists and which is being transacted over by research institutions and commercial firms or sold directly to healthcare providers and consumers appears to be of poor quality. Putting aside the issue of whether clinical laboratories can actually provide accurate test results (*i.e.* ensure analytic validity), the marketplace and healthcare sector are still confronted with a mass of biomarker data, the clinical utility of which is uncertain at best. Apart from the sheer complexity of the science, the reason can be parsed into two failures. First, companies have failed to rigorously “validate” biomarkers. That is, the companies did not wait to find statistically robust correlations between a particular biomarker and a specific disease state before embarking upon commercialization.<sup>86</sup> Secondly, firms have failed to “qualify” biomarkers such that the relationships, if any, that a given biomarker has with clinical endpoints remain unknown.<sup>87</sup> According to Wilson and colleagues, it is this dual failure to generate “definitive analytical validation and clinical qualification that contributes to the relatively slow integration of molecular biomarkers into patient management paradigms.”<sup>88</sup>

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84. FDA, DRUG-DIAGNOSTIC CO-DEVELOPMENT CONCEPT PAPER (DRAFT) (2005), available at <http://www.fda.gov/cder/genomics/pharmacconceptfn.pdf>.

85. PCAST, for instance, has complained that the FDA’s release of draft guidance with respect to IVDMIAs creates a series of problems for the industry that need to be addressed:

The IVDMIA draft guidance changed the IVDMIA development picture in two key respects. First, it implied a substantially increased overall regulatory burden. The increase would arise largely from hurdles imposed by FDA with respect to clinical efficacy such as new requirements for prospective clinical trials, but also in part from the imposition by FDA of quality system requirements for test manufacture that appeared to be duplicative of regulations already imposed on those labs performing LDTs under CLIA. Second, residual ambiguity in the FDA’s definitions of an IVDMIA and of risk left considerable uncertainty about the agency’s likely response to specific new products in or planned for development. For developers, the expected effect of these changes was increased cost, time, and risk for bringing a new product to market, effectively raising the hurdle for market access and putting in question the viability of the entire sector as a target for investment.

PCAST, *supra* note 3, at 39.

86. This occurs because companies using home-brews often do not pre-define performance metrics prior to carrying out studies comparing a disease population and a control population, and because there is an absence of assay performance standards across laboratories leading to problems of clinical reproducibility. Wilson et al., *supra* note 12, at 154.

87. *Id.* See generally Baker, *supra* note 23, at 301.

88. Wilson et al., *supra* note 12, at 155.

The current regulatory framework and business models taking advantage of the same are all-together too easy to blame for this situation: “companies think their job is done when they find differences in a control set versus a disease set, and neglect to integrate that information with relevant biology.”<sup>89</sup> To characterize this solely as a regulatory issue would, however, be facile. The present regulatory framework is, rather, only half of the problem for it is current intellectual property law standards and practices (primarily patent law standards and practices) that work to legitimate this business model, or at least make it temporarily viable. Worse, the lens of the debate around patenting early stage research appears to divert attention away from this quality-based concern.

### III. THE INTELLECTUAL PROPERTY DIMENSION: CHARTING THE DISCOURSE

The paucity of deals between smaller biomarker firms and larger (bio)pharmaceutical entities and the attendant consequences upon the quality of the science, much less the prospect of personalized medicine, have failed to generate much substantive discussion amongst those who study the impact and utilization of patent rights.<sup>90</sup> Experts have instead devoted their energies to predicting how the Supreme Court’s (non)decision in *Metabolite Laboratories, Inc. v. Laboratory Corp. of America Holdings*<sup>91</sup> will be received, extrapolating lessons from the now-infamous saga of the

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89. Baker, *supra* note 23, at 299 (quoting a regulatory official complaining that a “drug should treat a disease, not a biomarker”).

90. One notable commentator, Rebecca Eisenberg, predicted that the law may at some point require coordinated development and marketing of a pharmacogenomic test along with the therapeutic product. The question that Eisenberg leaves unanswered is how. See Eisenberg, *supra* note 27, at 572. For his part, John Barton suggested that parties holding patents over genetic sequences could be required to grant reasonable-royalty licenses to entities wishing to utilize the sequences as part of a micro-array or another pharmacogenomic device. However, it is not clear that this proposal would engender the kinds of inter-institutional relationships that are needed to increase biomarkers qualification so much as to do away with a certain amount of patent litigation. See Barton, *supra* note 29, at 941 (arguing that such licenses potentially represent an acceptable compromise from the point of view of patent-holders given the Supreme Court’s recent ruling that injunctions will no longer be automatically granted in instances of alleged patent infringement). See *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006).

91. *Lab. Corp. of Am. v. Metabolite Lab., Inc.*, 548 U.S. 124 (2006). Although the Supreme Court ultimately denied certiorari in *LabCorp*, Justice Breyer’s dissent, which openly questioned the patentability of a “basic science relationship” between bodily protein levels and vitamin B deficiency, has subsequently gained a little traction, especially at the Board of Patent Appeals. Given that patents similar to the one at issue in *LabCorp* are commonplace in the realm of biomarkers, commentators have hypothesized about the possible impact of this decision upon the field. See Barton, *supra* note 29; Cynthia Ho, *Lessons from Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 23 SANTA CLARA COMPUTER & HIGH TECH. L.J. 463 (2007).

Utah-based diagnostic company, Myriad Genetics, Inc.,<sup>92</sup> or sounding cautions about harms of medical process patents to physicians at the point-of-patient care.<sup>93</sup>

Each of these aspects is of course pertinent to biomarkers research. If the skepticism expressed in Justice Breyer's dissenting opinion in *LabCorp* is translated into binding law, an entire species of biomarker firms is likely dead in the water.<sup>94</sup> Assuming that a measure of uncertainty persists, Myriad is an informative precedent for what can go wrong when a diagnostic firm exercises (or appears to exercise) its exclusive patent rights over genetic sequences and related methods of testing.<sup>95</sup> With the possible exception of concerns about undermining quality of treatment at point-of-patient care, these concerns are of a very familiar tone: they raise hallmark questions about patentability standards, the effect of elevated patent counts, and rogue actors.

But therein lies a problem for which scholars are at least partially to blame. These frames, which scholars helped create, have shifted attention away from the impact of patents upon the overall quality of biomarkers research.<sup>96</sup> Commentators have, by and large, focused on discrete points or issues that arise in the commercialization process in relative isolation from one another, rather than the gamut of relationships and corresponding decision-making needed to develop biomarkers of proven clinical utility. Demonstrating these framing effects requires a detailed account of the patent debate as it has evolved over time, the data that has been collected to date, the evidence we are missing, and why.

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92. See Ozdemir et al., *supra* note 38, at 943; Williams-Jones & Ozdemir, *supra* note 55, at 36.

93. Aaron S. Kesselheim & Michelle M. Mello, *Medical-Process Patents – Monopolizing the Delivery of Health Care*, 355 NEW ENG. J. MED. 2036 (2006); see also Ozdemir et al., *supra* note 38, at 945; Williams-Jones & Ozdemir, *supra* note 55.

94. Justice Breyer's opinion continues to generate judicial debate. For example, in *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, Civil No. 04cv1200 JAH (RBB), 2008 WL 878910, at \*8 (S.D. Cal. Mar. 28, 2008), the District Court found Justice Breyer's reasoning in *LabCorp* persuasive. 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. The decision is presently under appeal. In contrast to *Prometheus*, Justice Rader was highly critical of Justice Breyer's logic in his dissenting opinion in *In re Bilski*, 545 F.3d 943, 1014-15 (Fed. Cir. 2008).

95. See Gold & Carbone, *supra* note 37, for an incredibly in-depth account of this saga as it played out in several jurisdictions, which debunks a number of false beliefs about Myriad's motivations and actions.

96. Again, the quality of the research does not extend to quality at point-of-patient care, which certain scholars have discussed. See Kesselheim & Mello, *supra* note 93.

A. *Before Myriad, Long Before LabCorp*

Upward and upstream—this is where patent counts and patentable subject matter have, in general, gone. There are examples of patenting compositions of matter derived from the human body such as adrenaline dating back to the early twentieth century,<sup>97</sup> and of academic institutions pursuing, to the health detriment of some, exclusive rights over inventions made with public funds.<sup>98</sup> Unquestionably, though, the overall scope of patentable subject matter has opened up considerably following the Supreme Court's decision in *Diamond v. Chakrabarty* to extend patentable subject matter to “anything under the sun made by man,” including genetically-modified organisms.<sup>99</sup> And the last thirty to forty years have been witness to an incredible rise in patent application filings, patent grants, licensing deals, sponsored research agreements, and spin-off companies, particularly at publicly funded research institutions<sup>100</sup> Accordingly, scholars went about studying these changes, and their impact upon dissemination of knowledge at the point where a decision to try to commercialize is initially made, as signaled by filing a patent application, entering into a research or licensing agreement with an existing company, or creating a start-up company.

The issue of patentable subject matter continues to stir academic debate every so often, typically in response to some morally contentious scientific achievement such as the derivation of human embryonic stem cells, the creation of animal-human chimeras or hybrids, or the development of a synthetic micro-organism.<sup>101</sup> In contrast, the Supreme Court, essentially, has treated patentable subject matter as a non-issue since the *Chakrabarty* and *Diamond v. Diehr*<sup>102</sup> decisions in the early 1980s. Whether *LabCorp* foreshadows real change remains speculative.

Meanwhile, the increase in upstream patenting has spurred controversy that has led to actual policy reforms of one kind.<sup>103</sup> Initially, the *Bayh-Dole Act* was widely credited with boosting commercialization of publicly

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

98. See Rima D. Apple, *Patenting University Research: Harry Steenbock and the Wisconsin Alumni Research Foundation*, 80 *ISIS* 375 (1989).

99. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980), quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952).

100. See, e.g., 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 (2001).

101. For a good discussion of some of these morally controversial patented technologies, see Margo A. Bagley, *Patent First, Ask Questions Later: Morality and Biotechnology in Patent Law*, 45 *WM. & MARY L. REV.* 469 (2003).

102. *Diamond v. Diehr*, 450 U.S. 175 (1981).

103. See *infra* Part III.B.

funded research.<sup>104</sup> However, the empirical evidence that scholars were later able to collect provided a very different picture. To begin, the rise in patenting at academic institutions, in fact, extends back to the early 1970s—prior to the enactment of this legislation—and is attributable to a combination of factors<sup>105</sup> Second, it remains unclear as to whether these changes actually facilitate commercialization (understood as the translation of basic scientific discoveries into marketable products), or simply encourage more “commercialization deals” (defined as any agreement between a university and private company).<sup>106</sup> In fact, *Bayh-Dole* itself seems to have been enacted on the strength of a similar misunderstanding by legislators of the data then available.<sup>107</sup> Third, notwithstanding the fact that the number of deals has increased exponentially post-*Bayh-Dole*, traditional channels of knowledge transfer (e.g. publications, conference presentations, and graduating students) continue to dwarf knowledge transferred through the full spectrum of commercialization deals (e.g. licenses, sponsored research agreements, material transfer agreements, joint

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104. Evidently, its main sponsors continue to champion the legislation as having that effect to emerging economies. For a critical analysis of that type of claim, see Anthony D. So et al., *Is Bayh-Dole Good for Developing Countries? Lessons from the US Experience*, 6 PLOS BIOLOGY 2078, 2078 (2008).

105. These include an increase in United States’ government funding for research generally that extended back to the former Soviet Union’s launch of Sputnik into outer space, the onset of commercial biotechnology spelled by Stanley Cohen and Herbert Boyer’s invention of recombinant DNA technology. JENNIFER WASHBURN, UNIVERSITY, INC.: THE CORPORATE CORRUPTION OF HIGHER EDUCATION 44, 49-50 (2004). There was also a broader shift in favor of ‘stronger’ intellectual property rights, of which *Bayh-Dole* is only one part. Mowery et al., *supra* note 100, at 103. Other elements of this shift were the Supreme Court’s decision to extend patentable subject matter to genetically-modified organisms in *Chakrabarty*, the creation of the Court of Appeals for the Federal Circuit as a specialized tribunal for intellectual property disputes, and the promulgation of a variety of international treaties. See *id.* The influence of a community of commercially-minded technology managers that began to coalesce around one bureaucrat, Norman Latker, and his efforts to facilitate commercialization of publicly funded research, also should not be discounted as an important factor in this broad shift. See WASHBURN, *supra* note 105, at 65-69.

106. Mark A. Lemley, *Are Universities Patent Trolls?*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 611, 622-623 (2008).

107. Proponents of *Bayh-Dole* were seemingly unaware of the potential distinction between the two. They argued that the 28,000 – 30,000 publicly funded inventions then sitting idle in public laboratories was proof enough that title should be divested from the federal government in order for commercialization—both translational and transactional—to increase. The truth, however, was that the majority (63%) of those inventions could have been patented by industry according to the terms attached to Department of Defense funding. But industry chose not to do so, thus explaining why only 1% of inventions from that same pool were licensed. In other words, the inventions sat idle not because of the government patent rights, but because they had already been deemed uninteresting from a commercial point of view. See Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 VA. L. REV. 1663, 1702 (1996).

ventures, and start-up companies).<sup>108</sup> Industry also claims to covet knowledge gained through traditional channels more than knowledge gained through patent deals, licenses, etc.<sup>109</sup>

With the impetus for—and impact of—*Bayh-Dole* so muddled by confounding data and other contextual factors, researchers began to sharpen their focus upon what is arguably the law's one unequivocal legacy: technology transfer offices (TTOs). A few TTOs pre-date *Bayh-Dole*, indeed they helped push for the legislation, but 122 new offices were established during the “boom years” of 1983 to 1999.<sup>110</sup> This machinery, these “brokers on the boundary” of academia and industry,<sup>111</sup> are the principal decision-makers about what, when, and where to patent, as well as with whom and how to share.<sup>112</sup> Indeed, that is how TTO performance is measured: by how many patent applications they file, how many patents they obtain, how many licensing agreements they enter into, whether those licenses are exclusive versus non-exclusive, and so forth.<sup>113</sup>

Occasionally, some have heralded TTO decision-making. The joint decision of Stanford University and the University of California to license the Cohen-Boyer recombinant DNA technology—non-exclusively to any and all interested parties for a nominal fee—is widely credited with enabling a new era of molecular biology, and spawning the commercial biotech sector.<sup>114</sup> But, in a second wave of research, scholars began to detect that research tools may not be shared at optimal levels, or that exclusive licenses were capable of precipitating pricing abuses. To critics,

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108. Even at institutions such as the Massachusetts Institute of Technology (MIT), where entrepreneurialism and science were wed long before most other academic research institutions in the United States, patents were estimated to account “for as little as 7% of the knowledge that was transferred from [MIT] labs to industry.” See Ajay Agrawal & Rebecca Henderson, *Putting Patents in Context: Exploring Knowledge Transfer from MIT*, 48 MGMT. SCI. 44, 45 (2002). This is consistent with another finding by Cohen “that only about 11% of the information obtained from university research was transferred through patents.” See *id.* at 46 (citing Wesley M. Cohen et al., *Industry and the Academy: Uneasy Partners in the Cause of Technological Advance*, in CHALLENGES TO RESEARCH UNIVERSITIES 171, 177 (Roger G. Noll ed., 1998)).

109. See *id.*; Wesley M. Cohen et al., *Links and Impacts: The Influence of Public Research on Industrial R&D*, 48 MGMT. SCI. 1, 16 (2002).

110. To be precise, 27 TTOs existed before 1980. ASS'N OF UNIV. TECH. MANAGERS, AUTM U.S. LICENSING SURVEY: FY 2005, SURVEY SUMMARY 17 (Dana Bostrom & Robert Tieckelmann eds., 2007), available at [http://www.autm.net/events/File/US\\_LS\\_05Final\(1\).pdf](http://www.autm.net/events/File/US_LS_05Final(1).pdf) [hereinafter AUTM SURVEY].

111. Donald Fisher & Janet Atkinson-Grosjean, *Brokers on the Boundary: Academic-Industry Liaison in Canadian Universities*, 44 HIGHER EDUC. 449, 449-450 (2002).

112. Of course, TTOs report to their institutions' administrations. But they have shown to be remarkably adept at safeguarding their autonomy. See *id.* at 453.

113. See, e.g., AUTM SURVEY, *supra* note 110.

114. Sally Smith Hughes, *Making Dollars out of DNA: The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974-1980*, 92 ISIS 541, 572 (2001).

what the deal was seemingly mattered less to TTOs than getting the deal done.<sup>115</sup> And policy-folk began to agitate.

### B. Stories & (Policy) Storms

The second wave of scholarly research galvanized around two or three overlapping narratives: Myriad, research tools, and the “tragedy of the anticommons.”<sup>116</sup> In the early 1990s several groups of researchers were competing to discover potential genetic determinants of breast and ovarian cancer. They collaborated, creating a research consortium and accompanying shared database of genomic information, but the group at the University of Utah led by Mark Skolnick was the first to identify and patent a gene (“BRCA1”) associated with breast and ovarian cancer.<sup>117</sup> In turn, the University’s TTO spun-off Myriad Genetics Inc., with an exclusive license to BRCA1.<sup>118</sup> On the eve of the publication of a second genetic sequence associated with breast and ovarian cancers (“BRCA2”) by a group in the United Kingdom, Skolnick’s outfit surreptitiously filed a patent application over the same.<sup>119</sup> Controversy ensued, but Myriad eventually secured the rights to BRCA2 as well. In total, Myriad would hold nine United States patents over the BRCA1/2 genes and related methods of diagnosis, as well as similar patents in Canada, Europe, Australia, and Japan.<sup>120</sup>

While Myriad’s intentions about suing institutions engaged in research on BRCA1/2 may have been misunderstood, the company did deliver “cease-and-desist” letters to a number of healthcare providers (in the United States as well as abroad) ordering them not to perform testing for BRCA1/2 or else risk liability for patent infringement.<sup>121</sup> Its business model was to become the sole provider of the full sequencing test, and at a significantly more expensive price than others had previously charged (reportedly \$3,600 instead of \$1,200).<sup>122</sup> Clinics and physicians especially were not pleased

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115. To be clear, TTOs did pay attention to what the deal was. The criticism was rather that the terms of the deal usually favored the interests of the private sector party instead of academic researchers. In other words, ‘getting the deal done’ entailed agreeing to certain conditions that made sharing research findings and tools more onerous.

116. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 *SCI.* 698, 698 (1998) [hereinafter Heller & Eisenberg, *The Anticommons*]

117. Gold & Carbone, *supra* note 37, at 7-8.

118. See NAT’L RESEARCH COUNCIL, *REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH*, 62-63 (2006) [hereinafter NRC, *REAPING THE BENEFITS*].

119. Gold & Carbone, *supra* note 37, at 9.

120. *Id.* at 6, 9.

121. *Id.* at 10, 24.

122. The details of Myriad’s actions in Canada are provided in E. Richard Gold, *From Theory to Practice: Health Care and the Patent System*, *HEALTH L. J.* (Special Edition) 21,

with Myriad's stance yet service providers opted not to challenge the company's claims, presumably fearing protracted and costly litigation.<sup>123</sup>

During the same period, there were grumblings amongst the research community that "research tool[s]"<sup>124</sup> were becoming increasingly difficult to access due to the terms and conditions attached to their use by TTOs and/or the time taken to negotiate the same.<sup>125</sup> In 1998, the National Institutes of Health (NIH) established a working group to investigate the issue, which validated the research community's complaint.<sup>126</sup> The working group concluded that a multi-layered response was warranted; including issuing guidelines for funding recipients, drafting a model material transfer agreement, and creating a forum for further discussion amongst the research community.<sup>127</sup>

The NIH responded in kind by releasing a set of principles and guidelines to help "ensure that unique research resources . . . are made available to the scientific research community."<sup>128</sup> Specifically, the guidelines stated that research tools need not always be patented, and in the event that they were, exclusive licenses should be avoided except when an exclusive license is deemed necessary to ensure further development of the tool.<sup>129</sup> In those exceptional cases, the institution (through its TTO) should seek to limit the exclusive license to the particular commercial field-of-use and retain the rights to use and distribute the tool for use in other research.<sup>130</sup> Compliance with the guidelines was not formally a condition of funding, however, the guidelines were said to express NIH's expectations.<sup>131</sup>

Many thought the type of patent "hold-up" or "blocking"<sup>132</sup> witnessed

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35 (2003).

123. *Id.* at 35-36. This is true in the U.S. but was a much more forceful reaction in Canada and Europe. Gold & Carbone, *supra* note 37, at 6.

124. NAT'L INSTS. OF HEALTH, REPORT OF THE NIH WORKING GROUP ON RESEARCH TOOLS 1, 3 (1998) [hereinafter NIH WORKING GROUP], available at <http://www.nih.gov/news/researchtools/>. Research tools were defined as "the full range of resources that scientists use in the laboratory," including "cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software." *Id.*

125. *Id.* at 2.

126. *Id.* "Many scientists and institutions involved in biomedical research are frustrated by growing difficulties and delays in negotiating the terms of access to research tools." *Id.*

127. *Id.* at 3.

128. Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Request for Comments, 64 Fed. Reg. 28,205, 28,207 (May 25, 1999) [hereinafter NIH Research Resources].

129. *Id.* at 28,208.

130. *Id.*

131. *Id.* at 28,205.

132. That is, situations where the individual patent-holders simply refuse to license



with Myriad, or inefficient research tool sharing, might represent only the tip of the iceberg. As indicated above, whether primarily attributable to *Bayh-Dole* or not, patenting by academic institutions had increased dramatically through the 1980s and 1990s.<sup>133</sup> Patent “thickets” were seen as emerging in the realm of basic science; to lawfully pursue a chosen avenue of research multiple licenses would have to be negotiated, and multiple royalties paid.<sup>134</sup> In their now (in)famous 1998 article in *Science*, Michael Heller and Rebecca Eisenberg labeled this situation the “tragedy of the anticommons.”<sup>135</sup> The authors hypothesized that the sheer proliferation of patent rights associated with upstream research inputs, particularly DNA sequences, would substantially increase “transaction costs” and imperil progress in biomedical research. In their view, there were structural impediments to any private ordering, contract-based solution. Such impediments include the heterogeneous—if not conflicting interests—of the two principal parties to any licensing negotiation (academic TTOs and private firms), the difficulty of accurately valuating upstream technologies, and the cognitive biases of researchers in favor of their own research.<sup>136</sup>

The anticommons hypothesis and Myriad story showed to have considerable rhetorical force, kick-starting policy-making exercises in the United States and several other countries.<sup>137</sup> Others meanwhile wondered whether patent blocking, the anticommons, and broader perceived cultural changes in the academic research environment (observable in part through TTO practices), would be borne out through empirical study.

### C. The Empirical Data

Overall, the empirical evidence amassed thus far is mixed. On one hand, in terms of genetic tests, the evidence shows a *bona fide* patent blocking problem. One study found that 30% of clinical laboratories reported not developing or abandoning testing for a gene associated with haemochromatosis once the patent issued.<sup>138</sup> Another investigation of over

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necessary inventions to researchers or healthcare providers (perhaps because the invention is already exclusively licensed to someone else) or require license fees that are prohibitively expensive.

133. See Mowery et al., *supra* note 100.

134. See Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, in 1 *INNOVATION POL’Y & THE ECON.* 119 (Adam B. Jaffe et al., eds., 2001), available at <http://faculty.haas.berkeley.edu/shapiro/thicket.pdf>.

135. See Heller & Eisenberg, *The Anticommons*, *supra* note 116.

136. See *id.*

137. Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 *NATURE BIOTECHNOLOGY* 1091, 1093 (2006) [hereinafter Caulfield et al., *Evidence and Anecdotes*].

138. Jon F. Merz et al., *Industry Opposes Genomic Legislation*, 20 *NATURE BIOTECHNOLOGY* 657 (2002).

100 laboratories found that 25% of respondents discontinued testing because of an existing patent or license.<sup>139</sup> Although the BRCA1/2 was the most commonly identified test, eleven other genetic tests ceased to be offered because of the existence of patent rights.<sup>140</sup> In terms of research use, 53% of respondents halted development of a new clinical test due to a patent or license.<sup>141</sup> Some instances of healthcare service providers continuing to conduct testing in the face of patent claims have been reported, but numerous other providers—fearing expensive litigation—have stopped testing outright.<sup>142</sup>

Evidence of an anticommons is less cogent. Some support for Heller and Eisenberg's theory can be derived from a study that examined a pool of 169 "patent-paper pairs"—each pair being tied to a single piece of scientific research or particular scientific achievement. According to the authors, anticommons theory would predict that "[r]elative to the expected citation pattern for publications with a given quality level . . . the citation rate to a scientific publication should fall after formal [intellectual property] rights associated with that publication are granted."<sup>143</sup> The authors found what they deemed to be a "modest" anticommons effect: "the citation rate after the patent grant declined by between 9 and 17%," with the decline becoming "more pronounced with the number of years elapsed since the date of the patent grant, and is particularly salient for articles authored by researchers with public sector affiliations."<sup>144</sup> Subsequent research using the same patent-pair methodology but encompassing a larger and more diverse sample of publications in the realm of human genetics, determined that the "negative impact of patent grants on future public knowledge production . . . was about 5%"—an effect that is exacerbated when the genes in question are linked closely to human disease.<sup>145</sup>

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139. Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. MOLECULAR DIAGNOSTICS 3, 5 (2003).

140. *Id.*

141. *Id.*

142. NRC, REAPING THE BENEFITS, *supra* note 118, at 68 citing Cho et al., *supra* note 139, at 5 and Michelle R. Henry et al., *DNA Patenting and Licensing*, 297 SCI. 1279, 1297 (2002).

143. Scott Stern & Fiona Murray, Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge? An Empirical Test of the Anti-Commons Hypothesis (Abstract) (Nat'l. Bureau of Econ. Research, Working Paper No. W11465, 2005).

144. *Id.*

145. Kenneth G. Huang & Fiona E. Murray, *Does Patent Strategy Shape the Long-Run Supply of Public Knowledge? Evidence from Human Genetics*, ACADEM. OF MGMT. J. (forthcoming) (manuscript at 40, 42, available at <http://ssrn.com/abstract=1249522>). Notably, the fact that the impact was exacerbated when the genes in question were more closely linked to a particular human disease, and that the patents over the same were more likely to be the subject of aggressive enforcement tactics led the researchers to conclude that the "negative effect of patents lies at the heart of the fight to improve human health." *Id.* at

However, other work led by John Walsh suggests that researchers, specifically researchers working in academia, may be largely immune to patent blocking or anticommons issues. In 2003, Walsh, Ahish Arora, and Wesley Cohen presented data from the United States indicating that barriers to access imposed by patents are often avoided by adopting “working solutions,” such as going offshore, inventing around the patent, licensing, using public databases and research tools, or simply using the invention without obtaining permission (i.e. infringing the patent).<sup>146</sup> A larger survey published in 2005 yielded similar findings, as did equivalent studies in other jurisdictions.<sup>147</sup> Walsh’s findings do point to a problem with obtaining research materials,<sup>148</sup> which some argue ought not be classified as a non-patent issue.<sup>149</sup>

David Adelman and Kathryn DeAngelis offer yet another criticism of anticommons theory as it has come to be propounded.<sup>150</sup> Their main point

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146. John P. Walsh et al., *Working Through the Patent Problem*, 299 SCI. 1021, 1021 (2003).

147. John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 SCI. 2002, 2002 (2005); JOSEPH STRAUS ET AL., EMPIRICAL SURVEY ON GENETIC INVENTIONS AND PATENT LAW (presented at the OECD Expert Workshop on Genetic Inventions, Intellectual Property Rights and Licensing Practices 2002); DIANNE NICOL & JANE NIELSEN, PATENTS AND MEDICAL BIOTECHNOLOGY: AN EMPIRICAL ANALYSIS OF ISSUES FACING THE AUSTRALIAN INDUSTRY (Centre for Law and Genetics, Occasional Paper No. 6, 2003).

148. Both Walsh-led studies document increasing difficulties with respect to sharing tangible research materials and tools that are strictly speaking not caused by patent rights, but rather the terms, conditions, and associated negotiating process of concluding material transfer agreements (MTAs) to govern materials exchange. Cf. Victor Rodriguez et al., *Do Material Transfer Agreements Affect the Choice of Research Agendas? The Case of Biotechnology in Belgium*, 71 SCIENTOMETRICS 239, 261 (2007) (unable to “conclude that agreements signed by industry and government affect research agenda setting in academia”); Victor Rodriguez et al., *Material Transfer Agreements and Collaborative Publication Activity: The Case of a Biotechnology Network* 16 RES. EVALUATION 123, 123 (2007) (finding that “material transfer agreements might not have interfered in such a way to limit co-publication activity of research organi[z]ations in the network” under the study).

149. As Matthew Herder and Richard Gold explain:

MTAs typically accord to the material providers reach-through rights to IP developed by the recipient. To the extent that bargaining breakdown is tied to those terms, then, access is properly characteri[z]ed as an IP issue. More fundamentally, it is highly artificial to separate these two forms – IP and physical property – of property protection. They are instead better understood as interacting with and reinforcing one another: MTAs, as a general rule, attach confidentiality obligations and use restrictions, in large part, for the purpose of safeguarding the ability of material providers (and/or their corresponding sponsors) to file subsequent patent applications.

MATTHEW HERDER & RICHARD GOLD, INTELLECTUAL PROPERTY ISSUES IN BIOTECHNOLOGY: HEALTH AND INDUSTRY 15 (OECD INTERNATIONAL FUTURES PROJECT ON ‘THE BIOECONOMY TO 2030: DESIGNING A POLICY AGENDA,’ 2008), available at <http://www.oecd.org/dataoecd/16/9/40181372.pdf>.

150. The authors note that Heller and Eisenberg were careful to tailor their theory to

is that elevated patent counts might be a necessary (but not sufficient) condition for an anticommons to emerge. Patent counts alone simply do not take into account the scope of the field of invention, which Adelman and DeAngelis contend is essentially “unbounded.”<sup>151</sup> This contention, coupled with observations that: (a) “in the great majority of cases, patents can be avoided by undertaking parallel lines of research;”<sup>152</sup> (b) the number of licenses needed to move forward with research “tends to be very low” despite diffuse patent ownership,<sup>153</sup> and; (c) the “continuous record of new market entrants,”<sup>154</sup> leads the authors to infer that biomedical research, whether carried out in academic or corporate environments, is in fact relatively “uncongested.”<sup>155</sup>

Turning to the academic context specifically, a study by Lori Pressman and colleagues provides at least preliminary evidence that technology transfer practices at large and experienced U.S. academic institutions “accommodate both economic goals, such as revenue generation and new company formation, and social goals, such as ensuring utilization and availability of federally funded inventions.”<sup>156</sup> Pressman et al. articulated two main findings. First, “simple reports on exclusive and nonexclusive licensing miss important nuances of licensing practice.”<sup>157</sup> On the contrary, “[t]echnologies can remain available while exclusively licensed, if the exclusivity is for a particular field of use, or if research or humanitarian-use exemptions have been included in the license.”<sup>158</sup> Further, the quantitative

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specific circumstances whereas later commentators, proponents of what Adelman and DeAngelis dub “generalized anticommons theory” are rarely so specific. See David E. Adelman & Kathryn L. DeAngelis, *Patent Metrics: The Mismeasure of Innovation in the Biotech Patent Debate*, 85 TEX. L. REV. 1677, 1684-86 (2007).

151. *Id.* at 1699.

152. *Id.*

153. *Id.* at 1697 *citing* Walsh et al., *View from the Bench*, *supra* note 147, at 2002. It is worth noting that while the actual number of licenses executed may be only a handful, several more could potentially be legally required if the patent holder had awareness of the researcher’s activities. Moreover, while a “handful” may not seem like many in the abstract, licensing and other types of research agreements (e.g. MTAs) can take weeks if not months to negotiate, on occasion, and accordingly invite considerable delay and expense.

154. *Id.* at 1681.

155. *Id.* at 1699.

156. Lori Pressman et al., *The Licensing of DNA Patents by US Academic Institutions: An Empirical Survey*, 24 NATURE BIOTECHNOLOGY 31 (2006). In terms of methodology, Pressman et al. contacted 30 leading academic research institutions in the U.S., which were assigned the largest number of DNA patents according to a search algorithm they had devised. *Id.* Nineteen institutions responded to the survey, providing detailed information from roughly 200 licensing agreements as well as written responses to open-ended questions regarding, for example, general practices and/or operating philosophies in relation to particular types of DNA-based patents. *Id.*

157. *Id.* at 38.

158. *Id.*

portion of the survey revealed that licenses typically contain provisions to those effects.<sup>159</sup> Second, TTOs exhibited considerable “market sensitivity:” as the costs of patent prosecution have increased, institutions have become more selective in what they decide to patent.<sup>160</sup>

The ubiquity of TTOs, regardless of their specific practices, arguably still speaks to broader cultural change. However, hard evidence of research agendas and scientific practices being shaped by commercialization goals has been more difficult to find,<sup>161</sup> attacked as being based on a purist account of the way things traditionally were,<sup>162</sup> or viewed as (at best) indirect evidence of change—not necessarily bad change.<sup>163</sup>

#### D. Ignoring Patents<sup>164</sup> as Straw Man

Interpreting the preceding body of data is complex. Arguably, above all else, what these studies indicate is that perceptions matter.<sup>165</sup> This point is crucial both in explaining why patent hold-ups and anticommons are not more pervasive, *and* why this framing of the issue—whether Myriad-like patent blocking is widespread, and whether potential for royalty stacking causes an anticommons—seems to have diverted attention away from the real barriers to better quality biomarkers research.

159. *Id.* Thus, “licensing practices at the large and experienced academic institutions . . . are largely in agreement” with the NIH guidelines (research tools and best practices). *Id.* at 38-39.

160. *Id.* at 39.

161. Empirical evidence of such a shift, for example, of faculty publishing more in applied science journals than they had previously, has been difficult to find. See Jerry G. Thursby & Marie C. Thursby, *Who Is Selling the Ivory Tower? Sources of Growth in University Licensing*, 48 MGMT SCI. 90 (2002). *But cf.* Huang & Murray, *supra* note 145, at 150-54. There are, however, several qualitative accounts of broader cultural change within publicly funded research institutions. See SHELDON KRIMSKY, *SCIENCE IN THE PRIVATE INTEREST: HAS THE LURE OF PROFITS CORRUPTED BIOMEDICAL RESEARCH?* (2003); WASHBURN, *supra* note 105; Risa L. Lieberwitz, *Confronting the Privatization and Commercialization of Academic Research: An Analysis of Social Implications at the Local, National, and Global Levels*, 12 IND. J. GLOBAL LEG. STUD. 109 (2005).

162. See Peter Shorett, Paul Rabinow, & Paul R. Billings, *The Changing Norms of the Life Sciences* 21 NATURE BIOTECHNOLOGY 123 (2003). *But cf.* Richard R. Nelson, *The Market Economy, and the Scientific Commons*, 33 RES. POL’Y 455 (2004).

163. See, e.g., Caulfield et al., *Evidence and Anecdotes*, *supra* note 137.

164. In an interesting article, Mark Lemley recently analyzed the costs and benefits of the status quo, where patents are often ignored, versus a world in which patent rights are effectively treated like real property: a world where ignoring patents is not possible and users of patented technologies must always obtain permission from patent-holders. See Mark A. Lemley, *Ignoring Patents*, 2008 MICH. ST. L. REV. 19 (2008). While he concluded that the practice of ignoring patents was not ideal but likely to continue (because the patent law reforms that would be needed represent a “radical” departure from the present system), Lemley did not specifically discuss the relationship between the practice of ignoring patents upon the direction of research activities. See *id.* at 33.

165. Herder & Gold, *supra* note 149, at 7-8 (discussing the importance of perceptions).

Beginning with the former observation, the fact that an academic experimental use research exemption no longer forms part of United States' law does not immediately matter if researchers act as though such an exemption is in place.<sup>166</sup> Of course, perceptions of risk can change “dramatically . . . and . . . even abruptly,”<sup>167</sup> if, for example, the Supreme Court revisited the state immunity doctrine that currently shields state universities from liability for patent infringement.<sup>168</sup> But while legally-minded commentators do not mask their discomfort with working solutions that amount to breaking the law, an increasing number of them appear to take solace in this kind of realism.<sup>169</sup> Ignoring patents is simply what goes on, seemingly for the good of science, research and development (R&D), and therefore, us all.

Therein lies the crux of the problem sought to be captured here in relation to biomarkers research. Perhaps actors are ignoring patents *of others*, and this allows research to continue to *go on*. But actors are not ignoring patents *of their own*, and it is an open question whether this allows research to *go forward*, for the good of science, R&D, and us all.

This point may seem trite at first. Why would researchers (and/or their parent institutions) ignore patents that they have pursued and paid for? The

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166. See Pressman et al., *supra* note 156 (finding that it does not matter legally if TTOs secure such a research exemption through contractual means).

167. An expert group assembled by the National Research Council highlighted two sets of circumstances in which this could occur:

Institutions, aware that they enjoy no protection from legal liability, may become more concerned about their potential patent infringement liability and take more active steps to raise researchers' awareness or even to try to regulate their behavior. The latter could be both burdensome on research *and* largely ineffective because of researchers' autonomy and their ignorance or at best uncertainty about what intellectual property applies in what circumstances. Alternatively, patent holders, equally aware that universities are not shielded from liability by a research exception, could take more active steps to assert their patents against them. This may not lead to more patent suits against universities—indeed, established companies are usually reluctant to pursue litigation against research universities—but it could involve demands for licensing fees, grant-back rights, and other terms that are burdensome to research. Certainly, some holders of gene-based diagnostic patents are currently active in asserting their intellectual property rights. Even if neither of these scenarios materializes, researchers and institutions that unknowingly and with impunity infringe on others' intellectual property could later encounter difficulties in commercializing their inventions.

STEPHEN A. MERRILL & ANNE-MARIE MAZZA, NAT'L RESEARCH COUNCIL, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH 134 (2006) (emphasis in original).

168. See Gary Pulsinelli, *Freedom to Explore: Using the Eleventh Amendment to Liberate Researchers at State Universities from Liability for Intellectual Property Infringements*, 82 WASH. L. R. 275 (2007), for an in depth discussion of this issue.

169. See Caulfield et al., *Evidence and Anecdotes*, *supra* note 137; Walsh et al., *Working Through the Patent Problem*, *supra* note 146; Walsh et al., *View from the Bench*, *supra* note 147.

problem, however, is that having patents of one's own can lead researchers to collaborate less with others. Less collaboration means that researchers may not avail themselves of all of the relevant knowledge and resources that might otherwise benefit their research project. Taken together, two recent studies of the stem cell research community in Canada—a community with high standing globally in terms of patents, publications, and prestige<sup>170</sup>—potentially provide a powerful illustration of this. Pairing the first and second studies together also shows how experts studying the impact of patents in the research domain often miss the significance of researchers not ignoring their own patents.

In the first study, Tim Caulfield and colleagues collected survey responses from 108 Canadian stem cell scientists regarding the perceived impact of patents, licenses, material transfer agreements, and commercialization objectives upon their research.<sup>171</sup> While almost half of the senior researchers (“primary investigators” or PIs) within the survey population viewed patents in a negative light, the authors found that very few PIs personally experienced negative effects, such as being refused a license to a patented technology.<sup>172</sup> Material and information sharing was high (93% of PIs reported “routinely” sharing research materials with scientists at other institutions or private firms), although 66% of PIs admitted to delaying such sharing in order to preserve patenting opportunities.<sup>173</sup> Overall, there was broad support for the commercialization objectives of the research network,<sup>174</sup> leading Caulfield et al. to conclude that there was only “minimal evidence of problems associated with patenting and commercialization of research.”<sup>175</sup> The study, in other words, echoed the findings of Walsh et al.<sup>176</sup>

The second study (of the same community) employed a different methodology, one that avoids the positive social response bias that may influence opinion surveys.<sup>177</sup> The methodology was basically twofold. First,

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170. See DAVID CAMPBELL ET AL., SCIENCE-METRIX & MNBC, POTENTIAL FOR STEM CELLS SCIENCE AND TECHNOLOGY IN CANADA: GREAT PROMISES AND CHALLENGES, available at [http://www.science-metrix.com/pdf/SM\\_2003\\_015\\_IC\\_Stem\\_Cells\\_Potential\\_Canada.pdf](http://www.science-metrix.com/pdf/SM_2003_015_IC_Stem_Cells_Potential_Canada.pdf).

171. Timothy Caulfield et al., *Patents, Commercialization and the Canadian Stem Cell Research Community*, 3 REGENERATIVE MED. 483, 483 (2008).

172. *Id.* at 486.

173. *Id.* at 487.

174. *Id.* at 489.

175. *Id.*

176. See Walsh et al., *Working Through the Patent Problem*, *supra* note 146, at 1021; Walsh et al., *View from the Bench*, *supra* note 147, at 2003.

177. Tania Bubela & Andreas Strotmann, *Designing Metrics to Assess the Impacts and Social Benefits of Publicly Funded Research in Health and Agricultural Biotechnology* 6 (The Innovation Partnership, Working Document, 2008), [http://theinnovationpartnership.org/data/ieg/documents/cases/TIP\\_Innovation\\_Metrics\\_Case\\_Study.pdf](http://theinnovationpartnership.org/data/ieg/documents/cases/TIP_Innovation_Metrics_Case_Study.pdf).

the authors, Tania Bubela and Andreas Strotmann, compiled a database comprised of: (a) all U.S., European, and Canadian patents filed or held by PIs; (b) all publications by PIs; and, (c) all other publications that the PIs cite themselves or which cite the work of the PIs.<sup>178</sup> The database contained hundreds of thousands of documents in total.<sup>179</sup> Second, Bubela and Strotmann used the database to develop a series of computational models of collaboration amongst scientists in the network.<sup>180</sup> They tracked and mapped who patented with whom, who published with whom, and citation patterns amongst the group as a whole.<sup>181</sup> The Canadian stem cell research community was found to be quite collaborative, both nationally and internationally.<sup>182</sup> But the central finding the authors made was this: the more patents a researcher held, the less collaborators she or he was likely to have.<sup>183</sup> Not ignoring one's own patents thus has a consequence: stem cell scientists that patent most seem to collaborate the least. How this impacts the overall quality of those scientists' research projects is difficult to say. Perhaps collaboration matters less to scientists who are in a position to patent inventions with any degree of frequency, and are thus more likely to command a full-fledged laboratory and/or to have considerable resources at their disposal. Also, Bubela and Strotman's study did not track how the number of patents correlated with licensing, which some might suggest is the form of collaboration we should care most about. However, the current state of biomarkers research would seem to undercut the suggestion that licensing has thus far positively influenced biomarker qualification.

But present discourse does not give pride of place to quality concerns. We, as scholars, are locked into a debate as to whether Myriad is one *in* a million versus one *of* a million and to what extent anticommons theory holds, such that the absence of clear and cogent empirical evidence of a problem effectively silences calls for improving the status quo. To be sure, further research is needed to assess the scope and unpack the complexity of this behavioral problem (of not sharing, or sharing less than optimal levels of data when patents are obtained at a particular point in the commercialization process) and what measures might be used to counter it effectively.<sup>184</sup> In the meantime, however, this behavioral tendency remains bound up in a conflict of agendas that some argue is already stunting the

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178. *Id.*

179. *Id.* at 3.

180. *Id.* at 6.

181. *Id.* at 4.

182. *Id.* at 17.

183. "Most importantly, . . . commercialization activity, measured by the number of patents, negatively impacted the total number of collaborators . . ." Bubela & Strotmann, *supra* note 177, at 26.

184. A series of research questions will be framed in the conclusion, *infra* Part V.



research environment<sup>185</sup>—a conflict that, if not better resolved, may fundamentally compromise the integrity of various research initiatives connected to personalized medicine, including a large-scale cancer research initiative set to embark upon integrating stem cell biology and biomarker technologies.

#### IV. CONFLICTING AGENDAS, SUB-OPTIMAL SHARING?

Recall that the gravest concern about biomarkers highlighted in the literature is poor validation and clinical qualification. Commentators attribute this to a flawed regulatory framework and the bad business models that can flourish, if only temporarily, as a result. Thus far, the conversation around biomarkers formally to do with patent law has focused exclusively upon whether biomarkers are patentable subject matter following *LabCorp*,<sup>186</sup> and the impact of such patents at point-of-patient care.<sup>187</sup> The latter poses an immense threat to quality-of-care in terms of denying physicians the ability to employ clinical tests. But it does not speak to whether those tests are valid and useful in the first place. And it is the broader framing of the debate around the impact of upstream patenting upon knowledge dissemination, coupled with the perception that the main challenges facing the biomarkers field are regulatory-related, has diverted attention from several concerns about the quality of biomarkers research, as well as potentially suboptimal levels of collaboration and information sharing.

True, the last two pieces of evidence cited in the foregoing speak only to individual (stem cell) researchers. If anything, though, it appears safe to assume that this same tendency to share less, and to collaborate less—for the purposes of biomarker qualification<sup>188</sup>—resonates within a corporate

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185. As Robert Cook-Deegan et al., *The Dangers of Diagnostic Monopolies*, 458 NATURE 405, 406 (2009), explain:

Academic institutions play an important part in clinical genetic testing. They own most of the patents relevant to Mendelian disease testing, and 60% of clinical genetic testing laboratories are within universities. *Academic institutions thus both own most genetic-diagnostic patents and operate many of the laboratories against which such patents are enforced. This paradox derives from technology licensing and clinical laboratory services that are run by different parts of universities and have different missions. These need to be aligned.*

*Id.* at 406 (emphasis added) (citations omitted).

186. See Barton, *supra* note 29, at 941; Ho, *supra* note 91, at 464; Kesselheim & Mello, *supra* note 93, at 2036.

187. Kesselheim & Mello, *supra* note 93, at 2036. See Ozdemir et al., *supra* note 38, at 942.

188. Keep in mind that this is prior to, or distinct from, the type of collaboration witnessed between Genzyme and Novartis in connection with Gleevec. Barton, *supra* note 29, at 940. In that case, Genzyme approached Novartis after Gleevec had received regulatory approval. *Id.*

vehicle. In some cases, this lack of sharing and collaboration could arise from the fact that smaller firms, especially start-ups, are often controlled or directed by the same type of inventor-scientists that Bubela and Strotmann captured in their study. More fundamentally, though, this simply flows from current business practices in the biotech sector. If (and once) a company believes they have valuable—but not necessarily clinically valid—biomarker data in hand, and it has taken steps to secure the intellectual property rights, then and only then is it likely to approach another corporate entity to co-develop a product. Witness the pattern of development that led to Gleevec. Herceptin would seem to stand alone as an example of *a priori* coordinated development amongst multiple actors.

One might think that healthcare providers and payers who have a vested interest in having more effective therapies, not to mention access to scores of data regarding patients and responses to treatment that would directly benefit firms attempting to commercialize biomarker technologies,<sup>189</sup> would help drive behavior in a different direction. However, many healthcare institutions today, particularly ones housing medical schools, have TTOs operating within the same set of parameters as university TTOs.<sup>190</sup> Numbers of patents, licenses, etc. are by and large how performance is measured. Therefore, like many of their university counterparts,<sup>191</sup> healthcare institution TTOs often do not contemplate how patenting and licensing decisions potentially impact development of the field as a whole. Since filing for a patent on a biomarker and getting a small biotech firm to assume the costs of patent prosecution going forward in exchange for a(n exclusive) license to the technology is typically seen as an intrinsically good thing,<sup>192</sup> healthcare TTOs often do not take the extra step of creating and maintaining a strong feedback loop between the firm's commercialization activities and patient profiles as they continue to unfold over time. In short, the deep conflict in agendas between those tasked with commercializing research findings and those offering clinical testing

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189. Allison, *supra* note 43, at 516.

190. Or, to put it differently, the majority of the institutions (60%) that offer clinical genetic testing services in the United States are also part of a university. See Cho et al., *supra* note 139.

191. Note that Pressman et al. found that more experienced, well-resourced TTOs appear to adequately balance both social and economic goals. Pressman, *supra* note 156, at 38-39. However, many TTOs are less than ten years old—the timeframe it usually takes TTOs to “get out of the red” financially—and many more are under-resourced, suggesting that the average TTO may not balance these goals as well as the elite institutions Pressman et al. surveyed.

192. See Matthew Herder & Josephine Johnston, *Licensing for Knowledge Transfer in Human Genetics Research: A Study of Business Models For Licensing and Technology Transfer in Human Genetics Patents*, in BIOTECHNOLOGY IP & ETHICS (Richard Gold & Bartha Knoppers eds., forthcoming 2009).

services based upon that same body of knowledge is left poorly resolved.<sup>193</sup>

This is not always the case. The British Columbia Cancer Agency (BC CA), for instance, follows a different approach.<sup>194</sup> At the BC CA, researchers have collected scores of data relating to the “genomic signatures” of biopsy tumor samples taken from the patient population the institution treats. The institution tracks how patients with different signatures respond to different courses of treatment and correlates them with other available patho-physiological indicators of the disease. These genomic signatures are patentable biomarkers that are of considerable interest to the private sector. However, the BC CA recognizes them as patient (as opposed to patentable) information. While industry representatives have expressed surprise when initially confronted with this position, BC CA has entered into several cooperative research agreements with private sector partners to develop new clinically proven diagnostic, prognostic, and theragnostic technologies from these genomic signatures.<sup>195</sup>

Adopting such an approach may be critical to overcoming the quality barrier to molecular personalized medicine. Meaningful partnerships with continual hard data exchange, not simply partnerships on paper or licenses to exploit intellectual property rights, are what make biomarker validation and clinical qualification realizable goals. What purpose, clinically-speaking, do preventive, diagnostic, prognostic, predictive, therapeutic, and toxicity biomarkers serve if they cannot be interpreted and used in conjunction with one another?

The BC CA appears, however, to constitute the exception that proves the rule. At present, the normal pattern seems to involve a *decoupling* of discovery and commercialization once the research agreement is signed, or the patent rights are assigned, licensed, etc. The architects of a new large-scale, cross-border research initiative, the Cancer Stem Cell Consortium, must attend to this decoupling problem or else risk perpetuating the trend to the detriment of a more personalized approach to treating cancer.

#### A. *The Cancer Stem Cell Consortium*

How to effectively treat cancer in any of its forms remains one of modern medicine’s greatest challenges. A growing proportion of the oncology research and treatment community believe that a specific type of cell contained found in cancerous tumors, so-called “cancer stem cells,” may hold the key to this mystery and give way to a new treatment

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193. Cook-Deegan et al., *supra* note 185, at 406.

194. *Id.*

195. Whether this strategy is necessary or sufficient to instill a stronger relationship between the parties involved in research, clinical, and commercialization activities merits further empirical study. *See infra* Part V.

paradigm. Evidence of cancer stem cells only dates back to 1997,<sup>196</sup> but there has been an explosion of research connected to this theory of cancer in recent years.<sup>197</sup> And the proponents of a new initiative called the Cancer Stem Cell Consortium (CSCC)<sup>198</sup> hope to capitalize upon this core biological insight:

The discovery of a rare class of tumour cells called cancer stem cells (CSC) has profound implications for treating cancer patients. Most current anti-cancer therapies are aimed at killing cells that comprise the bulk of the tumour mass, but are not responsible for the primary growth of tumours. CSC in many common malignancies are the major culprits at the root of cancer accounting for tumour growth and metastases. For reasons that are not yet understood, CSC are resistant to the toxic effects of current anticancer therapies including radiation and chemotherapeutic drugs; consequently tumours often recur leading to relapse of cancer patients treated with these agents. By specifically targeting CSC, new cancer treatments and potential cures will be within reach.<sup>199</sup>

The CSCC was conceived by members of Canada and California's stem cell research communities—the same groups who pioneered the discovery of cancer stem cells—as well as corresponding technology transfer and business communities.<sup>200</sup> However, it has since shifted to a Canadian-based, -staffed, and -funded initiative.<sup>201</sup> A strong link with California-based researchers and institutions was, however, established in June 2008, when the CSCC concluded a three-year agreement with the California

196. See Dominique Bonnet & John E. Dick, *Human Acute Myeloid Leukemia Is Organized As a Hierarchy that Originates from a Primitive Hematopoietic Cell*, 3 NATURE MED. 730 (July 1997).

197. *The Journal of Clinical Oncology*, for instance, recently devoted an entire supplement to the area. See Bruce M. Boman & Max S. Wicha, *Cancer Stem Cells: A Step Toward the Cure*, J. CLINICAL ONCOLOGY 2795 (2008) (providing an overview of the various research articles included in the supplement).

198. Cancer Stem Cell Consortium, <http://www.cancerstemcellconsortium.com/index.php?page=home> (last visited Mar. 16, 2009).

199. JOHN A. HASSEL & CATRIONA JAMEISON, CANADA-CALIFORNIA STRATEGIC INNOVATION PARTNERSHIP, CANCER STEM CELL CONSORTIUM, MAY 2007 CSCC POSITION PAPER 3 (2007) [hereinafter CCSIP Position Paper], available at <http://www.cancerstemcellconsortium.com/uploads/PDFs/CSC%20Consortium%20May%2010.pdf>.

200. More specifically, members of these two communities came together under the auspices of the “Canada-California Strategic Innovation Partnership,” and conceived of the CSCC during a meeting held at Stanford University in January 2007. *Id.*

201. The Board of Directors is comprised of presidents and executive directors of several Canadian research funding agencies as well as one leading stem cell scientist—all of which are located in Toronto or Ottawa, Ontario. To date, the CSCC has secured investments of more than \$100 million from a variety of Canadian partners. See Cancer Stem Cell Consortium, About Us, <http://www.cancerstemcellconsortium.com/index.php?page=about-us>.

Institute of Regenerative Medicine, the body charged with funding stem cell research in that state, to formally explore opportunities for collaboration.<sup>202</sup> The first such opportunity was announced in February 2009, with the release of CIRMs' request for applications for "Disease Team Research Awards."<sup>203</sup> Although the request is not limited to Canadian and Californian researchers,<sup>204</sup> it seems likely that one or more CSCC projects will be funded under this program.<sup>205</sup>

As with any large-scale research initiative the CSCC faces several immediate practical challenges, including ones related to intellectual property.<sup>206</sup> However, the more intractable issue stems from what the CSCC's stated vision of focusing upon commercialization—a "strategic priority" of the CSCC<sup>207</sup>—should entail. On one hand, the research and discovery program envisioned by the CSCC clearly aims to harness scores of patient tumor samples and associated clinical data for the purpose of biomarker validation and qualification:

The availability of highly enriched CSC populations from multiple diverse tumours (blood, breast, brain, prostate and colon) will enable genomic and proteomic analyses of these cells, a required first step to discover CSC biomarkers and molecular therapeutic targets. Genomic studies will include identifying all the genes that are expressed in CSC and learning whether these genes differ between CSC and the non-tumourigenic cancer cells from the same tumour, and between the CSC and the normal adult stem cells of the organ of origin of the tumour.

Candidate biomarkers and molecular therapeutic targets will be validated using patient tumour samples and cell cultures derived from tumours.

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202. *Id.*

203. CAL. INST. FOR REGENERATIVE MED., RFA 09-01: CIRM DISEASE TEAM RESEARCH AWARD, available at [http://www.cirm.ca.gov/RFA/pdf/rfa\\_09-01/RFA\\_0901\\_031009.pdf](http://www.cirm.ca.gov/RFA/pdf/rfa_09-01/RFA_0901_031009.pdf).

204. Other collaborative funding partners listed in the RFA are the Medical Research Council of the U.K. and the Spanish Ministry of Science and Innovation. *Id.* at 3.

205. The request for applications specifies that the CSCC aims to fund up to two projects, each to the tune of \$20M CDN. *Id.* at 25.

206. Given that this is a large-scale, cross-border research initiative, the CSCC will need to address a number of intellectual property management issues. See Herder & Gold, *supra* note 149, at 30-32. And there is also the possibility of encountering a variety of data-, materials-, patent-, and ethics-related barriers. See For an in-depth account of these potential barriers, see David E. Winickoff, Krishanu Saha & Gregory D. Graff, *Opening Stem Cell Research and Development: A Policy Proposal for the Management of Data, Intellectual Property, and Ethics*, 9 YALE J. HEALTH POL'Y L. & ETHICS 52 (2009). To date, no comprehensive patent landscape pertaining to cancer stem cells has been performed. However, as those behind the CSCC have noted, "70% of patents referring to [cancer stem cells] have been published in the last two years." See CCSIP Position Paper, *supra* note 199, at 3.

207. CCSIP Position Paper, *supra* note 199, at 10.

For example, we will study the expression of candidate biomarkers in organ-specific tumours (e.g., breast) of large numbers of cancer patients to ensure that they identify CSC. CSC biomarkers will be linked with clinical parameters such as patient prognosis and treatment outcome to firmly establish the clinical relevance of CSC.<sup>208</sup>

Such an approach is critical according, for example, to PCAST.<sup>209</sup> On the other hand, the CSCC is expected to yield a variety of commercial outcomes, including “build[ing] an exciting wave of new biotechnology companies based on CSCC discoveries.”<sup>210</sup> Whether those companies (or the individuals behind them) will turn a blind eye to the store of clinical data that the CSCC claims it will continue to amass once they have filed patent applications or garnered interest from larger commercial entities, in other words, adopt the same business model that appears to be guiding most biomarker firms in existence, essentially remains to be seen. Perhaps the CSCC’s stated intention of not seeking intellectual property rights of its own, but rather actively striving to enhance the value of any intellectual property secured by participating researchers and institutions by funding proof-of-concept, proof-of-principle and validation studies<sup>211</sup> will have a positive mitigating effect.

The issue would seem to reduce to a question of incentives, of how much funding the CSCC will be able to secure and thus devote to such value-adding functions, of what (potentially lucrative) deals with private entities further down the commercialization chain for the exclusive rights to a given cancer biomarker technology eventually surface, of what changes, if any, are made to the regulatory process perhaps necessitating the kind of robust validation that the CSCC is positioning itself to supply, or of any other new incentives that arise.

### *B. The Genomics and Personalized Medicine Act*

The proposed *Genomics and Personalized Medicine Act of 2008* (H.R. 6498) may help inform speculation about what the relative incentives will ultimately prove to be.<sup>212</sup> Amongst other objectives, the bill aims to clarify the respective roles of the FDA and CMS with respect to biomarkers and other technologies to reduce redundancy, which should reduce the disincentives associated with seeking regulatory approval.<sup>213</sup> H.R. 6498

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208. *Id.* at 7-8.

209. PCAST, *supra* note 3, at 2-3.

210. *Id.* at 2.

211. *Id.* at 10-11.

212. Assuming that a substantially similar version of this bill, H.R. 6498, is eventually re-introduced.

213. *See* Genomics and Personalized Medicine Act of 2008, H.R. 6498, 110th Cong. §

also stipulates that the FDA and CMS should seek to encourage firms to incorporate “companion diagnostics”<sup>214</sup> and “genetic screening tools”<sup>215</sup> into the technological platforms they develop on the strength of the assumption that a newly created information registry will work to ensure that such technologies are both analytically and clinically valid.<sup>216</sup> Finally, if enacted, the legislation would establish a tax credit for an “amount equal to the qualified research expenses paid or incurred by the taxpayer during the taxable year in connection with the development of a qualified companion diagnostic test.”<sup>217</sup>

The latter measure may act as a powerful incentive for improved coordination amongst biotech and biopharmaceutical companies. Unless the diagnostic is of robust clinical validity from the outset, however, this tax credit may not serve the bill’s underlying goal of realizing the potential of personalized medicine. The bill cleverly attempts to address this goal by requiring that manufacturers of genetic tests submit to the registry’s secretary evidence showing the analytical and clinical validity of the tests they intend to submit for regulatory approval.<sup>218</sup> But whether such a requirement would be practicable to enforce remains uncertain. Nor does this requirement squarely address why it appears that such tests and biomarker technologies more generally are lacking in quality: the behaviors and business strategies engendered by patent rights that can work against sustained collaboration and data sharing. It would appear radically more efficient to promote greater collaboration *a priori* than to ask (if not also subsidize through tax credits) commercial outfits to individually validate and qualify biomarker technologies. There is a risk that many of those efforts will in the end simply be duplicative of one another.<sup>219</sup>

In skirting the issue of intellectual property, the proposed legislation fails to address this possibility although it would commission the National Academy of Sciences (NAS) to develop recommendations about further

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7(a) (2008).

214. *Id.* § 7(c).

215. *Id.* § 7(d).

216. *Id.* § 7(a).

217. *Id.* § 8(a).

218. *Id.* § 7(a). There are essentially two exceptions to this requirement: first, if the test has been cleared under sections 510(k), 515 or 520(m) of the *Food, Drug and Cosmetic Act*, then no information need be submitted to the registry; second, if the “intended use of a laboratory-developed genetic test is limited solely to the measurement of an analytical property or characteristic,” that is, it is “not intended to be used to diagnose or screen for any disease or condition, or to otherwise aid in decisionmaking with respect to health,” then no submission need be made. *Id.*

219. See Baker, *supra* note 23, at 303. In other words, it is conceivable that H.R. 6498 will generate (even more) wasteful research: “there are multiple groups . . . working on the same problem, each gathering proprietary data . . . spending new money and not producing new value.” *Id.*

incentives to encourage companion diagnostics.<sup>220</sup> Assuming the NAS would be persuaded of the overarching argument developed throughout this paper, answers to the following research questions should help inform any recommendations made with respect to intellectual property rights and related practices in the realm of biomarkers.

#### V. CONCLUDING QUESTIONS: MIXING MARKERS WITH METAPHOR

Two sets of research questions follow from the foregoing. The first set arises from the above argument's underlying hypothesis; namely, that deciding *not* to patent a particular biomarker discovery at the earliest practicable opportunity<sup>221</sup> will lead to higher quality innovations that, subsequently, can become the subject of more valuable (economically and socially) patents—what we might term truly *choice patents*. In turn, this alternative course of development and (delayed) patenting could foster better business models, more sustainable economic growth, and clinically-proven healthcare interventions. Testing this hypothesis will, at the very least, require more systematic efforts to answer to the following:

- What factors (e.g. inventor interest, actual/projected licensing revenues, performance goals) inform an institution's decision to seek patent protection in respect of a biomarker, and when? Moreover, how are the different factors weighted, and why?
- Does the decision to file for patent protection, however made, at the earliest practicable opportunity undermine subsequent efforts (by the inventor(s), other academic scientists, and/or putative licensees) to validate and qualify the biomarker in statistical and clinical terms?
- Or, conversely, does the decision *not* to file a patent application at the earliest practicable opportunity—assuming other institutions are found to mirror, consciously or not, the approach adopted by the BC CA—facilitate subsequent efforts (by the inventor(s), other academic scientists, and/or putative licensees) to validate and qualify the biomarker in statistical and clinical terms?

We already know that most biomarker discoveries—as the product of university scientists' research—are licensed at a very early stage, almost always long before a patent is granted and often before a patent application

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220. H.R. 6498 § 7(b).

221. Defining with precision what the 'earliest practicable opportunity' will, of course, be critical to any inquiry along these lines. For the sake of discussion here, the phrase can be interpreted to mean the point at which 'proof of concept'—a phrase commonly used by scientists, research institutions, firms, and patent lawyers—has been achieved.



is even filed.<sup>222</sup> The question therefore becomes whether the quality of the biomarkers suffers as a result, and whether choosing to patent at a later point in commercialization process might have a mitigating effect. Assuming this is borne out through further empirical research, the second set of research questions aims to decipher what measures will best help correct these deficiencies in meaningful collaboration and sharing:

- Is it necessary to relegate biomarkers, or some portion thereof, to non-patentable subject matter in order to engender more meaningful research partnerships characterized by continuous data exchange?<sup>223</sup>
- Could researchers, institutions, and firms be encouraged through other means (e.g. the tax credit contemplated in H.R. 6498) to work more collaboratively?
- Could increasing awareness of the approach adopted by the British Columbia Cancer Agency, by itself or in conjunction with other incentives, facilitate greater levels of sharing?
- Might proprietary algorithms designed to integrate and analyse various biomarker data effectively nullify any benefits associated with relegating biomarkers to non-patentable subject matter or adopting an approach like the Cancer Agency? And, if so, what limitations should be placed upon patenting algorithms in connection with biomarkers?

This list of research questions is by no means exhaustive. There are those who would argue that any suggestion of exempting biomarkers from patentability is not a viable political proposition.<sup>224</sup> At base, such an argument is predicated on the notion that such an interference with the market is unwarranted in the absence of empirical evidence demonstrating that patent rights (and the practices they can engender) are in fact to blame for the current state of affairs. According to this view, other barriers to personalized medicine, especially the regulatory framework, should be given priority.<sup>225</sup>

This position may be a by-product of a conception of the relationship between quality, patent rights and attendant practices that is simply too

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222. See e.g., Daniel W. Elfenbein, *Publications, Patents, and the Market for University Inventions*, 63 J. ECON. BEHAV. & ORG. 688, 693-95 (2007).

223. Barton, for instance, has suggested this as a possible reform. See Barton, *supra* note 23, at 941. Justice Breyer's dissent in *LabCorp.* is also consistent with this. *Lab. Corp. of Am. v. Metabolite Labs., Inc.*, 548 U.S. 124, 134-38 (2006).

224. See PCAST, *supra* note 3, at 38ff. The PCAST Report, for instance, seems to take the position that changes in intellectual property law have already gone too far. *Id.*

225. See generally PCAST, *supra* note 3.

short-sighted, if not blind to the interconnectedness of patenting practices with other elements in the health innovation system.<sup>226</sup> Arguably, for example, the ambiguities and redundancies in existing regulatory standards are, at least partially, attributable to the paucity of biomarker data available in the public domain. Regulators may be ill-equipped in their efforts to reform the process without greater information at their disposal. In other words, perhaps, our rapidly increasing, but still nascent appreciation of the complexity of our own molecular biological make-up demands a different approach. That is, the burden should fall upon those electing to patent early-stage biomarkers to demonstrate that the quality of their discoveries and any healthcare interventions that they will be integrated into would, on balance, not be sacrificed as a result; in short, that license price speaks to patent quality (read: clinical utility) and not something else.<sup>227</sup>

To underscore this final point and at the same time further hypothesize as to why patent scholars have under-theorized and under-investigated biomarkers' poor quality, it is helpful to close with reference to the metaphor from which Heller and Eisenberg's anticommons theory was born: Garrett Hardin's "tragedy of the commons."<sup>228</sup> As with Heller and Eisenberg's piece thirty years later, Hardin's piece spawned a sprawling literature about shared or public resources of varying kinds, and whether they were in fact doomed to overuse as Hardin predicted. His theory was justly criticized for over-breadth,<sup>229</sup> but nonetheless showed remarkable staying power.<sup>230</sup>

Yet discussion of the problem of overpopulation, which served as the basis for Hardin's metaphor, is conspicuously absent from much of the ensuing literature. Hardin's main thesis was that "freedom to breed" would

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226. To be sure, some scholars have begun to gesture at this. Cook-Deegan and colleagues, for instance, note:

Monopoly effects on test quality are equivocal. For example, in 2006, Myriad's methods of BRCA testing were shown to miss some DNA deletions and rearrangements. Yet such problems cannot be ascribed only to the monopoly. Problems are apparent in genetic testing for other conditions offered by labs with non-exclusive rights. Test quality is a general problem but monopolies can exacerbate it.

See Cook-Deegan et al., *supra* note 185, at 405 (citations omitted). Note, however, that this statement appears directed primarily toward the analytic validity of the laboratory testing services, as opposed to the clinical validity of the tests themselves. See *infra* Part II.C.

227. E.g. Elfenbein, *supra* note 222, at 713. Elfenbein has shown that inventor and/or institution prestige can increase an invention's visibility, but seemingly not the price putative licensees are willing to pay for it.

228. Garrett Hardin, *The Tragedy of the Commons*, 162 SCI. 1243 (1968).

229. CAROL M. ROSE, PROPERTY AND PERSUASION, 140-45, 185-88 (1994) (arguing that privatization is not the best solution to some public resources or spaces, such as rivers and parks).

230. This may be attributable to the theory's rhetorical purchase, again, much like the anticommons after it.

bring “ruin to all”<sup>231</sup> because decisions made by individuals seldom benefit society as a whole. Just the opposite according to Hardin: In a world that is fundamentally limited, the tendency of every rational “man” to maximize his gain, to increase “his herd without limit,” spells disaster.<sup>232</sup> Hardin worked through a variety of examples involving common spaces or resources—from pastures to parking, parks, and pollution—to illustrate his point. But whereas successors in the debate expended their intellectual energies on the property implications of the tragedy, focusing on the same or similar examples, for Hardin, the real problem was the growing human population. That his call to limit individuals’ “freedom to breed” was later ousted by a narrower focus on the nature of various resources and whether they should be the subject of property rights probably did not surprise Hardin. He foresaw the inevitable unpopularity of his view.<sup>233</sup>

The normative thrust of Hardin’s piece nevertheless carries an insight that is critical to biomarkers research and development—one that has largely been lost in the midst of the current debate around patenting early stage research. At its core, Hardin’s argument questions the sustainability of certain behavior and practices. These behaviors and practices are not innate, but instead result from the system in which “[e]ach man is locked.”<sup>234</sup> The argument developed in of the foregoing parts of this paper, while not framed in such sweeping terms, is substantially similar. Most commercial biomarkers research to date is of questionable quality and utility, shortcomings that stem not simply from the complexity of the science, but owing to a regulatory framework that condones poor business models, a set of patent standards that legitimizes the same, and attitudinal tendencies typically engendered by patent rights that work against greater levels of collaboration. And having become preoccupied with testing the accuracy of Heller and Eisenberg’s hypothesis, interlocutors in the patent debate have neglected to question whether improving the status quo should rest on the validity of the anticommons.

Hardin was prepared to suggest that the freedom to reproduce should be limited to avert the ruin he foresaw. The success stories from biomarkers research have been few and far between, and performing the activity, unlike reproduction, is in no way integral to human nature. Yet no one remarking about the impact of increased patenting upon the conduct of scientific research has been willing to suggest that certain pathways to commercialize biomarkers research be foreclosed. The reason, perhaps, is that the latter smacks of socialism and is therefore frightening to (Western)

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231. Hardin, *supra* note 228, at 1248.

232. *Id.* at 1244.

233. *Id.* at 1246 (commenting on the UN Declaration of Human Rights).

234. *Id.* at 1244.

commentators.<sup>235</sup>

However, taking Hardin's concern about sustainability seriously need not be formulated as a new call to halt sexual activity, much less do away with the capitalist precepts of commercializing science. Rather, we must only recognize that greater intervention in the market is warranted in some cases in order to achieve specific objectives, and the form of the intervention should flow from those objectives and take into account the nature of the activity being influenced. Innovation and commercialization in any scientific field depends on regulatory frameworks, intellectual property rights as well as several other factors.<sup>236</sup> Therefore to correct the deficiencies that currently pervade the biomarkers market and advance the goal of personalized medicine, what is needed is a regime that integrates regulatory and patent reforms. Scholars together with scientists, representatives of the biopharmaceutical industry, and policy-makers must seize upon that task.

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235. MICHAEL HELLER, *THE GRIDLOCK ECONOMY*, 17 (2008).

236. See, e.g., Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575 (2003). See Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345 (2007), for a detailed account of the increasing importance of regulatory standards and process in light of changes in biopharmaceutical innovation.

