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Legal, Ethical, and Conceptual Bottlenecks to the Development of Useful Genomic Tests

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I. INTRODUCTION

Significant resources were marshaled for the Human Genome Project in the expectation that medical research breakthroughs would be forthcoming. The initial results of medical re-sequencing efforts have been published, yet the goal of translating this knowledge into clinically useful genomic tests remains elusive. Advances in disease diagnosis and treatment require continuing financial support, as well as the participation of patients and normal individuals in genomic analysis studies. As the cost-benefit ratio of genomic efforts continues to escalate, re-evaluation of the bottlenecks to translational research may be helpful. The barriers to successful translational genomics research efforts include the intrinsic complexity of human genetics, as well as extrinsic factors such as high expectations and statutory restrictions, including the Health Insurance Portability and Accountability Act (HIPAA).[1] Additionally, the Bayh-Dole Act, intended to facilitate translational research by promoting interaction between the public and private sectors, may have had unintended consequences.[2] Rewarding basic science researchers with strong intellectual property rights may not facilitate the development of clinical applications. The debate regarding gene patent rights and a theoretical biotechnology anti-commons is revisited in light of recent research results suggesting that genetic diversity among individuals is greater than previously anticipated. In addition, judicial decisions limiting the rights of patient-participants in the translational research enterprise are discussed in light of increasing

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1. *See* discussion *infra* Part IV.B.
2. *See* discussion *infra* Part III.B.

demands for patient participation. The ideal route to returning the investment in genomics research and providing benefits to society remains unclear. However, mutation profiling has suggested a power-law distribution, or long tail distribution, prompting consideration of open source strategies. Increasing patient participation and fulfilling the promise of genomic research may require creative approaches to intellectual property.

II. THE ETHICAL IMPERATIVE TO TRANSLATE SCIENTIFIC PROGRESS INTO USEFUL ART

The human genome project, whose completion was hailed on April 15, 2003 by a ceremony at the White House, is considered a starting point for large-scale medical "re-sequencing" efforts. For example, a study was completed at the Washington University School of Medicine to discover tyrosine kinase mutations in acute myeloid leukemia (AML).[3] A three-year, $100 million Cancer Genome Atlas project, and a 1,000 Genomes project have begun to provide voluminous data on mutated genes and the potential roles that these mutated genes play in the development of cancer.[4] Our goal in the AML study was to perform "translational research," i.e. to translate such basic research findings into useful improvements to clinical care. Both our funding agencies[5] (e.g. the National Institutes of Health) and patient advocacy groups[6] are very clear that they provide support for basic research with the expectation that these insights will have measurable impact on disease treatments.[7] The high cost of large-scale projects relative to previous biomedical endeavors is justified by the potential payoffs for medical advances.

In addition to biomedical researchers, integral participants in the human genetics research projects include, of course, the patient-participants, as well as private funding donors who raise money through fundraising events (such as races and walks) with the explicit goal of translating these moneys into cures for the diseases that often have affected participants' families.[8]

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3. Michael H. Tomasson et al., *Somatic Mutations and Germline Sequence Variants in the Expressed Tyrosine Kinase Genes of Patients with De Novo Acute Myeloid Leukemia*, 111 BLOOD 4797, 4798 (2008).

4. *See, e.g.*, The Cancer Genome Atlas Research Network, *Comprehensive Genomic Characterization Defines Human Glioblastoma Genes and Core Pathways*, 455 NATURE 1061, 1061 (2008).

5. *E.g.*, National Institutes of Health.

6. *E.g.*, Multiple Myeloma Research Foundation.

7. National Institutes of Health, About Us, http://clinicalresearch.nih.gov/about.html (last visited February 9, 2009); *see* Jerome Groopman, *Buying a Cure*, NEW YORKER, Jan. 28, 2008, at 38.

8. Genetic Disease Foundation, Fundraising, http://www.geneticdiseasefoundation.org/fundraising.html (last visited February 9, 2009).

Also, government agencies, including the National Cancer Institute, have begun to view money spent on genetics and cancer research as an investment.[9] This implies that the United States government, its citizens, and patients all view their participation, financial and otherwise, in this research endeavor at some level as a quid pro quo—with the expectation that returns on these investments will be forthcoming. Therefore, outside of the law, there is an ethical responsibility to try to meet these expectations. Accordingly, the issue becomes how to address the problems of searching for value and patient participation in an ethical fashion.

For decades, genetic researchers have made remarkable progress in our understanding of biology one gene at a time. In the age of genetics, the vastness of the human genome ensured that considerable mystery and uncertainty regarding "other factors" inevitably accompanied consideration of the role between genes and disease (or phenotype). However, recent breakthroughs in sequencing technology are rapidly changing the landscape of our understanding by eliminating unexplored areas of the genome as sources of uncertainty. Elucidating the vastness of the human genome by complete sequencing is no longer the rate-limiting step in our attempts to understand human biology.[10]

A. Terminology Can Be Misleading

Evolving and imprecise terminology is a significant problem in the field of genetics, where advancement is occurring so rapidly.[11] One issue includes the differences between the traditional field of "genetics" and the newer field of "genomics." The power and utility of traditional genetic approaches—including forward genetic screens using model organisms to identify genes responsible for particular phenotypes and linkage disequilibrium studies to identify genes associated with familial diseases—are well-established.[12] In contrast to genetics, which tends to examine *one gene at a time*, genomics is a newer discipline that examines the regulation and function of *many genes at once*.[13] Therefore, this article posits that the legal and cultural frameworks developed during the genetic era must be

9. *See generally* NAT'L CANCER INST., CONNECTING THE NATION'S CANCER COMMUNITY: AN ANNUAL PLAN AND BUDGET PROPOSAL FISCAL YEAR 2010 (2009), *available at* http://plan.cancer.gov/pdf/nci_2010_plan.pdf.

10. David R. Bentley et al., *Accurate Whole Human Genome Sequencing Using Reversible Terminator Chemistry*, 456 NATURE 53, 58 (2008).

11. *See* Mark B. Gerstein et al., *What Is a Gene, Post-ENCODE? History and Updated Definition*, 17 GENOME RES. 669, 671 (2007).

12. *See* Jonathan C. Cohen, *Genetic Approaches to Coronary Heart Disease*, 48 J. AM. COLL. CARDIOLOGY A10, A10 (2006).

13. *E.g.*, ENVTL. PROT. AGENCY, SCIENCE POLICY COUNCIL, INTERIM POLICY ON GENOMICS 2 (2004), *available at* http://epa.gov/osa/spc/pdfs/genomics.pdf.

refocused for the era of genomics.

Older terminology that has failed to keep up with the rapid evolution from genetics to genomics has resulted in a pervasive sort of synecdoche, where a part of the whole is used to refer to the whole.[14] We can start with the term "gene" itself. The concept of a basic unit of heredity was imagined by Gregor Mendel in the 1860s, and the term "gene" was coined in 1905 by Wilhelm Johannsen, who also studied the inherited characteristics of plants.[15] With extensive study of genes and their linear sequences (of adenine, A; guanine, G; cytosine, C; and thymine, T) over the past 50 years, George Beadle's and Edward Tatum's "one gene, one enzyme" hypothesis has collapsed under the weight of complexity.[16] Alternative splicing (editing of the RNA that transcribed from DNA), alternative translational starts (how the RNA is made into protein), and non-coding RNAs (the realization that "junk DNA" is not so junky after all), have all made the term "gene" a useful shorthand, but a beast to define rigorously.[17] When we refer to "the" gene for a certain disease or protein (e.g. BRCA1), we are using a shorthand for "genome" that remains useful for scientific communication, but may cause issues when applied to legal analyses.[18]

If a gene can be thought of as a paragraph in a book without punctuation, spacing, or indentation, then "the genome" of an organism can be viewed as a library filled with completed works of genetic information contained within the nucleus of each cell. In an age where digital reproductions are expected to flawlessly reproduce tests at our command, it is important to remember that, in truth, genetic information is analogue. Much like the laborious, line-by-line hand copying of manuscripts by medieval monks, the copying of genetic material from cell to cell and generation to generation by the process of cell division is not perfectly accurate.[19] In reality, therefore,

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14. *See* Gerstein et al., *supra* note 11, at 671.

15. *Id.* at 669.

16. PAUL BERG & MAXINE SINGER, GEORGE BEADLE, AN UNCOMMON FARMER: THE EMERGENCE OF GENETICS IN THE 20TH CENTURY (2003); Rowland H. Davis, *Beadle's Progeny: Innocence Rewarded, Innocence Lost*, 32 J. BIOSCIENCES 197, 202 (2007) (discussing the increased complexity in the study of genes in the aftermath of Beadle's hypothesis). The concept that genes, a vague unit of heredity, were somehow involved in making enzymes, the regulators of cellular processes, had been around since the turn of the century, but Beadle and Tatum set out to obtain experimental proof of the relationship. Working with bread mold as a manipulable system, they induced mutations in genes with radiation, and demonstrated that one mutation corresponded to the inactivation of one enzyme. Berg & Singer, *supra*, at 136-61. This was a milestone in the history of biology, but we know now that the relationship between genes and their products in much more complex. *See* Davis, *supra*.

17. *See* Gerstein et al., *supra* note 11, at 676-79.

18. *See, e.g.*, Paula W. Yoon, *Risk Prediction for Common Diseases*, 66 LA. L. REV. 33, 36 (2005).

19. *E.g.*, Genome News Network, Genome Variations, http://www.genomenewsnetwork

no two genomes are completely identical. Despite the common use of the phrase, "*the* human genome," in reality there is no such singular beast. The use of the term has been extremely helpful to conceptualize and emphasize the significance of genomic achievements,[20] and also to mobilize significant funding for genomic research. To rally the public and political interests, the sequencing community needed to communicate the potential utility and grand scale of sequencing efforts.[21] It is unlikely the necessary political and financial support could be summoned for this massive technical effort if it were more accurately titled, "Project to Sequence Nearly All of a Human's Genome." The genomes of identical twins and other clonal organisms are nearly identical, but it is an inherent and critical fact of biology that individual organisms within a species living outside the laboratory have unique genomes.[22]

Progress in our understanding of human genetics has revealed that commonly used terminology is vague and occasionally misleading.[23] In an era where researchers are sequencing genes and genomes, and are attempting to understand the meaning of single nucleotide differences and how they relate to human disease, the scientific community has often used the term "mutation" to mean a "nucleotide change that leads to disease."[24] However, this term may be fraught with difficulty as more single nucleotide changes are identified because of the negative connotation of the term and the possibility that some DNA changes are only weakly associated with disease, if at all.[25] When there is a difference at the nucleotide level, this difference can be termed a single nucleotide polymorphism (SNP), or a particular nucleotide letter that is not the same between individuals. The SNP is generally considered to be benign or neutral, whereas mutation is implies a causative association with disease.[26] However, the boundaries between these classes of nucleotide changes may be unclear. Somatic changes refer to DNA changes that occur after birth—in a cancer cell, for example—and a germline change is a congenitally-acquired change in the nucleotide that occurs during meiosis, or before birth.[27] Even the relatively neutral term SNP has, in the past, implied a certain frequency of occurrence

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.org/resources/whats_a_genome/Chp4_1.shtml (last visited Apr. 24, 2009).

20. *See generally* Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860 (2001).

21. *See* Catherine M. Valerio Barrad, *Genetic Information and Property Theory*, 87 NW. U. L. REV. 1037, 1041 (1993)

22. *Id.* at 1050 n.2.

23. *See, e.g.*, Yoon, *supra* note 18, at 36.

24. Genome News Network, *supra* note 19.

25. *Id.*

26. *Id.*

27. *E.g.*, EDWIN H. MCCONKEY, HOW THE GENOME WORKS 19 (2004).

that may not be true for rare polymorphisms.[28] Additionally, the difference between a rare polymorphism and a germline mutation is unclear.[29] Therefore, it may be wise to use the completely value-neutral base change or nucleotide change from a reference standard when discussing DNA heterogeneity.

A subtle but profound shift in our understanding of human genetics has recently begun to expose inaccuracies and inadequacies in the terminology commonly used to discuss human genetics.[30] For example, the article "the" is frequently misleading when used in biomedical research, as in "the human genome," or "the breast cancer susceptibility gene," when it actually refers to a single example of a class of nucleotide sequences united by similar functions. Accordingly, intellectual property law that is based on such inaccurate or misleading language may not sufficiently facilitate the development of useful genomic technologies.

B. Genomic Research Has Failed Thus Far to Yield Useful Genomic Tests

While it is well-known through decades of genetic research that mutations in single genes cause many congenital diseases, such as sickle cell anemia and cystic fibrosis,[31] the influence of multiple genes is required to cause more common diseases, such as cancer and hypertension. Thus, the relatively new field of genomics research emerged to develop understanding of the complex relationship between the changes to multiple genes and the potential effects on common diseases.[32] The vast potential of genomics research became evident with the invention of oligonucleotide microarrays.[33] However, using genomics research, microarrays, and now

28. *See generally* Anthony J. Brooks, *The Essence of SNPs*, 234 GENE 177, 177 (1999). High throughput re-sequencing studies (for example, Tomasson et al., *supra* note 3) are finding increasing numbers of "germline sequence variants" that occur at a frequency of 1% or less. *Id.*

29. *Id.* Germline changes that are clearly pathogenic, for example changes in the gene encoding the ion transporter causing cystic fibrosis, are usually referred to as "mutations" rather than SNPs, but where the change occurred during meiotic recombination or in utero, it cannot be ascertained definitively without genotyping both parents, which has not been done in large re-sequencing studies so far.

30. Yoon, *supra* note 18, at 36.

31. Lander et al., *supra* note 20, at 912; Rachel E. Ellsworth et al., *Comparative Genomic Sequence Analysis of the Human and Mouse Cystic Fibrosis Transmembrane Conductance Regulator Genes*, 97 PROC. NAT'L ACAD. SCI. U.S. 1172, 1172 (2000). Mutations in the beta globin and CTFR genes cause sickle cell anemia and cystic fibrosis, respectively. *Id.*

32. Jade Boyd, *Simulated Populations Used to Probe Gene Mapping*, RICE U., Mar. 29, 2007, http://www.media.rice.edu/media/NewsBot.asp?MODE=VIEW&ID=9430.

33. Mark Schena et al., *Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray*, 270 SCI. 467, 467-70 (1995). By using robotic methods

genome-wide sequencing efforts to understand complex traits, such as cancer, has been a daunting task.[34] Large sums of money have been spent, and are being spent, to determine and catalogue genetic sequences of diverse species, including humans; similarly, much money has been put into microarray and other genetic analyses of patient samples.[35] The problem is that researchers in the biomedical arena have yet to clearly demonstrate value and utility in medical care of the majority of DNA-based tests for common, polygenic diseases.[36] Are genome-sequencing technologies in the biotechnology era akin to that of the gold rush in the western United States, when the promise of gold stimulated economic activity and created opportunities for merchants who catered to the needs of the miners and families, even though the promise of gold never materialized for most prospectors? If so, the first issue becomes how to utilize these genomic tests and high throughput technologies, which we have imbued with such high hopes. Then, we must determine how to extract clinical utility from these technologies.[37]

Previous successful genetic analyses for single genes, such as sequencing of the beta globin gene in patients with sickle cell anemia, have had such

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adapted from the computer industry, the technology for measuring gene expression (i.e. how much RNA a gene is producing as an index of its activation/importance) was turned on its head. Instead of traditional methods that measured gene expression one gene at a time, microarrays assay thousands of genes simultaneously. For the first time, experiments could examine the entire genome (i.e. genomics) instead of having to focus hypotheses on one gene at a time (i.e. genetics). Sequencing DNA has undergone a similar revolution whereby 15 years ago one gene would be sequenced at a time, and now entire genomes are being decoded. Although the power of genomic approaches for basic science investigations has been tremendous, the clinical use of genomic technology is not yet common practice. *See* Andreas Rosenwald & Louis M. Staudt, *Clinical Translation of Gene Expression Profiling in Lymphomas and Leukemias*, 29 SEMINARS ONCOLOGY 258, 2580-63 (2002).

34. *Id.* at 145.

35. *Cf.* Deirdre Meldrum, Automation for Genomics, Part Two: Sequencers, Microarrays, and Future Trends, 10 GENOME RES. 1288, 1298 (2000) (describing technological innovations resulting in breakthroughs in genomic research, but noting that investments are necessary in order to spur more dramatic discoveries in the future).

36. *See infra* Part IV.A and accompanying notes.

37. John Hardy & Andrew Singleton, *Genomewide Association Studies and Human Disease*, 360 NEW ENG. J. MED. 1759 (2009). The authors review the current state of the art of genetic risk prediction science, and maintain great optimism that, "the jigsaw puzzle of understanding the causes of disease lies before us: we now have the edges and corners in place." *Id.* at 1767. However, the authors acknowledge that, "we will probably need reference sequences from tens or hundreds of thousands of subjects," to achieve these goals. *Id.* at 1765. In the same issue of the *New England Journal of Medicine*, another author points out that the study of common variants has been disappointing and will likely continue to be so, and that attention should turn to the study rare variants, i.e. search the genomes of many patients for particularly informative DNA variants. David B. Goldstein, *Common Genetic Variation and Human Traits*, 360 NEW ENG. J. MED. 1696, 1698 (2009); *see also* Joel N. Hirschhorn, *Genomewide Association Studies—Illuminating Biologic Pathways*, 360 NEW ENG. J. MED. 1699, 1699-1701 (2009).

strong predictive power that even studies using a small number of patient-participants could determine whether the tests were valid.[38] If genetic markers will have only small effects, however, combinations of these markers may need to be analyzed in parallel, and much larger numbers of patients will be needed to provide the statistical power necessary to demonstrate the validity of these tests.[39] Recent genome-wide association studies have shown relative risks that are very mild (i.e. "Patient A" has a 1.2 fold increased risk of developing breast cancer). Though such findings are *statistically valid*, they provide little or no *clinically useful* information. For example, while it is clear that the patient has an increased risk of developing breast cancer, the findings cannot predict whether or not a particular patient will develop cancer, and it is unclear what (if anything) the patient can do to address such a miniscule increase in risk.[40]

From the perspective of a physician-scientist in the genomics field, one clear challenge is that in order to identify meaningful implications in these tests, there must be enough patient participation in clinical trials to identify subtle effects. In the setting of tertiary academic research centers, where one of the primary missions is to put patients in clinical trials, it is understood that most patients treated for cancer in the United States are treated in the community, and are not enrolled in clinical trials.[41] Therefore, the corollary challenge is to increase patient participation in clinical trials in order to test and understand the validity of novel DNA tests.

The rarity of discovered mutations, or the perception of overlap with other intellectual property, may discourage the pursuit of exclusive patent rights on novel genetic findings. Our group recently conducted a genomic analysis of acute myeloid leukemia (AML) patient DNA in the proper, pharmaceutically-driven way, as a search for new drug targets for this disease.[42] We were the first group to describe such cancer-associated mutations in a gene called JAK1. Our group did not pursue a patent application on this potentially useful finding, because the low cost and widespread use of available AML tests made the development of complex

38. *E.g.*, Antonio A. Reyes et al., *Ligase Chain Reaction Assay for Human Mutations: The Sickle Cell by LCR Assay*, 43 CLIN. CHEMISTRY 40, 40 (1997). In a study of twenty-four subjects, researchers, using an assay to detect beta-globin sickle cell mutation, concluded that the assay unequivocally discriminated among normal, carrier, and sickle cell genotypes. *Id.*

39. *See* David C. Whitcomb, *Polygenetic Traits in Pancreatic Disorders*, 35 ENDOCRINOLOGY & METABOLISM CLINICS N. AM. 255, 256-68 (2006).

40. *See generally* Hirschhorn, *supra* note 37, at 1699-1701.

41. US Oncology, *Advancing Cancer Care*, June 1, 2007, ALLIANCE HEMATOLOGY & ONCOLOGY, http://www.yourcanceralliance.com/news_details.cfm?newsID=6.

42. *See* Zhifu Xiang et al., *Identification of Somatic JAK1 Mutations in Patients with Acute Myeloid Leukemia*, 111 BLOOD 4809, 4809-10 (2008).

clinical diagnostic tests less attractive than pursuing basic cell biology.[43] The development of pharmaceuticals that do not affect large numbers of patients might not proceed despite promising results in the laboratory.[44] JAK1 mutations have since been found to be more common in a different yet still rare form of leukemia,[45] and it remains to be seen what impact, if any, these findings will have on patient care.

C. Cultural Fears and Misperceptions

A strong cultural rejection of genetic determinism may represent a barrier to the adoption of genomic tests.[46] The value of genomic testing may reside most clearly in establishing risks for certain diseases and other genetic proclivities.[47] Such testing, therefore, would be an assay of germline changes present from birth.[48] The Hollywood movie *Gattaca* is an allegorical representation of this cultural rejection. *Gattaca* envisions a futuristic society, in which parents select fertilized eggs to carry to term on the basis of the eggs' genetic profiles.[49] Then, society directs one's future employment—whether one becomes a janitor or a rocket scientist—based on the results of these genetic profiles.[50] The dystopia portrayed in this film does not rely on any outlandish scientific progress.[51] Many of the technologies could conceivably exist, although the speed at which the genetic tests are performed in the movie is unrealistic.[52] The idea of a world in which privacy is routinely violated through detection and analysis of one's DNA based on the cells one leaves behind, and in which discrimination in the work place becomes commonplace, is viscerally

43. At the U.S. Patent and Trademark Office (USPTO) patent database, searching "JAK1" in the claims of issued patents yielded seven patents, and more patents affect the close family member JAK2. USPTO, Patent Full-Text and Full-Page Image Databases, http://patft.uspto.gov (last visited May 17, 2009).

44. *See* discussion *infra* Part II.C; Carol Rados, *Orphan Products: Hope for People with Rare Diseases*, FDA CONSUMER MAG., Nov.-Dec. 2003, at 10, *available at* http://www.fda.gov/fdac/features/2003/603_orphan.html.

45. *See* Elisabetta Flex et al., *Somatically Acquired JAK1 Mutations in Adult Acute Lymphoblastic Leukemia*, J. EXPERIMENTAL MED. 751, 751-58 (2008).

46. *See generally* David A. Kirby, *The New Eugenics in Cinema: Genetic Determinism and Gene Therapy in GATTACA*, 27 SCI. FICTION STUD. 193 (July 2000), *available at* http://www.depauw.edu/sfs/essays/gattaca.htm.

47. *See* Torsten O. Nielsen, *Human Germline Therapy*, 3 MCGILL J. MED. 126, 126 (1997).

48. *See id.*

49. Gattaca (Columbia Pictures 1997).

50. *Id.*

51. *See* Evan Brown, *Gattaca Now!*, NEW HAVEN ADVOCATE, Nov. 1, 2007, *available at* http://www.newhavenadvocate.com/article.cfm?aid=3943.

52. *See* Genetics Home Reference, What is the Cost of Genetic Testing, and How Long Does it Take to Get the Results?, http://ghr.nlm.nih.gov/handbook/testing/costresults (last visited Feb. 9, 2009).

abhorrent to most Americans.[53] When genes for a certain trait or disease are described, the probabilistic nature of the outcomes is not routinely explained or well understood.[54] Thus, even if the tests are used in a positive way, for example, to predict disease or to direct a therapy, there may be unrealistic expectations of the power these tests have in predicting biological future. Therefore, better science education, specifically in the area of biology, will teach society to reject the false dichotomy of nature versus nurture and to appreciate the power of genetic tests while understanding that genetic determinism is a rare phenomenon.[55] At the end of *Gattaca*, the hero demonstrated his ability to overcome the prejudices of society, which had catalogued him purely on the basis of his DNA sequence. Certainly, the message—that while our DNA sequence may change the probability of certain disease risks and outcomes, the environment and our own choices have a profound effect on the ultimate outcome of our lives—is valid.[56]

In addition to the public's poor understanding of the basics of genetics and biology, there is also a widespread cultural bias toward medicine as a pharmaceutical science.[57] The tremendous success of pharmaceutical medicine in providing antibiotics and successful chemotherapies has given rise to a biomedical research enterprise that is completely dominated by the pharmaceutical industry model.[58] This pharmaceutical model, simply stated, is that there is a drug for everything.[59] While there has been a recent

53. *See, e.g.*, NewsHour with Jim Lehrer (PBS television broadcast June 7, 2001) (transcript available at http://www.pbs.org/newshour/bb/health/jan-june01/genetest_06-07.html) (last visited Feb. 9, 2009).

54. *See* The National Health Museum, Understanding Gene Testing, http://www.accessexcellence.org/AE/AEPC/NIH/gene19.php (last visited Feb. 9, 2009).

55. *See, e.g.*, David B. Resnik & Daniel B. Vorhaus, *Genetic Modification and Genetic Determinism*, 1 PHIL. ETHICS & HUM. MED. 1, 9 (2006), *available at* http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1524970&blobtype=pdf.

56. *See id.*

57. *See generally* Iain M. Cockburn, *The Changing Structure of the Pharmaceutical Industry*, 23 HEALTH AFF. 10, 10-22 (2004), *available at* http://content.healthaffairs.org/cgi/reprint/23/1/10.

58. *See id.*

59. *See* MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES 250 (2004). Many are critical of the practices of the pharmaceutical industry. Recent attention has focused on the rebellion of medical students against the influence of the pharmaceutical industry on their educations. Duff Wilson, *Patching a Wound*, N.Y. TIMES, Mar. 3, 2009, at B1; Gardiner Harris & Benedict Carey, *Researchers Fail to Reveal Full Drug Pay*, N.Y. TIMES, June 8, 2008, at A1. My contention is that there exists a profound and underappreciated level of pharmaceutical industry influence on the biomedical research enterprise beyond the explicit financial ties that have recently made news. Specifically, the paradigm that, for example, cancer research should focus on "novel targets" for drug development ignores the potentially greater impact that cancer prevention could have. *See generally* DEVRA DAVIS, THE SECRET HISTORY OF THE WAR ON CANCER (2007). Dr. Davis' argument, although heavy with conspiracy, theorizes that the focus of the biomedical enterprise has been directed by

focus on the efforts of the pharmaceutical industry to influence the prescribing practices of physicians,[60] the influence of the pharmaceutical model on biomedical research is perhaps more profound. Based on this cultural outlook, the biomedical research enterprise is predominantly focused on understanding genetics and biology with an eye toward identifying molecular targets for drug development; at least, that is the rationale often put forth to justify research projects.[61]

While developing novel pharmaceuticals is certainly a worthwhile pursuit, increasingly the result of genetic research supports an anti-pharmaceutical model; i.e., a genetic test may determine which drugs an individual should avoid taking.[62] Thus, while there is much excitement about pharmacogenomics—the ability to match drug treatments to a particular individual's genotype—it is unclear how the pharmaceutical industry, which makes money by selling as much of a drug as possible to the largest number of patients, will deal with a model which decreases its market share.[63] It is very difficult to get a pharmaceutical company executive excited about a genetic test that promises to reduce the demand for his or her product.[64]

III. PATENT BARRIERS:

A. To Patent or not to Patent?

As researchers identify novel mutations, the question becomes whether patent applications are worth pursuing. The exclusive rights that patents provide are required for successful completion of translational research.[65] But what exactly should be patented, and when? Although those who pursue patents on early research results hope to share in downstream product development by virtue of so called "reach-through" claims, authors in the legal community have narrowly defined such claims.[66]

We published the results of our study (to discover tyrosine kinase

industrial, rather than scientific or public health concerns. *Id.* at 10-11.

60. *See, e.g.*, P. Komesaroff, *Ethical Issues in the Relationships Involving Medicine and Industry: Evolving Problems Require Evolving*, 35 INTERNAL MED. J. 203, 203-05 (2005).

61. *See, e.g.*, Elizabeth Iorns et al., *Utilizing RNA Interference to Enhance Cancer Drug Discovery*, 6 NATURE REVIEWS DRUG DISCOVERY 556, 556 (2007).

62. *See* Andrew Pollack, *Patient's DNA May Be Signal to Tailor Medication*, N.Y. TIMES, Dec. 29, 2008, at A1

63. *See id.*

64. *Id.*

65. *See* USPTO, General Information Concerning Patents, http://www.uspto.gov/web/offices/pac/doc/general/index.html#patent (last visited Feb. 9, 2009).

66. Stephen G. Kunin et al., *Reach-Through Claims in the Age of Biotechnology*, 51 AM. U. L. REV. 609, 638 (2002).

mutations in AML) in a scientific journal, which are also available via open access and are in the public domain.[67] We did not pursue patent rights for our initial findings for several reasons. First, our group is currently committed to a purely academic open source model where we view our mission as providing these data for the public domain. Second, however, the utility of our findings is unclear. Although we believe that there is some scientific value for the variants that we have identified in AML,[68] the clinical utility of these findings is currently unknown. One approach would direct us to stay within the traditional academic model, and not attempt to commercialize our findings.[69] On the other hand, it is explicitly clear from the National Institutes of Health research agenda that practical application is expected from the investment in medical genetic research.[70] Since the Constitution gives Congress the power to enact statutes that define the intent of intellectual property law to facilitate useful business innovation,[71] it seems that it is not a question of whether to pursue patents for our tests, but rather where in the research process we should consider them. Thus ensues a lively debate on the role of patent law in facilitating innovation.

Generally, the Court of Appeals for the Federal Circuit is responsible for interpreting patent law in this country, and has been noted to consistently favor strengthening intellectual property rights over the past several decades.[72] Recently, however, a number of experts in this field have challenged the wisdom of pursuing strong IP rights too early in the research process.[73] In the related field of biotechnology, some have argued that strong reach-through IP rights, for example, drug targets or molecular receptors would dissuade "me-too" drug development; consequently, they argue, the focus of biotech research would shift to the development of breakthrough pharmaceuticals and first-in-class applications.[74] Some legal practitioners, in sharp contrast, have suggested that reach-through claims

67. *See* Tomasson et al., *supra* note 3, at 4801; NCBI, Gene Expression Omnibus (GEO), http://www.ncbi.nlm.nih.gov/geo/ (enter "GSE10358" in the "GEO accession" field) (last visited Apr. 25, 2009).

68. Tomasson et al., *supra* note 3, at 4803.

69. Here, I use the phrase "traditional academic model" to refer to an old-fashioned pre-Bayh-Dole era role of the university as an engine of scholarly pursuit to the exclusion of the pursuit of profit, or practical application. *See generally* BOK, *infra* note 85.

70. National Human Genome Research Institute, Clinical Research Program Overview, http://www.genome.gov/10000331 (last visited Mar. 13, 2009).

71. U.S. Const. art. I, § 8, cl. 8.

72. *See* Michael A. Carrier, *Cabining Intellectual Property Through a Property Paradigm*, 54 DUKE L.J. 1, 16-17 (2004).

73. *See* JAMES BOYLE, THE PUBLIC DOMAIN: ENCLOSING THE COMMONS OF THE MIND 160-68 (2008), *available at* http://thepublicdomain.org/thepublicdomain1.pdf.

74. Robert A. Bohrer, *Reach-Through Claims for Drug Target Patents: Rx for Pharmaceutical Policy*, 26 NATURE BIOTECHNOLOGY 55, 56 (2008).

must meet extremely stringent criteria in order to be successful.[75] These commentators advocate increasing the stringency of such criteria because they believe reach-through claims are inconsistent with a central tenet of IP—promoting science by granting exclusive property rights.[76] Identification of molecular receptors and pathways can be viewed somewhat differently as medical genetic testing certainly, but parallels remain.[77]

B. Academia and the Culture of Secrecy

If the private sector has yet to figure out successful solutions to medical genetics testing, what roadmap can be found in the academic culture? The view from within medical schools reveals two poles of thinking regarding the privatization of knowledge. A "culture war" may be too dramatic a turn of phrase, but certainly distinct subcultures are discernible within academia. The first, and perhaps most basic approach, is the open access to knowledge generation that can be found in some circles; for example, the DNA sequencing arena developed some guiding principles stating that during the heavy competition for sequencing milestones, the sequence data would be made public.[78]

The second culture, in essence, values exclusive rights and secrecy as a way to facilitate greater benefit to society from medical research generally. The Bayh-Dole Act of 1980 was passed "to promote collaboration between commercial concerns and nonprofit organizations including universities."[79] This statute gives universities IP rights over their inventions, with the hope

75. *See* Kunin et al., *supra* note 66, at 638.

76. *Id.* An exhaustive study of the effects of IP practice and genomic research concluded that "the licensing of some gene-based diagnostic tests does appear to [have] an inhibiting effect on research and related clinical practice." BD. ON SCI., TECH., & ECON. POLICY, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 131 (2006). Interestingly, although insufficient evidence was found for a genetic research patent thicket, the lack of researcher constraint was associated with a research community largely ignorant of salient IP issues. *Id.* A follow-up report commissioned by the Secretary of the U.S. Department of Health and Human Services (HHS) concluded that, unlike in other fields, patents "do not serve as powerful incentives for either genetics research in the diagnostic arena or development of genetic tests." SECRETARY'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, PUBLIC CONSULTATION DRAFT REPORT ON GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS 110 (2009).

77. Just as the identification of a receptor in a biological assay may be used as the basis for a "reach-through" claim against a drug targeting that receptor, the mutations or SNPs can be identified before a clear understanding of how these finding will be practically useful in medical practice.

78. National Human Genome Research Institute, NHGRI Policy for Release and Database Deposition of Sequence Data, http://www.genome.gov/pfv.cfm?pageID=10000910 (last visited Mar. 13, 2009).

79. Bayh-Dole Act, 35 U.S.C. § 200 (2006).

that an increased stake in the profits will motivate universities to maximize commercial applications of their research.[80] Essentially, therefore, Congress has given a green light to, and has encouraged an alternative university culture which focuses attention on entrepreneurial activities.[81] Indeed, some university researchers view involvement with privatization and commercial applicability of their research as the upper echelon of medical academic success.

The debate within medical academia has somewhat paralleled the debate in legal circles regarding the merits of strong IP rights versus a noncommercial, purely scientific approach.[82] While the purely basic science/academic approach seeks to continue to gather more information through research so that commercial applications can be developed, statutory and ethical obligations require that we work actively to develop useful clinical applications in addition to collecting genomic data. And so we return again to the salient question, which is not whether to pursue IP rights, but how to pursue them, and where they should fit into the research agenda.

A certain amount of "secrecy culture" is unavoidable in competitive scientific enterprises where credit and accolades are awarded to individuals for scientific innovation.[83] Scientists do not want to lose recognition for long years of labor by being scooped by the competition.[84] The Bayh-Dole Act has nurtured the competitive urges of scientists, allowing strong IP culture to flourish within academic medicine while eroding the public domain.[85] Thus, aside from creating a patent thicket[86] problem, the Bayh-Dole Act also may have reduced a potentially important source of creativity and innovation.[87]

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80. *Id.*

81. *See, e.g.*, Technology Transfer Commercialization Act of 2000, H.R. 209, 106th Cong. (2000) (enacted) (amending the Bayh-Dole Act).

82. *See generally, e.g.*, Arti Kaur Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 NW. U. L. REV. 77, 78 (1999) (applying the law-and-norms theory to the study of scientific research and arguing that legal change has been insufficient to maximize the central goals of intellectual property rights).

83. *See id.* at 92.

84. *Id.*

85. *See* Zhen Lei et al., *Patents Versus Patenting: Implications of Intellectual Property Protection for Biological Research*, 27 NATURE BIOTECHNOLOGY 36, 39 (2009); *see also* DEREK BOK, UNIVERSITIES IN THE MARKETPLACE: THE COMMERCIALIZATION OF HIGHER EDUCATION 64, 143 (2003).

86. Defined, colloquially, as "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology." Carl Shapiro, Competition Policy Ctr., Working Paper No. CPC00-11, Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard-Setting 2 (2000).

87. *See* Lei et al., *supra* note 85, at 39. Empirical evidence for an anti-commons effect in biotechnology research has been subtle, but a recent survey of academic researchers in the agricultural sciences revealed strong beliefs among researchers that patents do inhibit

C. The Current Model Does Not Appear to be Working

A recent medical sequencing project that examined the genomics of patients with acute myelogenous leukemia (AML) provides a useful example of the unexpected complexity of human genomes, and will be used to illuminate roadblocks to the practical application of genomic knowledge.[88] AML was chosen because current therapies are successful in only half of patients under the age of sixty-five, and these therapies have not been significantly improved in the past four decades of determined effort.[89] The intent behind sequencing the genomes of patients with AML was to uncover mutations that form the basis of novel diagnostic tests and the target for pharmacologic therapies.[90]

Mutations known previously to occur in AML were identified at expected frequencies, validating the high-volume re-sequencing approach.[91] While four novel somatic mutations were identified, the most dramatic finding was the large amount of normal sequence in these cancer patients—in other words, a lack of "useful mutations."[92]

Researchers conducting tissue banking studies have ethical obligations not only to prevent harm to patients, but also to derive some societal benefit from the genetic information obtained from patient materials. Previous studies in AML, and preliminary studies from these samples, demonstrate a complexity that confounds our initial goal of identifying a small number of extremely informative mutations.[93] Rather, what we are finding is that both germline and somatic mutations may be cooperating in a subtle fashion to give rise to disease.[94]

Our finding of unexpected changes in the skin DNA of our patients (changes they were born with) led us to consider the possibility that these changes contributed to a predisposition toward the development of leukemia in our patients.[95] Such variations, single nucleotide polymorphisms, most often are of no significance whatsoever, but a small subset of such variants, or alleles, have been found to be statistically associated with disease development. Despite powerful statistical

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scientific research. *Id.*

88. Tomasson et al., *supra* note 3.

89. *See generally* Asa Rangert Derolf et al., *Improved Patient Survival for Acute Myeloid Leukemia: A Population-Based Study of 9729 Patients Diagnosed in Sweden Between 1973 and 2005*, 113 BLOOD 3666, 3666 (noting that while AML survival has improved during the last decades, the majority of AML patients die of their disease).

90. *See* Tomasson et al, *supra* note 3, at 4797.

91. *Id.* at 4803.

92. *Id.*

93. *See, e.g.*, Tomasson et al., *supra* note 3.

94. *Id.* at 4804-07.

95. *Id.* at 4798.

association, most alleles imply only a small increase in relative risk.[96] Homozygosity, (i.e. two copies of a risk allele) may increase risk yet further,[97] but still not provide a large enough increase in risk to be useful to patients or physicians.

Can we look to the private sector for a roadmap on how to perform human genetics usefully in the 21st century? deCODE genetics, Inc., through a unique arrangement with the Icelandic public and health care system, is arguably the world leader in human medical genetics.[98] deCODE has published dozens of high-profile scientific articles describing germline variations that predispose individuals to cancer, heart disease, and common neurological diseases.[99] Compared to our small university study, deCODE's efforts are comprehensive, large-scale, and extremely farsighted.[100] In addition to its discovery work, deCODE offers genetic testing for the alleles it and others have discovered, and deCODE is developing novel pharmaceutical compounds targeted to the gene products it has identified in the screening process.[101] In this way, deCODE stands as an example for us to follow.

However, in the face of soaring academic success, the business model of deCODE is on the verge of complete failure.[102] As of this writing, the stock price of deCODE genetics is in the vicinity of $0.20 per share, very near its fifty-two week low.[103] The general stock market decline in 2008 certainly contributed, but deCODE's stock price has been falling for several years, with a steady downward trajectory.[104] The market capitalization of deCODE is approximately $12 million, which appears to be an extremely small sum to pay for one of the leaders in medical genetics, but due

96. *See id.* at 4803-05.

97. *See* Kristleifur Kristjansson et al., *Linkage of Essential Hypertension to Chromosome 18q*, 39 HYPERTENSION 1044, 1044-49 (2002), *available at* http://hyper.ahajournals.org/cgi/reprint/39/6/1044.

98. deCODE genetics, About deCODE genetics, http://www.decode.com/Company/Index.php (last visited Apr. 5, 2009).

99. A complete listing of these publications is available on the deCODE website. deCODE genetics, Publications, http://www.decode.com/Publications/Index.php (last visited Apr. 5, 2009).

100. *See* deCODE genetics, http://www.decode.com/ (last visited Apr. 5, 2009).

101. *Id.*; *see also* deCODE genetics, Using Genetics to Empower Prevention of Common Diseases, http://www.decode.com/From-Genes-to-Drugs.php (last visited Mar. 14, 2009); deCODE genetics, Drug Discovery, http://www.decode.com/Drug-Discovery.php (last visited Mar. 14, 2009).

102. *See* Meredith Wadman, *Icelandic Biotech Feels the Pinch*, 455 NATURE 842, 842 (2008).

103. NASDAQ, DCGN: Stock Quote and Summary Data, http://quotes.nasdaq.com/asp/SummaryQuote.asp?symbol=DCGN&selected = DCGN (last visited Apr. 5, 2009) (52-week low is $0.15 per share).

104. Wadman, *supra* note 102, at 842.

diligence finds that deCODE has a large debt burden, which potential managers and owners would have to deal with.[105]

In 2009, it is highly probable that deCODE will become insolvent and will either declare bankruptcy or be bought outright by a larger pharmaceutical company.[106] What should we take from the fact that this scientifically outstanding company faces financial crisis? Despite fulfilling the ultimate goal of identifying dozens of extremely informative SNPs, and developing clinical tests for these mutations as well as novel pharmaceutical compounds, deCODE's business model is unsuccessful. deCODE's diagnostic model has not yet succeeded because of the gap between the powerful statistical significance of the SNPs deCODE has discovered and the lack of practical predictive significance of these findings. Searching the United States Patent and Trademark Office database for "deCODE Genetics" as the assignee pulls up twenty-three issued patents and sixty pending patent applications including issued patents for "human narcolepsy gene" and "osteoporosis gene." Defining IP for such genetic information has not proved very useful. The second aim of their strategy is to develop drugs targeting the cellular pathways implicated by the DNA findings, and the company may yet find commercial success with more traditional drug structure IP. The story of deCODE is a cautionary tale, and highlights the difficulties involved with translating basic laboratory success into clinically useful, commercially viable practice.

IV. OTHER POTENTIAL BARRIERS

A. Effects of Medicare Legislation on Diagnostic Testing Research

Healthcare policy also presents a hurdle in the effort to identify DNA markers that can be used as the basis for novel and useful clinical tests. For instance, the language of Medicare's "Reasonable and Necessary" clause defines the landscape of clinical research, and may affect the development of genomic tests by outlining which tests will be reimbursed by health insurance. Medicare's enabling legislation states that "[n]o payment may be made . . . for any expenses incurred for items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury."[107] New genetic tests with potential utility are considered experimental, and may not be covered by medical insurance until they

105. *Id.*; NASDAQ, *supra* note 103.

106. Meredith Wadman, *Gene-Testing Company Fights to Retain Listing*, NATURE NEWS, Nov. 11, 1008, http://www.nature.com.flagship.luc.edu/news/2008/081111/full/news.2008.1220.html.

107. Social Security Act of 1965 § 1862(a)(1)(A) (current version at 42 U.S.C. § 1395y(a)(1)(A) (2006)).

prove sufficiently safe and effective to be considered reasonable and necessary.[108]

Healthcare policy has set a high bar for genomic tests. Genetic tests performed "in the absence of signs, symptoms, complaints, personal history of disease, or injury are not covered except when there is a statutory provision that explicitly covers tests for screening."[109] Even for tests that the research community considers "home runs," Medicare requires a long process to establish that they are reasonable and necessary.[110] In 1994, an international mapping effort identified inherited mutations in the BCRA1 and BRCA2 genes, which confer a high risk for the development of breast and ovarian cancer.[111] Researchers identified BRCA1 and BCRA2 using classical genetic techniques, including positional cloning, to identify genes in association with a clear heritable phenotype.[112] The degree to which BRCA1 and BRCA2 accounted for the heritable phenotype was unexpectedly low.[113] Very few patients with strong familial cancer histories have mutations in BRCA1 or BRCA2.[114] This gap has been referred to as "missing heredity" and has been observed in numerous studies looking for genetic markers for heritable health traits.[115]

The identification of the BRCA1 and BRCA2 genes was a scientific tour-de-force. Soon after this effort, clinical tests for these genes became available which enable clinicians to identify whether an individual is strongly predisposed to develop breast or ovarian cancer.[116] Yet health

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108. *See generally* Ctrs. for Medicare & Medicaid Servs., Transcript from Medicare Evidence Development and Advisory Committee Meeting (Feb. 25, 2009) [hereinafter Advisory Committee Meeting] (discussing the merits of diagnostic use of genetic testing and whether it improves health outcomes for Medicare beneficiaries).

109. CTRS. FOR MEDICARE & MEDICAID SERVS., PUB. NO. 100-04, MEDICARE CLAIMS PROCESSING MANUAL ch. 16, § 120.1 (2009), http://www.cms.hhs.gov/manuals/downloads/clm104c16.pdf; CTRS. FOR MEDICARE & MEDICAID SERVS., LCD for Genetic Testing (L24308) (2009), http://www.cms.hhs.gov/mcd/viewlcd_pdf.asp?lcd_id=24308&lcd_version=10&contractor_id=129; *see also* 42 U.S.C. § 1395y (2006); 42 C.F.R. § 410 (2008); Medicare; Negotiated Rulemaking: Coverage and Administrative Policies for Clinical Diagnostic Laboratory Services, 66 Fed. Reg. 58,788 (Nov. 23, 2001).

110. *See id.*

111. P. Andrew Futreal et al., *BRCA1 Mutations in Primary Breast and Ovarian Carcinomas*, 266 SCI. 120, 120-22 (1994); Yoshio Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1*, 266 SCI. 66, 66-71 (1994).

112. Miki et al., *supra* note 111, at 66.

113. *Id.* at 70.

114. *Id.*

115. *See* Brendan Maher, *The Case of the Missing Heritability*, 456 NATURE 18, 18 (2008).

116. Futreal et al., *supra* note 111; Miki et al., *supra* note 111; *see also* NAT'L CANCER INST., FACT SHEET: GENETIC TESTING FOR BRCA1 AND BRCA2: IT'S YOUR CHOICE 3 (2002) [hereinafter FACT SHEET], *available at* http://www.cancer.gov/images/Documents/abcb7812-a132-4e78-a532-f002c92fa9b9/fs3_62.pdf; Breast Cancer Action, Policy on Genetic Testing for Breast Cancer Susceptibility, http://bcaction.org/index.php?page=genetic-testing-policy

insurance coverage to test for BRCA1 and BRCA2 mutations was difficult to obtain because of the need to satisfy the reasonable and necessary clause.[117] The test is neither "necessary" for the diagnosis nor for the treatment of patients with breast cancer. Rather, the utility of the test is in identifying a small subset of individuals with a family history of breast cancer that are at high risk for developing breast or ovarian cancer.[118] Once an individual is identified as a BRCA1 gene carrier, several therapeutic options exist, including prophylactic mastectomy and/or oopherectomy, but the optimal approach for these patients is still evolving.[119] Additional genomic tests are being handled on a case-by-case basis, and the criteria for whether or not a new genomic test improves healthcare outcomes are currently under debate.[120]

The statutory language is written to support the use of tests in the treatment of illnesses, but ironically, the emerging data suggest that genomic tests create the greatest benefit for health outcomes when performed on individuals *before* they develop a disease —i.e., in the design of preventive medicine strategies.[121] Therefore, since federal programs do not provide the financial support for clinical research, including the development of genetic tests, such support is by and large left to companies motivated by the goal of future profits.[122]

The road from gene identification to covered test is a long one. In addition to the "missing heredity," investigators must also search for the "missing money" needed to support the development of tests on undefined genetic loci to improve health care outcomes in unclear ways.[123]

(last visited Mar. 14, 2009).

117. *See* FACT SHEET, *supra* note 116, at 7. Even if a person has private insurance coverage for such testing, many prefer to pay out-of-pocket to prevent insurers from practicing genetic discrimination by increasing premiums or canceling coverage based on a positive test for the BRCA1 or BRCA2 alteration. *Id.*; *see also* Muin J. Khoury et al., *The Evidence Dilemma in Genomic Medicine*, 27 HEALTH AFF. 1600, 1600 (2008) (discussing the need for a balance between genomic testing innovation and reasonable evidence thresholds to move new technology into clinical practice).

118. Heidi D. Nelson et al., *Genetic Risk Assessment and* BRCA *Mutation Testing for Breast and Ovarian Cancer Susceptibility: Systematic Evidence Review for the U.S. Preventive Services Task Force*, 143 ANNALS INTERNAL MED. 362, 363 (2005).

119. Dimitrios H. Roukos & Evangelos Briasoulis, *Individualized Preventive and Therapeutic Management of Hereditary Breast Ovarian Cancer Syndrome*, 4 NATURE CLINICAL PRAC. ONCOLOGY 578, 580-87 (2007).

120. *See* Advisory Committee Meeting *supra* note 108.

121. *See* LCD for Genetic Testing, *supra* note 109.

122. *See* Gillian Haddow et al., *Tackling Community Concerns About Commercialisation and Genetic Research: A Modest Interdisciplinary Proposal*, 64 SOC. SCI. & MED. 272, 273 (2007).

123. *See* Maher, *supra* note 115, at 19 (noting that enthusiasm to complete studies on missing heritability should increase as the costs of sequencing decrease).

B. *Effects of HIPAA on Genomic Research*

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 modified the Medicare legislation in ways that affect clinical research, and may profoundly affect the process of developing genomic tests.[124] The law was intended to improve Medicare and Medicaid statutes, with an eye toward preventing unintended harm that may be inflicted by the dissemination of personal patient information.[125] HIPAA aimed to allow individuals to maintain their employer-provided health insurance coverage as they changed jobs.[126] To counter concerns that sensitive medical information could be inappropriately (and easily) disclosed through the use of electronic medical records (EMR), HIPAA required the Secretary of Health and Human Services (HHS) to develop regulations to prevent such disclosure.[127] Therefore, the Privacy Rule emerged in 2000, and was amended in 2002, to prevent inappropriate transfer or disclosure of protected health information (PHI).[128] Notably, HIPAA does not identify a patient "right to privacy," rather the Privacy Rule restricts the ways that covered entities may use clinical data.[129] The Privacy Rule provides civil and criminal penalties for the unlawfully using, obtaining or disclosing protected patient information in electronic or other formats[130] and has given rise to a significant bureaucracy dedicated to ensuring that policies and procedures are compliant with the regulations embodied in the law.[131]

In addition to the Privacy Rule, HHS adopted the Security Rule in 2003 to set specific standards which covered entities must follow to protect

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124. *See generally* Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 94-101, 110 Stat. 2033 (requiring the Secretary of Health and Human Services to develop recommendations regarding the uses and disclosure of individually identifiable health information).

125. *See* CTRS. FOR MEDICARE & MEDICAID SERVS., Health Insurance Portability and Accountability Act of 1996: Summary of Administrative Simplification Provisions, http://www.cms.hhs.gov/HIPAAGenInfo/Downloads/SummaryofAdministrativeSimplificationProvisions.pdf (last visited Mar. 14, 2009).

126. *See* Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191, § 101, 110 Stat. 1936, 1942 (1996).

127. *Id.* § 264.

128. U.S. DEPT. OF HEALTH & HUMAN SERVS., PROTECTING PERSONAL HEALTH INFORMATION IN RESEARCH: UNDERSTANDING THE HIPAA PRIVACY RULE 2 (2003) [hereinafter UNDERSTANDING THE HIPAA PRIVACY RULE], *available at* http://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf; *see also* 45 C.F.R. § 160 (2008).

129. *See, e.g.*, UNDERSTANDING THE HIPAA PRIVACY RULE, *supra* note 128 at 5. A covered entity is defined as a health plan, a health care clearinghouse, or a health care provider who transmits health information electronically. 45 C.F.R. § 160.103 (2008).

130. *E.g.*, UNDERSTANDING THE HIPAA PRIVACY RULE, *supra* note 128, at 2.

131. *See, e.g.*, Washington University in St. Louis, HIPAA Privacy Office, https://secpriv.wusm.wustl.edu/privacy/default.aspx (last visited Apr. 23, 2009).

PHI.[132] Compliance with the Security Rule includes, but is not limited to, mandatory training and compliance modules that healthcare providers must complete, locking the doors of rooms and cabinets that contain any patient information, and ensuring that every computer, handheld PDA and mobile phone capable of receiving clinical data in any form (e.g. email) is user restricted and password protected.[133] Whether the HIPAA bureaucracy impedes clinical research in any significant way is unknown. The intention of HIPAA was not to impede medical research, and PHI can be used in medical research in compliance with the Privacy Rule by eliminating specific data that might be used to personally identify study subjects.[134] Such "de-identification" includes eliminating eighteen identifiers, including name, address, and other individually identifiable information.[135]

Recent technical developments (e.g. whole genome sequencing) have made HIPAA statutory compliance for covered entities more complex by generating PHI that resist de-identification.[136] As the genetic resolution of newer studies has increased dramatically, the standard methods for ensuring that medical research using patient samples is compliant with HIPAA by de-identifying samples has become nearly impossible because the genomic data itself can be used to determine individual identity.[137] With high throughput sequencing technology, we now have the new situation of genetic data that is detailed enough that it is inseparable from identifying information.[138]

Large resolution genome studies create genetic fingerprints that can be used to identify the individual and cannot easily be de-identified.[139] De-identifying PHI by the usual means (e.g. no names, no dates of birth) may

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132. Health Insurance Reforms, Security Standards, 68 Fed. Reg. 8,334 (Feb. 20, 2003); *see also* 45 C.F.R. §§ 160.103, 162.103, 164.103-.318, 164.500, .501, .504 (2008).

133. 45 C.F.R. §§ 164.304, .306, .308, .310, .312 (2008).

134. 68 Fed. Reg. 8,338 (Feb. 20, 2003); *see also* UNDERSTANDING THE HIPAA PRIVACY RULE, *supra* note 128, at 9-10.

135. 45 C.F.R. § 164.514(b)(2)(i) (2008).

136. *See generally* William W. Lowrance, Nat'l Human Genome Research Inst., Privacy, Confidentiality, and Identifiability in Genomic Research 5-6 (2006) (discussion document for Human Genome Research Institute, Oct. 3 to 4, 2006) (discussing the challenges involved in simultaneously protecting individual privacy and fostering genomic research, including strategies for identifying, as well as de-identifying genomic data), http://www.genome.gov/Pages/About/OD/ReportsPublications/IdentifiabilityWorkshopWhitePaper.pdf.

137. *See id.* at 12-20 (discussing various strategies for identifying non-identified genomic data and for de-identifying genomic data).

138. *Cf. id.* at 5 ("The NHGRI Medical Sequencing Program and many other projects will . . . generate data that are . . . person-specific, [will] categorize many data with respect to . . . disease diagnosis . . . [and will] maintain links, at least indirectly, to clinical, family, social, and demographic data . . . .").

139. *Id.* at 6.

be insufficient for HIPAA compliance.[140] Our institution is pursuing sequencing studies with revised patient consent forms addressing privacy issues. Also, PHI may be used in medical research without de-identification, but this requires an authorization in addition to and separate from informed consent.[141] Such authorization allows the use of PHI for specific research projects.[142]

Although surmountable, privacy issues are likely to remain significant, and may change the landscape of genomic efforts. Early genetic marker studies accessed a limited amount of patient information, such as type of cancer or overall survival. However, as the search intensifies for useful genetic markers, patient clinical data with the greatest possible depth will be required, e.g. detailed family histories, employment and environmental histories, and reactions and responses to medications.[143] Currently, this type of data is extremely unwieldy, both difficult to collect and difficult to access using traditional paper medical records.[144] The Obama administration plans a large effort to use information technology to improve the efficiency of healthcare delivery in the United States.[145] In addition to efficiency, an electronic medical data system would provide a powerful tool for genomics researchers looking for correlations between genetic markers and important health parameters.[146] However, lawmakers must contend with discordance between the healthcare industry and consumer groups that disagree about whether HIPAA regulations are satisfactory to safeguard patient confidentiality.[147]

HIPAA prohibits the sharing of personal health information by provider-based research programs (covered entities).[148] Privacy protection for

140. *Cf. id.* (noting that current protections for de-identification are inadequate).

141. 45 C.F.R. § 164.506(b)(2), 508(a)(1) (2008).

142. 45 C.F.R. § 164.508(b)(1)(i), .508(b)(3) (2008).

143. *See generally* Berrie Rebecca Goldman, *Pharmacogenomics: Privacy in the Era of Personalized Medicine*, 4 NW. J. TECH. & INTELL. PROP. 83, 84, 87, 88, 91 (2005) (explaining the need for a comprehensive database containing genetic profiles, as well as patient outcomes and side effects, and proposing federal legislation to expand HIPAA to protect such information).

144. *See generally* Karoline Kreuser, Introduction, *The Adoption of Electronic Health Records: Benefits and Challenges*, 16 ANNALS HEALTH L. 317, 319 (2007).

145. Robert Pear, *Privacy Issue Complicates Push to Link Medical Data*, N.Y. TIMES, Jan. 18, 2009, at A16.

146. *E.g.*, Goldman, *supra* note 143, *at* 90 ("Pharmacogenomics cannot succeed unless a system is developed where a large number of genetic profiles and individual responses to drugs may be compared to evaluate drug efficacy and potential adverse reactions.").

147. Pear, *supra* note 145; Patient Privacy Rights, HIPAA – The Intent vs. The Reality, http://www.patientprivacyrights.org/site/PageServer?pagename=HIPAA_Intent_Vs_Reality (last visited Apr. 17, 2009).

148. 45 C.F.R. § 160.102, .103; *see also* U.S. DEPT. OF HEALTH & HUMAN SERVS., SUMMARY OF THE HIPAA PRIVACY RULE, at 2-4 (2003), *available at* http://www.hhs.gov/ocr/privacy/hipaa/understanding/summary/privacysummary.pdf.

patient data is likely to get even stronger with the federal push for a nationwide EMR system,[149] and therefore genomic research approaches using commons or network-based approaches must be used with caution.[150] However, with patient consent and authorization, research groups can obtain exceptions to the HIPAA Privacy Rule.[151] Genomic research performed by medical schools can proceed in compliance with HIPAA's regulatory hurdles.[152] On the other hand, institutions that are not HIPAA covered entities (e.g. business schools, private non-healthcare corporations) do not face these regulatory constraints and may be more efficient at genomic research in the years ahead.[153] By regulating the playing field, HIPAA regulations may inadvertently influence where genomic research is conducted. HIPAA's provider-specific regulatory schema makes it easier for non-provider groups to analyze patient health information using novel open network strategies. We should not be surprised if Google or 23andMe, a retail DNA test provider, are able to extract important data.[154]

C. The Absence of Patient Rights

The Privacy Rule and informed consent requirement codify ethical norms that govern human subject research, but patients in tissue banking and analysis studies are provided no specific rights.[155] Researchers will

149. President Obama recently signed the American Recovery and Reinvestment Act of 2009, which appropriated $1.5 billion for investment in health information technology systems. Pub. L. No. 111-5, 123 Stat. 115, 175. In addition, the HITECH Act is intended to promote health information technology and includes new standards for electronic health records. HITECH Act, Pub. L. No. 111-5, 123 Stat. 226 (2009).

150. *See generally* Patient Privacy Rights, Legislation, http://www.patientprivacyrights.org/site/PageServer?pagename=Legislation (last visited Apr. 17, 2009).

151. 45 C.F.R. § 164.508; UNDERSTANDING THE HIPAA PRIVACY RULE, *supra* note 128, at 9-18.

152. UNDERSTANDING THE HIPAA PRIVACY RULE, *supra* note 128, at 128.

153. Non-healthcare organizations, such as business schools and corporations, are not covered entities under HIPAA and therefore are not subject to the regulations. *See* 45 C.F.R. § 160.103 (2008). However, such an organization might be a "business associate" (BA) under HIPAA if it receives individually identifiable health information from a covered entity (or another BA) for use in its research. *Id.* The BA must sign an agreement with the covered entity which requires the BA to implement appropriate safeguards under the Security Rule. 45 C.F.R. § 164.308, .314, .502(e)(1), .504(e)(1), (2008). Recent amendments to HIPAA now subject BAs to the Privacy and Security Rules. HITECH Act §§ 13400-08, 123 Stat. at 258-71. Further, the HITECH Act requires the Secretary of Health and Human Services (and the Federal Trade Commission) to produce a report to determine whether security and privacy provisions are necessary for non-covered entities that access information held in personal health records. *Id.* § 13424(b).

154. *See generally* Anita Hamilton, *The Retail DNA Test: Invention of the Year*, TIME, Nov. 10, 2008, at 68, 68-70 (describing 23andMe, a company providing a $399 saliva test that identifies and interprets 600,000 genetic markers and can identify a person's predisposition for over ninety traits).

155. 45 C.F.R. § 46.101(b)(4) (2008) (exempting studies from the HHS Policy for the

require more participation and access to more detailed PHI, with the hopeful goal of developing useful (and profitable) diagnostic tests, but patients have no ownership rights to their own tissue, regardless of its potential value.[156] The patients who provide informed consent and agree to participate in research studies are told that they will neither profit nor benefit from their participation, and they may incorrectly assume the same is true for the doctors and scientists performing the research.[157] *Greenberg v. Miami Children's Hospital* involved a group of parents with children afflicted with Canavan disease. The parents were stunned to learn that researchers, using tissue samples taken from the children, developed a diagnostic test for Canavan disease and obtained the exclusive patent rights, thereby restricting its availability.[158] The court held that the families had no ownership stake or control over the IP of the test whose creation they had facilitated.[159]

The perception that the legal framework for distributing profits from a hypothetical "home run" test is unethical may be preventing efficient discovery and development.[160] *Diamond v. Chakrabarty* established that that genetically engineered bacteria, in essence living things, can possibly be patented which opened the door to other biological patients.[161] However, courts have consistently applied the doctrine of simultaneous conception and reduction to practice as a prerequisite to claim inventorship.[162] The

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Protection of Human Research Subjects, including exemption from informed consent requirements, if the "[r]esearch involv[es] the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens . . . if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects."); *cf.* 45 C.F.R. § 164.512(h) (2008) ("A covered entity may use or disclose protected health information to . . . entities engaged in the procurement, banking, or transplantation of . . . tissue for the purpose of facilitating . . . donation and transplantation."); *see also* Donna M. Gitter, *Ownership of Human Tissue: A Proposal for Federal Recognition of Human Research Participants' Property Rights in Their Biologic Material*, 61 WASH. & LEE L. REV. 257, 285 (2004).

156. Gitter, *supra* note 155, at 319-320, 327, n.295; Moore v. Regents of the Univ. of Cal., 793 P.2d 479, 492-93 (Cal. 1990).

157. Cynthia M. Ho, *Who Deserves the Patent Pot of Gold? An Inquiry into the Proper Inventorship of Patient-Based Discoveries*, 7 DEPAUL J. HEALTH CARE L. 185, 199 (2004).

158. Greenberg v. Miami Children's Hosp. Res. Inst., Inc., 264 F. Supp. 2d 1064, 1066-67 (S.D. Fla. 2003). Over the course of seven years, the plaintiffs provided tissue and blood samples, including a tissue sample of their son's organs after his death from Canavan disease. *Id.*

159. *Id.* at 1074-76.

160. *See* Ho, *supra* note 157, at 199-201.

161. Diamond v. Chakrabarty, 447 U.S. 303 (1980), *aff'g In re* Bergy, 563 F.2d 1031 (C.C.P.A. 1977), *aff'g* 596 F.2d 952 (C.C.P.A. 1979) (holding that genetically engineered organisms are patentable subject matter within the plain language of the Patent Act); Ho, *supra* note 157, at 201.

162. *E.g.*, Brown v. Regents of the Univ. of Cal., 866 F. Supp. 439, 442-43 ("Under the doctrine of simultaneous conception and reduction to practice, the Federal Circuit has held

conception element "requires both the idea of the invention's structure and possession of an operative method of making it."[163] Patients who are tissue donors, as in *Greenberg*, are not co-inventors even though they may have originally envisioned the diagnostic test that resulted from their donations, and had intended that the test be freely available.[164] Further, the court in *Buildex, Inc. v. Kason Industries* found that recognizing a problem is also insufficient to state a valid co-inventorship claim.[165]

The analysis of patient tissue banks is not wholly dissimilar from the concerns of "bio-piracy" of Indigenous Populations.[166] Researchers may be "genetic gold diggers," but courts consider allegations of fraud in such cases to be "much-abused and too often last-resort allegation[s]."[167]

V. NEW APPROACHES: CREATIVE COMMONS AND OPEN SOURCE

The human genome has become cluttered with patents, and patent ownership is often fragmented, raising the possibility that access may be limited by complex licensing agreements.[168] Some argue that the patent system should be abolished.[169] While outright abolition might be too drastic, clearer outlines of patent "property" and transparency are needed.[170] One goal is to find a way to sift genomic data for the "gold nuggets" of useful data without contributing to patent thickets. Another point to consider is whether we can allow patient-participants an ownership stake in the search to encourage greater participation in genomic research projects.

The UK Biobank is a large scale tissue banking and research effort funded by the Wellcome Trust.[171] UK Biobank Ltd. is a charitable

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that complex chemical compounds are not conceived until they have been reduced to practice.").

163. *Id.* (quoting Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991).

164. *See, e.g.*, *Greenberg*, 264 F. Supp. 2d at 1067, 1074.

165. Buildex, Inc. v. Kason Indus., 849 F.2d 1461, 1464-66 (Fed. Cir. 1988).

166. *See generally* Ho, *supra* note 157, at 235-42 (discussing "bio-piracy," where those who provide raw materials that result in the production of patentable material are denied patent rights).

167. Preemption Devices, Inc. v. Minn. Mining & Mfg. Co. 732 F.2d 903, 908 (Fed. Cir. 1984); *see also id.* at 228.

168. Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239, 239 (2005).

169. *See Generally* Michele Boldrin & David K. Levine, Against Intellectual Monopoly (2008) (arguing that intellectual property is not necessary to promote innovation and it inhibits growth), *available at* http://www.dklevine.com/papers/imbookfinalall.pdf.

170. *See generally* JAMES BESSEN & MICHAEL J. MEURER, PATENT FAILURE: HOW JUDGES, BUREAUCRATS, AND LAWYERS PUT INNOVATORS AT RISK 8-25 (2008) (suggesting that policy reforms to improve the notice function of property to improve transparency and create well-defined boundaries could make the United States more economically competitive).

171. UKBiobank – What Is It?, http://www.ukbiobank.ac.uk/about/what.php (last visited Apr. 19, 2009).

company that exercises management oversight of UK Biobank and is the legal owner of the database.[172] The UK Biobank rejected the idea of tissue "ownership" for a "partnership" model, however David Winikoff, of the University of California-Berkeley, has noted that partnership has a specific legal meaning that is not truly relevant to the Biobank example.[173] UK Biobank enforces certain ethical standards, such as the non-commodification of samples, and the requirement for affirmative consent, but the research participants (tissue donors) possess little control share, and no equity share in the common pool resource.[174] As such, the project does not achieve its own ideals concerning "partnership," and in so doing, loses a potential source of strength.[175]

Finding value in genomic testing may be amenable to a social network approach to value creation.[176] To facilitate the discovery phase of genomic research that is problematic using current approaches, individuals may share their data in a creative commons.[177] In fact, data emerging from large scale sequencing efforts may be pointing toward these approaches.[178] Specifically, the genomic diversity that is being discovered appears to describe a power-law distribution,[179] in that as mutations and SNP databases increase in size, they also decrease in frequency.[180] One embodiment of a creative commons, termed "The Long Tail," has been described as a business model phenomenon of the internet era where companies can aggregate niche markets.[181] For example, while Blockbuster Video, by virtue of limited shelf space, deals primarily in renting "hit" movies, Netflix has found that the bulk of its revenue results from customers renting a large

172. UK BIOBANK, LTD., UK BIOBANK ETHICS AND GOVERNANCE FRAMEWORK 3 (version 3.0, 2007), *available at* http://www.ukbiobank.ac.uk/docs/EGFlatestJan20082.pdf.

173. David E.Winickoff, *Partnership in U.K. Biobank: A Third Way for Genomic Property?*, 35 J.L. MED. & ETHICS 440, 440-56 (2007).

174. *Id.* at 5 *passim*.

175. Winickoff, *supra* note 173, at 445.

176. YOCHAI BENKLER, THE WEALTH OF NETWORKS: HOW SOCIAL PRODUCTION TRANSFORMS MARKETS AND FREEDOM 344-53 (2006), *available at* http://www.benkler.org/Benkler_Wealth_Of_Networks.pdf.

177. *See* Lawrence Lessig, Commentary, *The Creative Commons*, 65 MONT. L. REV. 1, 1-14 (2004).

178. *See* Thomas Goetz, *The Gene Collector*, WIRED, Aug. 2008, at 134, *available at* http://www.wired.com/images/press/pdf/genecollector.pdf.

179. *Cf.* Lander et al., *supra* note 20, at 914 ("To realize the full promise of comparative genomics, however, it needs to become simple and inexpensive to sequence the genome of any organism. Sequencing costs have dropped 100-fold over the last 10 years, corresponding to a roughly twofold decrease every 18 months. This rate is similar to 'Moore's law' concerning improvements in semiconductor manufacture.").

180. Hap Map: About the Project, http://snp.cshl.org/abouthapmap.html (last visited Apr. 19, 2009).

181. Chris Anderson, *The Long Tail*, WIRED, Oct. 2004, http://www.wired.com/wired/archive/12.10/tail.html.

variety of less-common and rare films.[182] Chris Anderson wrote about the entertainment industry, noting that "[w]e're stuck in a hit-driven mindset—we think that if something isn't a hit, it won't make money and so won't return the cost of its production."[183] This language is apropos of our genome-wide sequencing efforts in cancer. Originally, we sought to find common, i.e. "hit" mutations, but instead uncovered rare mutations that were initially discounted.[184] If this power law distribution of mutations holds up, and most of the mutations in different cancers are rare ones, then a distributed approach to reverse genetic analysis (i.e. validating the clinical or biological significance of discovered genetic changes), is almost imperative.[185] In the Personal Genome Project, researchers at Harvard University Medical School are trying a cooperative approach to collecting DNA samples and assembling diverse phenotype data using volunteers.[186] This project may point the way for future disease research.[187] The Personal Genome Project takes an "open source" approach to genomics research by asking volunteers to contractually forfeit intellectual property rights by putting their personal and genomic data in the public domain so that research can proceed without the distractions and impediments posed by IP concerns. Once open source mechanisms identify informative genetic loci, patent pools or clearinghouses may be used as mechanisms to overcome patent thickets, if any remain.[188]

PXE International provides a distinct model based on a contractual relationship between researchers and patients to ensure that the products of research conducted with donated tissues return benefits to patients with the rare genetic disorder pseudoxanthroma elasticum (PXE).[189] The parents of two children with PXE established PXE International to facilitate research and accelerate the development of tests and treatments.[190] They recognized that tissue donations were critical to the identification of the gene

182. *Id.*

183. *Id.*

184. *Cf.* Anna D. Barker & Francis S. Collins, *Mapping the Cancer Genome*, SCI. AM., Mar. 2007, at 50, *available at* http://www.sciam.com/article.cfm?id=mapping-the-cancer-genome (discussing the importance of mapping an entire human and cancer genomes to pinpoint genes that cause cancer).

185. *See* Goetz, *supra* note 178 (explaining that disease detection and other correlations must be derived from an entire population).

186. *See* Personal Genome Project, http://www.personalgenomes.org (last visited Apr. 19, 2009).

187. *See id.*

188. Geertrui Van Overwalle et al., *Models for Facilitating Access to Patents on Genetic Inventions*, 7 NATURE REVIEWS GENETICS 143, 146 (2006).

189. *See* Gitter, *supra* note 155, at 315-16.

190. *Id.*

responsible for PXE and for the success of clinical research.[191] Accordingly, they established a tissue bank that gave contractual benefits to tissue donors, ensuring patients affordable access to tests and treatments developed by using their samples.[192] This was a unique way of sharing IP rights with patient research participation that avoided the problems that occurred in *Greenberg v. Miami Children's Hospital*, but required a substantial amount of activism and involvement on the part of patient families. It is unclear whether this approach could be replicated with more common diseases.

VI. CONCLUSION

What began as a straightforward idea—to sequence genes so that we may have new genetic tests useful for improving human health—in the final analysis turns out to be a project fraught with complexity. The passage of the Bayh-Dole Act may have contributed to an erosion of the scientific culture at medical schools, spurring a metamorphosis of the university from a place of pure research and scientific inquiry to a source of valuable intellectual property.[193] But the transformation of academic culture towards a more corporate model is wider spread and has been underway since well before 1980.[194] Recently, something of a backlash is occurring against the involvement of pharmaceutical companies in the process of medical research, but response has been pallid at best.[195] It is surprising that doctors that fail to report drug company support, and also fail to appreciate the domination the pharmaceutical industry has come to hold over the fundamental model of medical research in this country.[196] Modern cancer research is focused on the identification of genes and pathways as exciting new drug targets, ignoring the fact that the identification of tobacco as a carcinogen was one of the greatest breakthroughs in cancer medicine of the past 100 years.[197]

Our genomes, however, have not received the drug company memos. The glimpses we are getting of the genetic component of this disease have

191. *Id.*

192. *Id.*

193. DAVID C. MOWERY ET AL., IVORY TOWER AND INDUSTRIAL INNOVATION: UNIVERSITY-INDUSTRY TECHNOLOGY TRANSFER BEFORE AND AFTER THE BAYH-DOLE ACT (2004); *see also* BOK, *supra* note 85, at 11 *passim*.

194. FRANK DONOGHUE, THE LAST PROFESSORS: THE CORPORATE UNIVERSITY AND THE FATE OF THE HUMANITIES (2008).

195. Andrew Pollack, *Stanford to Ban Drug Makers' Gifts to Doctors, Even Pens*, N.Y. TIMES, Sep. 12, 2006, at C2.

196. Gardiner Harris & Benedict Carey, *Researchers Fail to Reveal Full Drug Pay*, N.Y. TIMES, June 8 2008, at A1.

197. *See* Stephen S. Hecht, *Tobacco Carcinogens, Their Biomarkers and Tobacco-Induced Cancer*, 3 NATURE REVIEWS CANCER 733 (2003).

not—and may not—facilitate the development of new drugs in the near term. Does this mean genomic research is a failure? Perhaps not. As genome resequencing becomes commonplace, the practice of medicine without regard to the individual genetic makeup of patients may become untenable because our genomes may be most informative about which drugs *not* to take.[198] Although the details of how genomic research will provide clinical utility remains unclear, there is no doubt that research is continuing apace, which at the very least will provide vast amounts of potentially useful biomedical data.

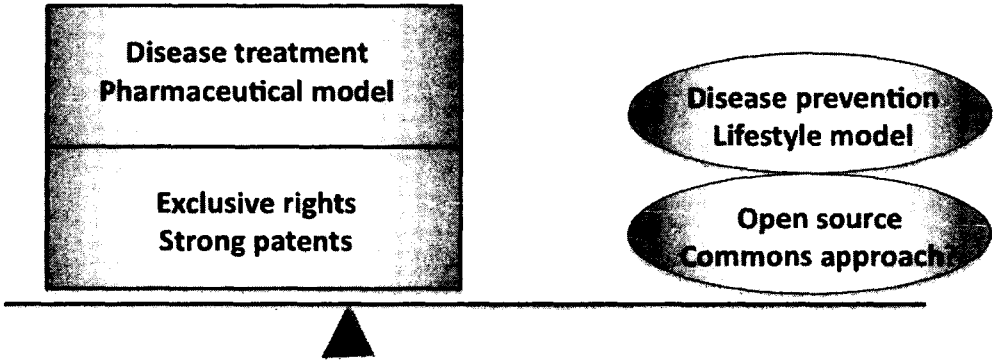

Figure 1: A conceptual framework for competing models of medical research. Large boxes represent the dominant biomedical research models that have been supported by the pharmaceutical industry and statutory efforts. Smaller ovals represent potential alternative approaches. The fulcrum is placed to the left to symbolize a potential shift emphasized by genomic research and ethical imperatives including the need to empower patient research participants.

A startling degree of genetic diversity has been uncovered in patient samples analyzed using high throughput sequencing technology.[199] Translating the vast amount of genomic data being generated into health benefits for society, e.g. by creating useful diagnostic tests, will require significantly greater participation of patients and healthy volunteers in tissue banking and genomic analysis trials. And yet, our current legal

198. *See generally*, Russell A. Wilke et al., *Identifying Genetic Risk Factors for Serious Adverse Drug Reactions: Current Progress and Challenges*, 6 NATURE REVIEWS. DRUG DISCOVERY 904 (2007).

199. *See, e.g.*, Xiang et al., *supra* note 42.

framework disenfranchises patients who donate tissue for research by denying ownership rights and by restricting the sharing of information. In the future, successful development of clinically useful genomic tests may require more positive incentive structures[200] to engage individuals needed to contribute tissue and personal health information. Our medical practice model, currently dominated by the pharmaceutical industry, may also have to be reconsidered (see Figure 1). Finally, genomic research has revealed unanticipated complexity and a "long tail" of genetic variants that may demand data mining approaches unfettered by strong IP constraints (perceived or actual). Creative commons approaches may facilitate broad-based searches for needed healthcare solutions. These approaches may put personal and genomic data IP in the public domain while we search for useful genomic tests (as with the Personal Genome Project). Alternatively, IP ownership rights may be shared contractually with patients to encourage their participation in, and to acknowledge their value to, continuing genomic research.

200. The courts have ruled that patients do not share in ownership rights of intellectual (or even physical) property arising from their donated tissues. *See* discussion *infra* Part IV.C. Researchers looking for useful genomic tests may be motivated (presumably) by several factors, including benevolence, potential notoriety, and potential monetary rewards. Yet patients who contribute tissue necessary for this research can only be motivated by benevolence under the current system. Providing greater incentives for patients to donate tissue may be accomplished contractually, as opposed to a legislative change. Harvard economist Roland Fryer's controversial experiments, whereby schools remunerate children for good grades, provide a possibly relevant parallel to the subject matter at hand. *See* Claudio Chavez, Pay-to-Behave Program Debuts in D.C. Schools, *All Things Considered* (NPR radio broadcast Oct. 21, 2008), *available at* http://www.npr.org/templates/story/story.php?storyId=95949912.