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DNA Patent Licensing Under Two Policy Frameworks: Implications for Patient Access to Clinical Diagnostic Genomic Tests and Licensing Practice in the Not-for-Profit Sector



BY LORI PRESSMAN

Introduction

In 2009, the Association for Molecular Pathology and a group of physicians and patients filed a lawsuit¹ against the U.S. Patent and Trademark Office (USPTO) and Myriad Genetics based in part on the premise that certain patents owned by and licensed to Myriad Genetics obstruct patient access to diagnostic tests for the presence of mutations in the BRCA1 and BRCA2 genes, and by implication that patents of that type, so-called “gene patents,” obstruct patient access generally. Stimulated by a combination of theory² and case studies,³ proposals for improving access often in-

¹ *Association for Molecular Pathology v. U.S. Patent and Trademark Office*, in which the Court of Appeals for the Federal Circuit overruled the decision of the U.S. District Court for the Southern District of New York in deciding that DNA was patentable subject matter. The parties have petitioned the Supreme Court to hear the further appeal.

² Michael A. Heller, Rebecca S. Eisenberg, “Can Patents Deter Innovation? The Anticommons in Biomedical Research,” *Science*, Vol. 280, pp. 698-791, May 1998.

³ Appendix 1 of the Report of the Secretary’s Advisory Committee on Genetics, Health, and Society, *Gene Patents and*

clude removing or mitigating certain presumed identifiable proprietary positions, i.e. “gene patents,” via non-exclusive licensing,⁴ in some cases by compulsory licensing,⁵ patent pooling,⁶ or by rendering certain subject matter patent ineligible.⁷

The Department of Health and Human Services (HHS) Secretary’s Advisory Committee on Genetics Health and Society (SACGHS) identified an opportunity to conduct a natural experiment on the effect of the scope of exclusivity in patent licenses. Prior data on licensing practices of DNA Patents⁸ at academic institutions (AIs),⁹ could be compared to similar data from the National Institutes of Health’s Office of Technology Transfer (NIH OTT), which is more restricted, by statute and policy, in the scope of exclusivity it grants in its patent licenses¹⁰ than are AIs. Thus, the SACGHS commissioned a study of DNA Patent licensing activities at the NIH OTT in order to provide empirical data and other context necessarily absent from theoretical ap-

Licensing Practices and Their Impact on Patient Access to Genetic Tests (SACGHS Report).

⁴ Lee Bendekgey and Diana Hamlet-Cox, “Gene Patents and Innovation,” *Academic Medicine*, Vol. 77, No. 12, December 2002.

⁵ “The Ethics of Patenting DNA,” Nuffield Council on Bioethics 2002, pp. 54-55, esp.

⁶ Ted J. Ebersole, Marvin C. Guthrie, and Jorge A. Goldstein, “Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics,” *Intellectual Property & Technology Law Journal*, Vol. 17, No. 1, January 2005.

⁷ *AMP v. PTO*; see *supra*, fn. 1.

⁸ Patents found by a Boolean search algorithm. See <http://dnapatents.georgetown.edu/>. The algorithm finds patents that reference nucleotides in the claims.

⁹ Lori Pressman, Richard Burgess, Robert M. Cook-Deegan, Stephen J. McCormack, Io Nami-Wolk, Melissa Soucy, and LeRoy Walters, “The licensing of DNA Patents by U.S. academic institutions, an empirical survey.” *Nature Biotechnology*, 24: 31-39, 2006 (the AI Survey).

¹⁰ The NIH as a federal laboratory is required to ensure that “the proposed scope of exclusivity [in licenses] is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application,” 35 U.S.C. § 209(a)(2), and also that “granting the license will not tend to substantially lessen competition” 35 U.S.C. § 209(a)(4).

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proaches or case studies alone. The study was published in preliminary form as Appendix 2 of the SACGHS report.¹¹ Data received after the final SACGHS report, and analyzed more comprehensively here, provide further insight.

Factors Influencing Patient Access

Clearly, many disparate, interrelated factors—scientific, socioeconomic, and legal—influence patient access to clinical diagnostic tests, including tests informed to at least some degree by an understanding of the underlying genetics. Such tests will be referred to here as genomic tests, because many tests informed by an understanding of the underlying genetics neither detect nor use nucleic acids.¹²

Scientific factors related to the utility of diagnostic tests include the sensitivity and specificity of the test, the available medical or psychosocial interventions after receiving a result, and the tests' applicability to particular populations or subpopulations. The underlying testing technology, and therefore ease, cost, and speed of performing the test, are inherently scientific in nature and also affect economic factors.

Social factors include fear of genetic discrimination¹³ and personal preferences concerning knowing one's own genotype and its potential impact on relatives who may have inherited the same traits. The manner in which the test is advertised also has a social component, for example, through physicians versus directly to the consumer via internet and television advertisements. Establishing a test as a standard of care has an impact on patient acceptance as well as cost. Statements supporting and defining clinical utility by the American College of Medical Genetics or by other physician groups representing a medical consensus favor insurance reimbursement, thereby improving patient access.

The regulatory framework of diagnostic testing also affects patient access. Tests regulated as medical devices, for example, the multi-loci prognostic tests that rely on analyzing the presence or expression of many sequences—the so-called In Vitro Diagnostic Multivari-

ate Index Assays (IVDMIA)—have a significantly greater regulatory burden than Laboratory Developed Tests (LDTs). Direct-to-consumer testing, which bypasses physicians and insurance companies, is under review by the FDA,¹⁴ potentially impeding access, or protecting public health, depending on one's viewpoint.

Economic factors for the recipients of the results of genetic tests include patient access to medical care in general, patient access to or an ability to afford insurance coverage, and patient net cost after insurance reimbursement. Economic factors for the commercial developers of the tests include overall market size, the relative ease and likelihood of receiving regulatory clearance, and the relative ease and likelihood of introducing a test that is or will become a standard of care, thus ensuring insurance coverage. Economic factors influencing the test providers include overall market size and how, how much, by whom, and when they are paid. Note that insurance reimbursement decisions are influenced by physician consensus on the utility of the test, an illustration of the interplay among scientific, social, regulatory, and economic factors.

The law influences access in several ways. A law prohibiting genetic discrimination in the workplace and by insurance companies presumably increases patient access by removing some of the concerns surrounding genetic testing.¹⁵ Patent law also could affect patient access via mechanisms discussed in more detail below.

Theories About the Negative Influence of Patents

Some have argued that patents diminish the availability of clinical diagnostic tests,¹⁶ the quality—broadly defined—of such tests, and access to independent confirmatory testing, while increasing test costs by reducing competition. One theoretical argument for believing patents impede patient access goes: "It is not possible to 'engineer around' a nucleic acid sequence." From this assertion, it follows that exclusive licensing could restrict the number of providers and block development of subsequent, possibly improved tests which require the presumed uniquely necessary nucleic acid sequence.

The "patent thicket" theory states that even if any single patent is not problematic, many will be.¹⁷ The "thicket" theory persists in part thanks to misquotes and out-of-context excerpts of the Jensen-Murray study.¹⁸ Most of the Jensen-Murray 4,270 "gene patents," as they define them, are not to "genes," as they define them. The authors define a "gene" as "a set of cotranscribed protein-encoding exons," but "gene patent" as a "patent disclosing and claiming a human gene sequence or some fraction thereof [emphasis added]."¹⁹ Note also that "a set of cotranscribed

¹¹ SACGHS Report, April 2010.

¹² For example, some tests measure the quantity (HER2 immunoassay for predicting response to Herceptin) or function (hexosaminidase functional assay for Tay-Sachs) of the protein encoded by the sequence, while others use antibody binding to measure the presence of a protein that would not be present in unaffected people (HIV-1 antibody-based blood screening, auto-antibodies in autoimmune disease) or would be at abnormal levels in affected people (prostate specific antigen). The type of test is also to some degree a function of its historical context in the last 25 years. If the human immunodeficiency virus (HIV) had been isolated before the tools of genetic engineering and antibody production were readily available, it is possible that a blood screening test could have been developed starting from collecting pooled sera of infected individuals, as was the case with hepatitis B for many years. However, once the virus was isolated and cloned, it was easier to start from knowledge of its antigenic surface proteins, and use that information to develop an antigen-antibody based blood screening assay and later a nucleic acid assay as that technology became commercially feasible.

¹³ Lawrence Low, Suzanne King, Tom Wilkie, "Genetic discrimination in life insurance: empirical evidence from a cross sectional survey of genetic support groups in the United Kingdom," *British Medical Journal*, pp. 1632-35, Vol. 317, Dec. 12, 1998.

¹⁴ "Direct-to-Consumer Genetic Testing and the Consequences to the Public," Statement of Jeffrey Shuren to the U.S. House of Representatives, July 22, 2010.

¹⁵ Genetic Information Nondiscrimination Act of 2008.

¹⁶ Debra Leonard, "Medical Practice and Gene Patents; A Personal Perspective" *Academic Medicine*, Vol. 77, No. 12, December 2002.

¹⁷ Heller, Eisenberg; see *supra*, fn. 2.

¹⁸ Kyle Jensen and Fiona Murray, "Intellectual Property Landscape of the Human Genome," *Science*, 310, 239 (2005).

¹⁹ Also see, Christopher M. Holman, "Will Gene Patents Impede Whole Genome Sequencing": Deconstructing the Myth

protein-encoding exons” is not a biologist’s definition of a “gene.”^{20,21,22}

Thus, Jensen and Murray found patents relating to *fractions of sequences* in 20 percent of human “genes,” and did not show that “twenty percent of human genes have already been patented.” This is an extremely important distinction as small genetic sequences (single nucleotide polymorphisms, or SNPs, for example) are useful in their own right when associated with disease conditions or susceptibility, and offer clear design-around opportunities (different SNPs, for example) because they often fall near but not in a particular gene. Some genomic patents claim narrow uses. Indeed the authors’ statement: “some genes have up to 20 patents asserting rights to various gene uses and manifestations including diagnostic uses, single nucleotide polymorphisms (SNPs), cell lines, and constructs containing the gene” inherently suggests that patents are not blocking further research. In addition, patents on specific sequences are also easy to design around. See Supplement S1, at <http://op.bna.com/hl.nsf/r?Open=rkun8sjl9c>, for a discussion of the NIH OTT-managed patents on nucleic acid sequences associated with Tay-Sachs disease for an example of how claims on both long and specific nucleic acid sequences and short and specific nucleic acid sequences offer easy design-around opportunities.

The “thicket” theory has been bolstered by invoking future patents and whole genome sequencing. If whole genome sequencing, the act of recording the order of nucleotides in an individual’s genetic material, infringes too many patents, including those on nucleic acid sequences, then it is theoretically possible that the license royalty costs could greatly exceed the rapidly declining cost of sequencing.²³ However, legal scholar Chris Holman has posted an analysis saying this is implausible: “To my knowledge, after extensive research into the issue, no U.S. court has ever interpreted a claim to an isolated or purified DNA molecule so broadly that it would be inevitably infringed by DNA sequencing. In fact, there is judicial precedent that, while not directly on point, would support a relatively narrow interpretation of isolated DNA claims, such that these claims would not be infringed by at least some forms of DNA sequencing, particularly next-generation technologies that do not require DNA amplification.”²⁴

that 20% of the Human Genome is Patented,” *IP Theory*, Vol. 2, Issue 1, <http://scholarworks.iu.edu/journals/index.php/ipt/article/viewFile/856/1303>.

²⁰ A biologist’s definition of “gene” includes regions which direct protein production and assembly, which are not necessarily themselves exons. See page 13, “Genetic Twists of Fate,” by Stanley Fields and Mark Johnston, MIT Press, 2010: “gene” is “a stretch of DNA that contains the *instructions* [emphasis added] for the cell to manufacture a protein.”

²¹ H. Pearson, “Genetics: what is a gene?” *Nature*, 441 (7092): 398–401, 2006.

²² Elizabeth Pennisi, “DNA Study Forces Rethink of What It Means to Be a Gene,” *Science*, 316, (5831): 1556–1557, 2007.

²³ John A. Robertson, “The \$1,000 Genome: Ethical and Legal Issues in Whole Genome Sequencing of Individuals,” *The American Journal of Bioethics*, Vol 3, No. 3, 2003.

²⁴ Christopher Holman, Working Draft: “Will Gene Patents Derail the Next-Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not,” page 16, downloadable at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2001574.

Future multifactorial genotype-to-phenotype diagnostic associations, so the theory goes, again will require licenses to too many patents on individual sequences, thereby creating a cost barrier to access. If such patents are licensed exclusively, they on the one hand block needed future aggregation—because some of the markers are already exclusively licensed—and on the other, result in unneeded expense when testing a smaller subset of markers than the subset in the pre-packaged, presumably more costly test is medically indicated. A case study on Long QT syndrome and the Familion® test for channelopathies²⁵ reports that PGx Health initially aggregated markers for only five of the most common of the 12 known phenotypes, and did not add additional markers to Familion® until another company aggregated the markers for the omitted phenotypes exclusively, providing some competition. However, upon careful reading, this case study appears to suggest that there is more than one marker per phenotype.²⁶ In either case, both a possible market-motivated cross-license as well as the possible existence of multiple markers for the same phenotype appear to weaken the thicket concern. Contextual sequencing, and bioinformatic sampling approaches also may mitigate the thicket concern.²⁷ For example, a sample of interesting single nucleotide polymorphisms (SNPs) plus family or other context information may determine a clinically interesting haplotype.

Also moderating conjectured thickets, no new patents can issue on previously published genes or sequences. Thus, since the 2001 publication of the human genome sequence, future human nucleic acid sequence-containing patents will have to be on i) novel sequences, such as nongermline mutations associated with tumors, antibodies, or T-cell receptors, ii) new uses of the already-published sequences, which will require novel genotype-phenotype insights, iii) clinically important novel aggregations of sequences such as array or other multi loci tests, iv) novel constructs such as nucleic acid based vectors for drug delivery, v) rare and previously unknown genomic sequences that have a positive or negative effect on health, or vi) organisms other than humans, whose sequences have not been published. Note that patents which claim a clinically important aggregation of markers could be easy to design around, as any test that uses fewer, or substitute, markers will not infringe.

Another “patents impede access” argument is that widespread and routine use of modern laboratory equipment, such as a polymerase chain reaction machine, ensures that negligible commercial development is needed to find clinically actionable coding sequences in a clinical setting once those sequences have been published. Thus, the argument goes, since patents are not needed to incentivize development of clinical diagnostic tests, the standard for showing benefit should be

²⁵ Misha Angrist, Ph.D., Subhashini Chandrasekharan, Ph.D., Christopher Heaney, B.A., and Robert Cook-Deegan, M.D., “Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome,” *Genetics in Medicine*, Vol. 12, No. 4, April 2010 Supplement.

²⁶ This conjecture arises because the authors stop short of reporting a cross license, and the phenotypes tested for by both providers overlap. The number of phenotypes offered in the both panels is 10.

²⁷ See U.S. Patent Application No. US2010/0057374A1, “Genotype Calling.”

high, and the standard for showing harm should be low.²⁸ In this view, genomic diagnostic patents contrast with patents on pharmaceuticals or other biotech inventions that are putatively harder to discover and commercialize, but much easier to copy or engineer around without patent protection.²⁹

Theories About the Positive Influences of Patents

A rationale for believing that patents lead to improved patient access to diagnostic tests is that patents incentivize beneficial commercial development that, absent patent protection, might not have occurred. Commercial incentives could make such tests available more rapidly, or in a more convenient or accurate form, or with more medically useful clinical data correlating genotype to phenotype, thereby assuring more comprehensive insurance coverage, than otherwise would have occurred absent patents. Indeed, in an interview,³⁰ the legal scholar Arti Rai commented that the Becerra-Weldon bill “to amend title 35, United States Code, to prohibit the patenting of human genetic material”³¹ could hinder development of personalized medicine by removing incentives for research correlating phenotype with genotype, which is needed to develop therapeutics and necessary companion diagnostics.

Also, potentially supporting the “patents can foster access” proposition is evidence that a proprietary position is associated with biotech start-ups in general.³² The “diagnostics require little incentive and thus patents do little good and can impede patient access” generalization is called into question by the experience of Genomic Health, which spent roughly \$164 million to obtain FDA approval and insurance reimbursement coverage of its OncotypeDx test,³³ and ArcticDx, whose

founders and chief executive officer elected to raise little capital, but instead rely on “intellectual property assembly” to attract a strategic partner for MaculaRisk.^{34,35}

An additional theoretical reason for believing that patents do not impede access or that any impediment is moderate is that there are natural alternatives to nucleic acid detection of full protein coding sequences. These alternatives include: i) for infectious agents, host-produced antibodies to the pathogen³⁶ and detecting proteins or other surface markers such as polysaccharides characteristic of the pathogen; ii) detection of abnormal proteins made by an abnormal/mutated gene,³⁷ or antibodies raised in response to the abnormal protein, or using an antibody to characterize the quantity of protein expression,³⁸ itself a proxy for gene expression; iii) partial nucleic acid sequence detection; iv) detection of noncoding nucleic acid regions closely associated with the coding region of interest, such as SNPs; and v) detection of biomarkers associated with a disease process or condition, where biomarkers are not necessarily nucleic acid sequences.³⁹ Future methods also might include the measurement of epigenetic changes, such as DNA methylation patterns, that are associated with a medical condition.

Finally, 89 of 99 patents reported to cover the tests in the SACGHS-funded case studies have priority dates before publication of the human genome, suggesting that though the past is prologue, it is not dispositive. [See Genetics in Medicine Patent Priority Dates at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjpzm>.]

Evolution of Patent Law and Publication of the Human Genome

Just as the type of test, nucleic acid or protein-based, synthesized or purified from biological material, is to some degree a function of its historical context, so are patent claims. When a phenotypically important sequence is discovered, absent knowledge of the protein

²⁸ James P. Evans, “Putting Patients Before Patents,” *Genetics in Medicine*, Vol. 12, No. 4, April 2010 Supplement.

²⁹ Rebecca S. Eisenberg, “Why the Gene Patenting Controversy Persists,” *Academic Medicine*, Vol. 77, No. 12, December 2002.

³⁰ “An Audience with Arti Rai,” *Nature Reviews Drug Discovery*, Vol. 6, p. 264, April 2007. As a convenience, the full question and answer is copied here: “Will this Bill [Becerra Weldon] hinder personalized medicine? It certainly could. In addition to preventing patenting of nucleotide sequences per se, it also specifically prohibits patenting of associations of nucleotide sequence with particular conditions and as such probably covers diagnostic tests for determining subgroups of patients to whom a particular drug should be prescribed. Given that the US FDA has just come out with guidelines for the approval of pharmacogenomics-based medicines, there’s an interesting tension here. The FDA might argue that these tests could emerge without patent protection, and in a diagnostic-market context that might be the case. But in terms of the way therapeutics are currently discovered and developed there’s a need for these patents.”

³¹ H.R. 977, the “Genomic Research and Accessibility Act,” introduced Feb. 9, 2007.

³² *Nature Biotechnology*, 24: 31-39, 2006, figure 5; see *supra*, fn. 9.

³³ Oncotype Dx total operating expenses from 2001 to 2006 based on the 10-K SEC filing for 2006, item 6, page 45, <http://www.sec.gov/Archives/edgar/data/1131324/000095013407005979/f27728e10vk.htm>, and 10-K for 2005, item 6, p. 53, <http://www.sec.gov/Archives/edgar/data/1131324/000095013406005637/f18552e10vk.htm#110>. See also, slide 8, Session C3, Association of University Technology Managers (AUTM) 2010 Annual Meeting, “Understanding Incentives in

the Diagnostic Marketplace,” showing timing of insurance companies’ decisions to reimburse the product overlaid on a graph of product sales.

³⁴ Full quote: “The model is to demonstrate economic viability of our products, grow organically and ultimately to find a strategic partner. This relieves us of the necessity to go out and raise much money, allowing us to concentrate on growing our business. Our value is in the identification of medical opportunities, intellectual property assembly, clinical evaluation and test marketing. We recognize that our core strength is not mounting an expensive sales force. We prefer to leave that to a partner,” <http://biotuesdays.com/2009/12/15/in-conversation-with-dr-brent-zanke/>, accessed Feb. 28, 2012.

³⁵ <http://www.macularisk.com/home>, accessed Feb. 28 2012.

³⁶ Some of these antibodies may also be patented, and some may be patented at the time the patent referencing the nucleic acid sequence is filed by the owner of the patent on the nucleic acid sequence.

³⁷ Sara Simonetti, et al., “Detection of EGFR mutations with mutation-specific antibodies in stage IV non-small-cell lung cancer,” *Journal of Translational Medicine*, 2010 8:135.

³⁸ Zaina Sangale, Cynthia Prass, Amy Carlson, Eliso Tikishvili, Jorge Degrado, Jerry Lanchbury, Steven Stone, “A robust immunohistochemical assay for detecting PTEN expression in human tumors,” *Applied Immunohistochemistry & Molecular Morphology*, Vol. 19, No. 2, pp. 173-83, March 2011.

³⁹ Tay-Sachs is an example of a genetic disease which is diagnosed from an assay for the enzyme hexosaminidase.

for which it codes, sequence and protein and antibody to the protein claims may all be available. If the protein is characterized, and the sequence is not, then only sequence claims might be available, and vice versa. Furthermore, the order in which such claims issue is completely unpredictable. Some of the protein claims may be in the same patent family and owned by the same party as the nucleic acid sequence claims and some others may not.

Furthermore, the scope of a patent depends on the particular claim language based on the sequences disclosed in the patent specification (narrative that provides the basis for the claims) as well as evolving judicial guidance on patentable subject matter and claim interpretation. A patent may disclose specific sequences, yet the actual claims may broaden the scope to include other sequences with a certain percentage of homology, or modified sequences that hybridize to the disclosed sequences under certain defined conditions. On the other hand, recent judicial decisions have raised both the utility⁴⁰ and enablement⁴¹ bar with regard to patents, tending to limit claimable subject matter. Thus the issued patent might claim a broader set of sequences than is readily legally enforceable. The additional risk in interpreting patent claims is that the broader the reading, the more likely a claim would capture matter that was previously disclosed or claimed in other patents, and such “prior art” matter would therefore invalidate such a broad claim.

Following the *In re Fisher* decision and subsequent USPTO guidelines, sequences must have substantial, not only specific, utility, ruling out sequences used for tagging purposes alone. The *University of Rochester v. Searle* decision had the effect of drawing a distinction between the more predictive arts, generally speaking the physical sciences, and the less predictive arts, generally speaking biology, and requiring more experimental data to support patent claims, thus increasing the difficulty of generalizing the claims in the biological sciences beyond the disclosed examples. The *in re Fisher* decision and *University of Rochester v. Searle* decision, combined with the publication of the human genome cumulatively moderate the theoretical reasons for believing genomic patents impede access.

Method Claims and Bilski

Last year the Supreme Court in *Bilski v. Kappos* provided clarification for courts deciding the patentability of method claims in general.⁴² Since then, the U.S. Court of Appeals for the Federal Circuit (CAFC) has addressed the patentability of biomedical method claims based on *Bilski*.

In *Prometheus v. Mayo*,⁴³ the CAFC ruled favorably on method claims directed to a method of administering thiopurine drugs to certain autoimmune disease patients and measuring serum levels of the drug to determine whether the level was within the stated efficacious

⁴⁰ *In re Fisher*, U.S. Court of Appeals for the Federal Circuit, decided Sept. 7, 2005.

⁴¹ *University of Rochester v. G.D. Searle*, 358 F.3d 916 (Fed. Cir. 2004).

⁴² 130 S. Ct. 3218 (2010). The court found the *Bilski* method for hedging risk in commodities markets not to be patentable subject matter.

⁴³ <http://www.genomicslawreport.com/wp-content/uploads/2010/12/Prometheus-v.-May-FedCir-Remand.pdf>.

and nontoxic range. A second claim included the correlation step but did not explicitly include as part of the claim the step of administration of the drug. The CAFC found these to be methods of treatment as opposed to natural correlations and data-gathering steps. However, the U.S. Supreme Court on March 20, 2012, reversed the CAFC rulings, finding that the claimed methods did not constitute patentable subject matter.⁴⁴

The CAFC found in *Classen Immunotherapeutics v. Biogen IDEC*⁴⁵ that claims that do not put knowledge into practical use are unpatentable, such as those “directed to the abstract principle that variation in immunization schedules may have consequences for certain diseases”; whereas, they found patentable claims comparing immunization schedules and the occurrence of chronic disease and administering a vaccine on the lower risk schedule.

In the *Myriad* case, there were diagnostic method claims at issue in addition to the question of whether DNA could be patented. Using the same standards for patentability of method claims in these other cases, the CAFC found that methods of analyzing the sequence of a person’s BRCA1 gene and comparing it to sequences known to be associated with a higher risk of cancer are not patentable because they involve only abstract mental processes.⁴⁶ Thus, we can expect that issued diagnostic method claims that only involve abstract mental processes of comparison will no longer be held patentable by the courts. The Supreme Court may have the final say in the *Myriad* case but is not anticipated to overrule the court’s decision on the method claims.

Study Motive and Design

A first goal of the comparative study of DNA Patent licensing was to determine if the DNA Patent Database bioinformatic algorithm,⁴⁷ alone, or supplemented by expert curation, could identify NIH OTT patents, and by implication, patents in general, which cover commercially available genomic diagnostic tests, the putatively identifiable “gene patents,” or “gene diagnostic patents.” A second goal was to try to apply the epidemiological criteria⁴⁸ for causation to the topic of patents, li-

⁴⁴ *Mayo Collaborative Services v. Prometheus Laboratories Inc.*, U.S., No. 10-1150, 3/20/12.

⁴⁵ <http://www.cafc.uscourts.gov/images/stories/opinions-orders/06-1634-1649.pdf>.

⁴⁶ <http://www.cafc.uscourts.gov/images/stories/opinions-orders/10-1406.pdf>; Representative claim: Claim 1, U.S. Patent No. 5,710,001. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises gene comparing a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample, and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample, and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample [emphasis added].

⁴⁷ Patents found by a Boolean search algorithm. See <http://dnapatents.georgetown.edu/>; see *supra*, fn. 8.

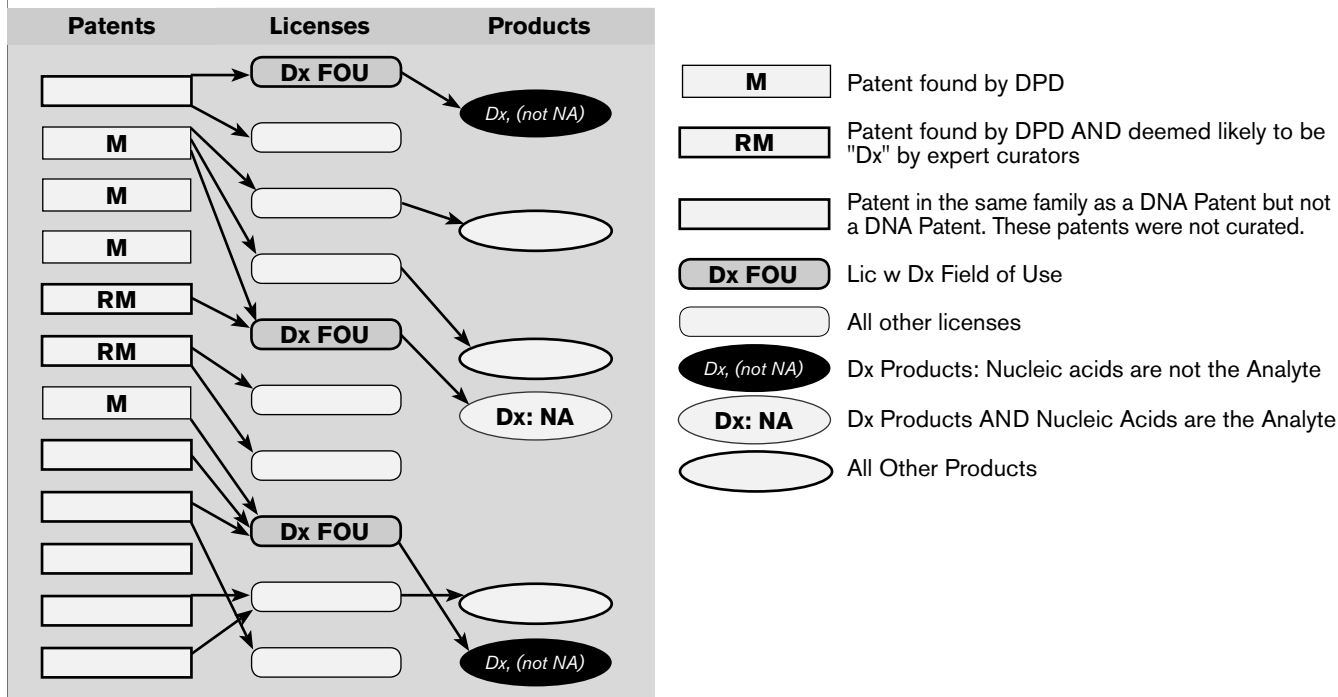
⁴⁸ Austin Bradford Hill, “The Environment and Disease: Association of Causation,” *Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

censes, and clinical diagnostic genomic tests. Can exclusivity in DNA Patent licensing be found to cause any effects?

As was done for the study of AI-managed DNA Patents, a relational database mapping NIH OTT-managed DNA Patents to licenses and products was created. See Figure 1.

tables and calculated metrics.] Figure 2, the ROC plot, illustrates the results. The bioinformatic algorithm alone is reasonably sensitive but extremely nonspecific. The false positive rate is high, and similar to the true positive rate. The refined marker—the patents selected by the expert curators—is more specific and associated with a lower false positive rate, but also is less sensitive

Figure 1
Relationships and Categories in the NIH OTT Relational Database



“DPD” means DNA Patent Database algorithm. “Dx” means “Diagnostic”. “FOU” means “Field of Use”. “M” stands for “marker” and identifies a patent found by the DPD. “RM” stands for “refined marker” and identifies a patent found by the DPD AND deemed likely to be Dx by the expert curators. The NIH OTT provided the license field of use and product categories.

A BNA Graphic/lsr06g1

As noted earlier, since the NIH OTT generally grants less exclusivity in its licenses than AIs do, such a comparison could be a revealing natural experiment on the effect of the scope of exclusivity in DNA Patent licenses.

Defining Meaningful Patent Taxonomies

If patents related to genomic diagnostic tests were clearly identifiable and distinct from those that are not, then licensing policies and statutes could be focused on these particular patents. The DNA Patent database (DPD) algorithm,⁴⁹ alone, and refined by expert curators,⁵⁰ was tested as a predictive classifier for patents that will be associated with genomic diagnostic tests. The field of use of the license for DNA Patents also was tested as a predictive classifier. [See Supplementary Tables S8A-G, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjld8>, and Supplement S9, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjldl>, for contingency

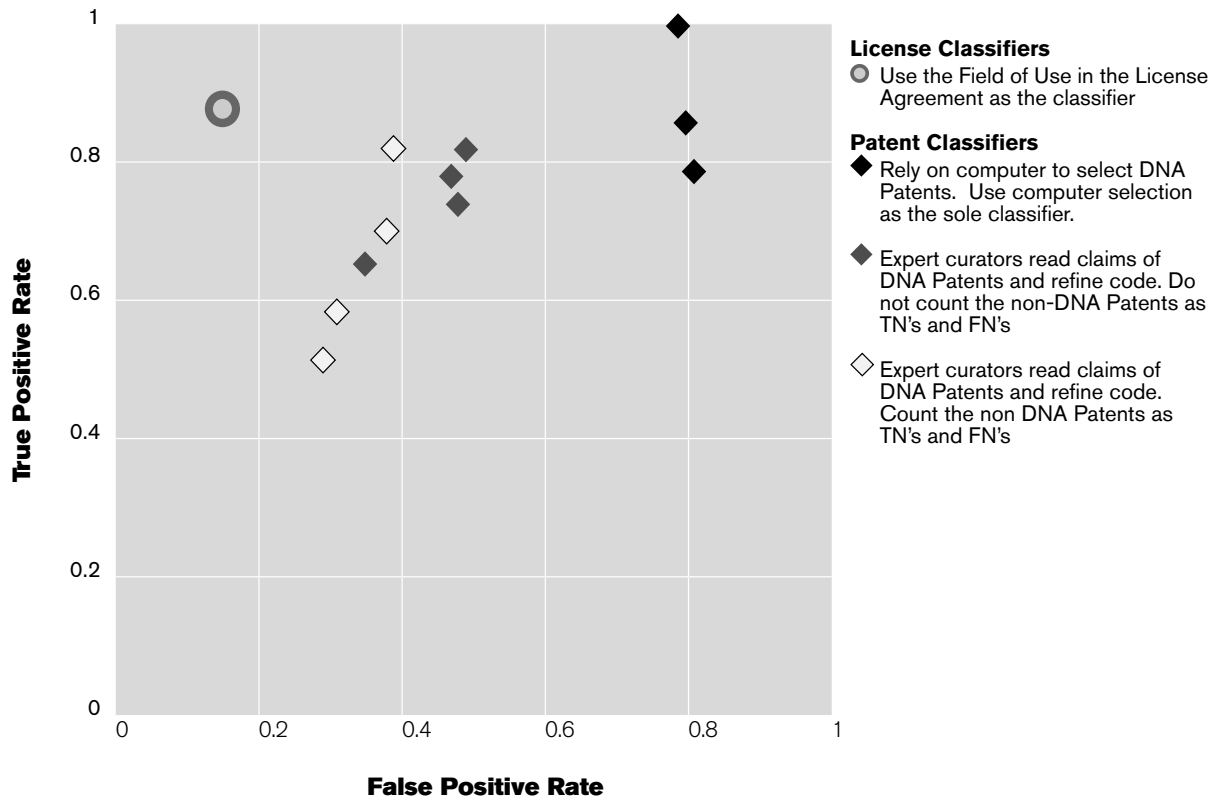
and has a lower true positive rate. NIH OTT-managed DNA Patents, even a subset selected by expert curators, do not map persuasively to genomic diagnostic products.

To underscore this point, the NIH OTT noted that it has many clinical diagnostic products⁵¹ that are not even in a family of a patent found by the DPD algorithm. Obviously, not all diagnostics are “genomic.” However, an expressed intent to develop a diagnostic product on the part of a potential licensee at the time of the license negotiation, and captured in the field of use of the license, is a far superior predictor of the character of the product than the patent alone (see green circle on ROC plot), suggesting that concerns about patient access should not be a big factor in adjudicating patent eligibility. If the license negotiation is the point in time with the most visibility on the character of the product, what can be observed and learned about licensing practices and their effect on commercial product availability?

⁴⁹ *Nature Biotechnology*, 24: 31-39, 2006; see *supra*, fn. 9.

⁵⁰ Dr. Subhashini Chandrasekharan and Dr. Carla Rydholm.

⁵¹ A biomarker need not be either a nucleic acid, or even a protein.

Figure 2**Test: "Does the patent/license cover a genomic diagnostic product: Y/N?"****ROC Plot**

A BNA Graphic/Isr06g2

Licensing Policy and Practice Contrast

The AIs and the NIH OTT operate under different legal frameworks: the Bayh-Dole Act⁵² for the AIs and the Stevenson-Wydler Technology Innovation Act⁵³ and the Federal Technology Transfer Act of 1986⁵⁴ for federal laboratories such as the NIH. Both approaches are consistent with each of their statutory frameworks and strive to optimize public benefits.

The licensing paradigm established by Bayh-Dole permits a high degree of autonomy on behalf of AIs making inventions with federal funding. Beyond a preference for small businesses in the United States, institutions can license in the manner that serves the overall Bayh-Dole objective.⁵⁵ AIs generally utilize the same in-

⁵² 35 U.S.C. § 35 200-212.

⁵³ Pub. L. No. 96-480.

⁵⁴ Pub. L. No. 99-502.

⁵⁵ 35 U.S.C. § 200: "It is the policy and objective of the Congress to use the patent system to promote the utilization of inventions arising from federally supported research or development; to encourage maximum participation of small business firms in federally supported research and development efforts; to promote collaboration between commercial concerns and nonprofit organizations, including universities; to ensure that inventions made by nonprofit organizations and small business firms are used in a manner to promote free competition and enterprise without unduly encumbering future research and discovery; to promote the commercialization and public availability of inventions made in the United States by United

stitutional framework even for inventions that are not made with federal funding and thus technically are not subject to Bayh-Dole.

The statutory framework⁵⁶ for Federal laboratories differs from that for AIs in that it adds an explicit pre-

States industry and labor; to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions; and to minimize the costs of administering policies in this area."

⁵⁶ 35 U.S.C. § 209(a) AUTHORITY.-A Federal agency may grant an exclusive or partially exclusive license on a federally owned invention under section 207(a)(2) only if-

(1) granting the license is a reasonable and necessary incentive to-

(A) call forth the investment capital and expenditures needed to bring the invention to practical application; or

(B) otherwise promote the invention's utilization by the public;

(2) the Federal agency finds that the public will be served by the granting of the license, as indicated by the applicant's intentions, plans, and ability to bring the invention to practical application or otherwise promote the invention's utilization by the public, and that the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public;

(3) the applicant makes a commitment to achieve practical application of the invention within a reasonable time, which

erence for non-exclusive licensing and a prior public notice-and-comment period before granting a license with exclusivity [See S1, for a glossary of license terms, including “exclusivity,” at <http://op.bna.com/hl.nsf/r?Open=rkun-8s189>]. NIH OTT policies reflect the statutory requirements: “NIH seeks to ensure that a licensee obtains the appropriate scope of rights necessary to develop a potential application of the technology. . . . This is accomplished through: Negotiating non-exclusive or co-exclusive licenses whenever possible . . . Negotiating and awarding exclusive licenses for specific indications or fields of use, . . . Negotiating provisions for mandatory sublicensing by exclusive licensees, particularly where a broad exclusive license is granted.”⁵⁷

Regarding 35 U.S.C. § 209, the NIH OTT policy statement acknowledges both the realities of commercial competition, and states its intent to provide incentives for technology development and transfer: “NIH recognizes that companies typically need an exclusive market position to offset the risk, time, and expense of developing biomedical diagnostic or therapeutic products, however, companies do not necessarily need to achieve that position by exclusively licensing a government technology used to develop that product. Instead, they frequently are able to add their own proprietary technologies to the technology licensed from the government to ultimately achieve some level of uniqueness and exclusivity for the final product.”⁵⁸

Als of course are not monolithic in their policies, though many, including 17 of 19 respondents to the AI Survey, have endorsed the Association of University Technology Managers’ Nine Points,⁵⁹ which echo NIH policy statements on moderating the scope of exclusivity, the need for a transferrable research use right, and the need for diligence in license agreements. As a whole, Als are more able to have their technology be the technology on which a business depends for initiation than the NIH OTT. Als can and do grant licenses to start-up companies and other companies that rely on the licensed technology, and not their own proprietary technology, to start a new company or develop a new product. The definition of “start-up” in the AUTM surveys states explicitly that the start-up is “dependent on licensing the institution’s technology for initiation.”⁶⁰

time may be extended by the agency upon the applicant’s request and the applicant’s demonstration that the refusal of such extension would be unreasonable;

(4) granting the license will not tend to substantially lessen competition or create or maintain a violation of the Federal antitrust laws; and

(5) in the case of an invention covered by a foreign patent application or patent, the interests of the Federal Government or United States industry in foreign commerce will be enhanced.

⁵⁷ http://www.ott.nih.gov/policy/pshlic_policy.aspx, accessed March 19, 2012.

⁵⁸ http://www.ott.nih.gov/policy/pshlic_policy.aspx, accessed March 12, 2012.

⁵⁹ Nine Points to Consider in Licensing University Technology, released March 6, 2007, AUTM, http://www.autm.net/Nine_Points_to_Consider.htm, accessed March 13, 2012.

⁶⁰ See, Instructions and Definitions of the AUTM Surveys: “**START-UP COMPANIES:** As used in this Survey, START-UP COMPANIES are companies that were dependent upon licensing the institution’s technology for initiation. If a technology was licensed to an existing start-up company, but not to a START-UP COMPANY (as defined here), this company should be counted as a SMALL COMPANY when responding to Ques-

tion 6.c, as opposed to a START-UP COMPANY. START-UP COMPANIES, as used in this Survey, will continue to refer only to those companies that were dependent upon your institution’s technology for initiation.

Unlike the NIH OTT, Als are able to grant licenses with exclusivity without having to advertise the opportunity or without a starting preference for non-exclusivity, and are able to assist in the formation of a company and hold equity in it. Since early business plans and products are less precisely characterized than more mature ones, if a company is less certain, what, exactly, it will make and sell, it may be easier for that company to negotiate a license of somewhat broader scope from an AI under Bayh-Dole than from the NIH OTT under Stephenson-Wydler and the Federal Technology Transfer Act.

Many Als make special efforts, via entrepreneurship centers, or specialized personnel,⁶¹ to form start-up companies, including in the diagnostics space. The NIH OTT has not sought to form start-up companies but has licensed to start-up companies founded by others. The NIH OTT recently launched an experimental initiative whereby it will encourage and expedite the grant of licenses with exclusivity to start-ups, but at this time only for “vaccines, drugs and therapeutics to prevent or treat disease in humans.”⁶² Als can and sometimes do take equity in start-ups in partial consideration for patent license rights. The NIH OTT does not take equity in partial consideration for patent license rights, though it has linked fees to liquidity events as found in the new program for licensing to start-ups.

Als can and do grant exclusive options to patents. The NIH OTT grants roughly the AI equivalent of non-exclusive options, which are called “Commercial Evaluation Licenses.”⁶³ These contracts are reported as a type of license contract on the NIH OTT website. While these licenses have only been non-exclusive in the past, including the period of this study, the new start-up license program will grant exclusive options for one year to start-up companies.⁶⁴

There are no exclusive all-field-of-uses licenses to NIH OTT managed patents. However, the NIH has granted licenses on an exclusive basis for FDA-approved diagnostic kits, but not for genomic diagnostic services under patents it solely owns or jointly owns and has the lead licensing.⁶⁵ The NIH OTT also negotiates a type of license contract, a Commercial Internal Use License (CIU) which corresponds generally to what

tion 6.c, as opposed to a START-UP COMPANY. START-UP COMPANIES, as used in this Survey, will continue to refer only to those companies that were dependent upon your institution’s technology for initiation.

⁶¹ For example: Centers: The MIT Deshpande Center for Technological Innovation, USC Stevens Institute for Innovation. Personnel, position titles: Ms. Renuka Babu, Director of Business Development for New Ventures, Office of Technology Development (OTD), Boston University; Michael Poisel, UPSTART Program Director, Center for Technology Transfer, University of Pennsylvania.

⁶² <http://www.ott.nih.gov/startup/default.aspx>, accessed Sept. 20, 2011.

⁶³ An AI would call a “Commercial Evaluation Use” license an option. These are reported in AUTM Surveys, but were explicitly excluded from the prior AI survey; see *supra*, fn. 9.

⁶⁴ Under the new experimental initiative, the NIH will grant exclusive options to start-ups. See <http://www.ott.nih.gov/startup>

⁶⁵ The NIH OTT granted an exclusive license to the University of Utah and Myriad Genetics to settle an inventorship dispute for an application previously filed by Utah and Myriad, but settlement-interference agreements were not included in this study.

AIs call a Materials Transfer Agreement (MTA) when materials and patent rights are licensed.⁶⁶ Roughly half of NIH OTT's CIUs are for materials alone. For patent rights alone, AIs might use an Internal Research License. For materials alone, NIH uses a Biological Material License Agreement-Internal Use.⁶⁷ Neither MTAs nor Internal Research Licenses are reported as a license in the AUTM Survey, nor were they in the AI questionnaire.⁶⁸ Sometimes the right to internal use is transferred explicitly by AIs in a clause in a sponsored research agreement, and thus is also not counted separately. In contrast, the NIH OTT reports CIUs as a type of license and they have been counted as licenses in government reports.⁶⁹

Both the NIH and AIs historically have reserved the rights to their own inventions to practice for their own internal research purposes. NIH has a long history of reserving the right to grant internal use research licenses to for-profit and nonprofit entities even when a technology is otherwise licensed exclusively. Though comprehensive data are lacking, AIs also reserve transferable research-use rights. "We accumulated evidence of a strong and expanding retained and transferable research-use right, even within exclusive, all-fields-of-use licenses. The 19 respondent AIs retain research use rights themselves and insist on the right to transfer these research-use rights to other nonprofit institutions."⁷⁰

The NIH OTT maintains a monitoring group of specialized personnel to identify commercial products that utilize technologies claimed in NIH- and FDA-owned patents and, if the commercial party does not have a license from the NIH OTT, to encourage them to obtain a license. These contracts are called "Settlement Agreements," and coded as such. There is no known or documented parallel effort at AIs to license companies after product sales have begun.

Results: NIH Data Obtained, and Its Comparability to Prior AI Data

The two studies, the one conducted on NIH OTT-managed DNA Patents, and the earlier study on AI-managed DNA Patents, both selected patents objectively, using the same computer algorithm, and gathered reasonably comparable license data for DNA Patents licensed one to nine times, and created a relational database mapping patents to licenses and licenses to products. See Table 1. [An expanded version of Table 1 is Supplementary Table S2, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjl9x>.] The data are not comparable for patents licensed more than nine times, as the AI study, for practical reasons, asked re-

⁶⁶ MTAs, by definition, always involve the transfer of materials along with a license. About half of CIU licenses from NIH do not involve material transfers and some materials are transferred to companies under MTAs without explicit license rights.

⁶⁷ www.ott.nih.gov/pdfs/PHS-Biological-Materials-Agreement-License-Internal-Use-model-102005.pdf.

⁶⁸ *Nature Biotechnology* 24: 31-39, 2006; see *supra*, fn. 9.

⁶⁹ Government Accountability Office, "Technology Transfer: Number and Characteristics of Inventions Licensed by Six Federal Agencies," GAO-RCED-99-173, pp. 28, 29 (1999); 200 of 990 NIH licenses granted through Oct. 1, 1998, are characterized as "exclusive," and 87 of 607 NIH licenses granted for fiscal years 1996-1998 are characterized as "exclusive."

⁷⁰ *Nature Biotechnology* 24: 35, 2006; see *supra*, fn. 9.

spondents for aggregate data only for patents licensed more than nine times, while the NIH provided data on every license for patents licensed more than nine times. Patents licensed very often constitute an expected group of outliers, as "skew," or slant in the data, is a well known phenomenon in patent licensing⁷¹ and other economic sets.⁷² A well-known example of an outlier in commercial AI patent licensing is the set of 400-plus licenses to the Cohen-Boyer family of patents, and a well known example of an outlier in NIH commercial patent licensing is the group of roughly 40 commercial licenses to the Gallo-Montaigner HIV-related patents.

The imperfect comparability of the data also is due to database design, itself reflecting organizational priorities. For example, the NIH OTT keeps far more detailed data on contract type, exclusivity, and field of use than AIs do. On the other hand, AIs generally distinguish, in their databases, between start-ups, small entities, and large entities, whereas over the time of the study the NIH OTT tracked only small and large entities.

Exclusivity Practice Contrast

Since exclusivity practice is so often a focus of interest, the data were analyzed carefully for the most comparable contract types. [See Supplementary Tables S3A, S3B, S3C, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjl9a>.]

While there is no doubt that the NIH on the whole grants fewer licenses with exclusivity to DNA Patents than AIs do, the exclusivity practice as a whole is more similar than previously has been appreciated. There are two basic reasons for the misconception. First, the AUTM Survey respondents have long lumped exclusive by-field-of-use licenses⁷³ in with exclusive all-field-of-use licenses, thereby hiding their own existing nuanced exclusivity practice. Second, when giving a summary snapshot of NIH exclusivity practice, the NIH,⁷⁴ and others,⁷⁵ counted some contract types the AIs do not count, the Patent Internal Use contract type, for example, which is roughly the equivalent of a university MTA when materials are transferred along with patent

⁷¹ F.M. Scherer and Dietmar Harhoff, "Technology policy for a world of skew-distributed outcomes," *Research Policy*, Vol. 29 (2000), 559-566.

⁷² Herbert A. Simon and Charles P. Bonini, "The Size Distribution of Business Firms," *The American Economic Review*, Vol 48. No. 4, pp. 607-617, September 1958.

⁷³ Definition of Exclusive License from FY 2000 AUTM Survey Instructions and Definitions: **EXCLUSIVE LICENSE:** The assignment of a license as exclusive or non-exclusive should adhere to the terms of the license agreement. If a license is designated as exclusive in the license agreement, it should be assigned to exclusive licenses under this Survey, *including licenses that are designated as exclusive by field of use, territory, or otherwise.* (See Questions 6.b and 6.d.) [emphasis added].

⁷⁴ Claire T. Driscoll, "Genomic Inventions: Evolving NIH Patent & Licensing Policies and Practices in the Post-Human Genome Project Era," ACMD Conference, Nashville, March 22, 2007, Slide 12: ">80% of Licenses are Non-Exclusive (note: this is exactly the opposite of what happens in academia)."

⁷⁵ Government Accountability Office, "Technology Transfer: Number and Characteristics of Inventions Licensed by Six Federal Agencies," GAO-RCED-99-173, pp. 28, 29 (1999). Two-hundred of 990 NIH licenses granted through Oct. 1, 1998, are characterized as "exclusive." Eighty-seven of 607 NIH licenses granted for fiscal years 1996-1998 are characterized as "exclusive."

Table 1
Data on NIH OTT licensing of DNA Patents and its comparability to prior AI data

Data	Academic Institution Study	NIH OTT Study
Initial Study Group of Patents	DNA Patents found by the DNA Patent Database Algorithm managed by 19 Academic Institutions*. 17 responded completely, 2 partially, out of 30 invited.	DNA Patents found by the DNA Patent Database Algorithm managed by the NIH OTT
Issue Dates of Patents	11/23/1971 - 1/14/2003	11/16/1976- 8/14/2007
Effective Dates of Licenses	FY 1981-FY2003	2/24/1982 - 9/11/2007
Date of Response	2003, some policy responses received 2004	Fall 2007 –Spring 2010
Licensing Frequency Information	Yes , for approximately 2600 distinct patents.	Yes , for 585 patents found by the DPD algorithm, <i>and also for 118 others in the same patent family</i>
Data on patents in the same family as a DNA Patent, but not DNA Patents	No	Yes
Structure and Format of Data	Relational Database for 2600 patents licensed 1-9 times. <i>Separate questionnaire for patents licensed >9 times. Detailed license data, including company type, start-up, small entity, large entity, for 179 license agreements to 487 distinct patents representative, by age of patent. of patents licensed 1-9 times. Aggregate data for 21 patent families (48 patents) licensed >9 times</i>	Relational Database for 585 DNA based patents plus 118 other patents. <i>Same form of data for patents licensed 1-9 times as for those licensed > 9 times. Detailed license data for all patents and licenses, including on product types, but no systematic data on company type (start-up, small entity, large entity).</i>
Types of Agreements about which there is information	Commercial Patent License	Commercial Patent License Biological Material Commercial Settlement Infringement Patent License Internal Use Biological Material Internal Use Settlement Interference Commercial Evaluation
Exclusivity Information	<i>Sample of 179 Agreements for patents licensed 1-9 times, aggregate only for patents licensed >9 times</i>	<i>Every license agreement</i>
Field of Use Information	<i>No, except by implication that there is a Field of Use for licenses "Exclusive, by Field of Use"</i>	<i>Yes, including "Diagnostic Sales", "Therapeutic Sales" and "Materials Sales".</i>
Timing of License Execution, Product Sales, and License Termination	Yes for Agreements to patents licensed 1-9 times. Less complete for those patents licensed > 9 times	Yes
Information on the Types of Products	No. Can try to infer from patent titles	Yes, as implied from the License Field of Use. For diagnostics, whether a nucleic acid is the analyte.
Diligence Information	Yes	No
Revenue Information	Some	No
Answer to "were there competing interested parties at the time the license was signed?"	<i>Yes, for the Agreements to patents licensed 1-9 times.</i>	No
<p>Bold marks data found in both studies <i>Italic marks data found only in one study</i></p> <p>*Harvard University, California Institute of Technology, Cornell University, Massachusetts Institute of Technology, University of Pennsylvania, Rockefeller University, Stanford University, University of Chicago, University of Florida, University of Michigan, Wisconsin Alumni Research Foundation, Columbia University, the Salk Institute, the Research Foundation of the State of New York, University of California, University of Utah, Washington University at Saint Louis, Yale University, the Whitehead Institute.</p>		

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rights. Since these licenses typically are non-exclusive at the NIH OTT, they contribute to the higher proportion of non-exclusive licenses reported by the NIH relative to AIs. Comprehensive data are readily available on the NIH OTT website,⁷⁶ but are not always fully appreciated.

Nonetheless, the NIH OTT clearly is more cautious, by statute and policy, in granting exclusivity than the AIs. A key difference is that the NIH OTT grants no exclusive, all-field-of-use commercial licenses to its patents, and often modulates the field of use even in its commercial non-exclusive licenses. The practice of granting non-exclusive licenses by field of use cleverly preserves the possibility of granting broader exclusivity when warranted and merits increased attention. For example, NIH has granted exclusive licenses limited to FDA-approved test kits for a few protein-based assays but has retained the right to grant non-exclusive licenses for laboratory testing services.

When AI DNA Patents licensed more than nine times are included, even including all *but* Cohen-Boyer (as a special case of an outlier among outliers), the rates of exclusivity become more similar. When AI licenses to start-ups are omitted (as potentially creating a noncomparable set, since the NIH OTT, unlike AIs, does not use patent licenses to catalyze its own start-up formation), the rates of exclusivity become still more similar. This is an important analysis as the NIH OTT did not, until very recently, make special efforts to start companies based on licensed technology, and these activities generally are regarded as a plus for society.

Quantitatively, 20 percent to 25 percent of NIH OTT licenses to DNA Patents have some exclusivity and none has complete exclusivity. Between a third and a half of AI licenses to DNA Patents have some exclusivity,⁷⁷ and, in noticeable contrast to the NIH OTT practice, between 13 percent and 36 percent of AI licenses to DNA Patents are exclusive, all fields of use. The 13 percent results when start-ups are omitted and all the “outlier” type of licenses are included, including Cohen Boyer. The 36 percent results when licenses to start-ups are included and all licenses to patents licensed more than nine times are omitted.

Finally, when exclusive is defined as any exclusivity at all, including “Exclusive, By Field of Use,” indeed most AI licenses are “exclusive.” On the other hand, if non-exclusive were to include any non-exclusivity at all (defined as any license which is not 100 percent exclusive), then most AI licenses, like NIH licenses, would be “non-exclusive.”⁷⁸

License Outcome Contrast

More AI-managed DNA Patents have been licensed—about 70 percent relative to NIH OTT-managed DNA

Patents—about 52 percent.⁷⁹ See Figure 3. About 3.1 percent (18 out of 585) of NIH OTT patents are or were licensed more than nine times, whereas only 1.7 percent (45 out of 2607) of AI-managed patents are or were licensed more than nine times.

How many licenses can be associated with earned royalty-generating products? For reasons discussed in the section on exclusivity contrast, a comparison of the fraction of licenses associated with such products is problematic. Twenty-four percent of the NIH licenses to patents licensed one to nine times are or were associated with earned royalty-generating products (84/355). Seventeen percent of the representative sample of AI licenses to patents licensed one to nine times are or were associated with earned royalty-generating products (31/179).

Forty-eight percent of the NIH OTT licenses to patents licensed more than nine times are or were associated with earned royalty-generating products (79/169). Undoubtedly, many of the 961 licenses of AI patents licensed more than nine times also are or were associated with such products, but data are lacking. Obviously, calculating a percent of all AI licenses that are or were associated with earned royalty-generating products depends on how many of the licenses associated with patents licensed more than nine times are added in, and whether Cohen-Boyer, an outlier among outliers, is included.⁸⁰ Depending on the assumption, AI licenses look either more, or less, likely to be associated with earned royalty-generating products than NIH OTT licenses. On average, 31 percent of the NIH OTT licenses to DNA Patents they manage are or were associated with such products (162/524). Note that products sold by sublicensees are not captured, which could increase the overall tally of AI-associated products more than the tally of NIH-associated products. This is so because the right to grant sublicenses—which is a negotiated term in license agreements—generally is given only to licensees with exclusivity, and not given to non-exclusive licensees.

Having more licenses that are or were associated with earned royalty-generating products does not automatically translate into more current sources of product. Figures 4A, 4B, and 4C, a mini-case study of the licensing of the Gallo-Montaigner sextet⁸¹ of patents, illustrates this phenomenon. Note that only one of the six,⁸² the last to issue, references nucleic acid se-

⁷⁹ Included in the NIH OTT licenses are Patent Commercial, Biological Material Commercial, Patent Commercial/Settlement, and Settlement-Infringement. Not included are the Patent Internal Use, Biological Material Internal Use, Commercial Evaluation, and Settlement-Interference.

⁸⁰ Seventeen percent of licenses to patents licensed one to nine times are or were associated with products. Thus, one would expect 203 licenses of the total 1176 licenses to patents licensed one to nine times to be or have been associated with products. There were 964 total licensed to patents licensed more than nine times, of which 461 were for the Cohen-Boyer technology. Thus, the AI fraction of licenses that are or were associated with products is highly dependent on how the licenses to patents licensed more than nine times are counted. Example: $(203 + (400)) \div (1176 + 961) = 29$ percent, etc.

⁸¹ Patent Nos. US4708818, US5135864, US6395495, US6428952, US6600023, US6627395.

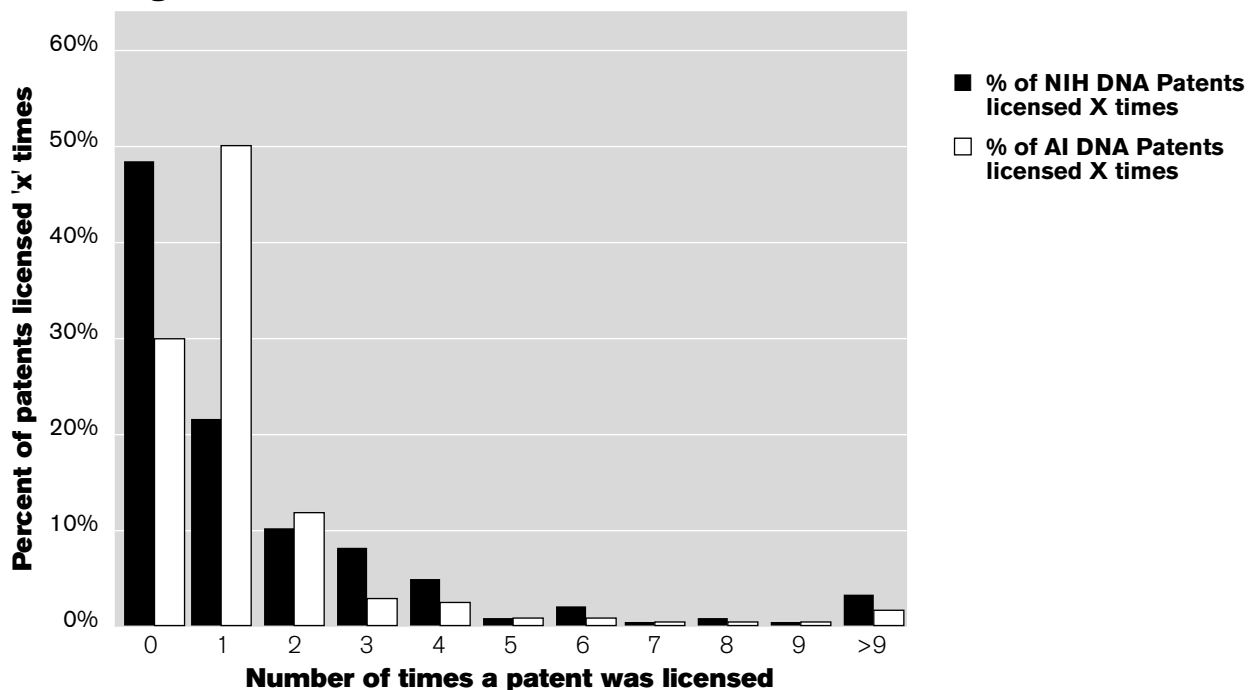
⁸² Patent No. US6627395, Methods for the propagation, isolation, identification, and preparation of human immunodeficiency virus type 1 (HIV-1).

⁷⁶ http://www.ott.nih.gov/about_nih/statistics.aspx, accessed Sept. 12, 2011.

⁷⁷ Depending on whether the 461 nonexclusive Cohen-Boyer licenses are counted, and depending on whether licenses to start-ups are counted.

⁷⁸ Between 75 percent and 87 percent of AI licenses to DNA Patents are not completely exclusive, depending again on whether start-ups are included (as potentially creating a non-comparable set, since the NIH does not engage in start-up formation), and patents licensed more than nine times are included, and whether the 461 licenses to the Cohen-Boyer technology is subtracted out as a special case.

Figure 3
A comparison of the licensing frequency of AI and NIH
OTT managed DNA Patents



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quences in the claims, the other five earlier-to-issue patents do not. The figures are anchored to the earliest priority date of the first to issue, as a proxy for “invention.” The timelines show that not all licenses remain active, and not all active licenses remain associated with earned royalty-generating products. Of the 15 licenses associated with such products in the fall of 2007,⁸³ figure 4C, nine were settlement agreements. Ten of the 15 in effect at the time the data were received were characterized as covering “diagnostic” products and for only two of these products is a nucleic acid the analyte.

One of the arguments favoring exclusivity in license agreements is that these contracts contain more diligence—more requirements to actually commercialize, and keep commercializing—the licensed technology in order to maintain the scope of rights initially granted. Diligence also can include provisions aimed at patient care, such as a contractual requirement to publish data or to permit confirmatory testing by a provider other than the licensee. A much higher percentage of NIH licenses to DNA Patents terminate unforeseeably⁸⁴ overall relative to AI licenses, roughly 70 percent to 30 percent. [See Supplementary Tables S4A and S4B, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjlav>, and Figure 5.] This can be explained two ways. One explanation is that greater license retention is emblematic of a greater commitment to commercialize on the part of AI

⁸³ Date of license data collection.

⁸⁴ For AIs, “unforeseeably” means for reasons other than patent expiration. For the NIH OTT, “unforeseeably” means for reasons other than patent expiration, or a time limited license at the time the license became effective.

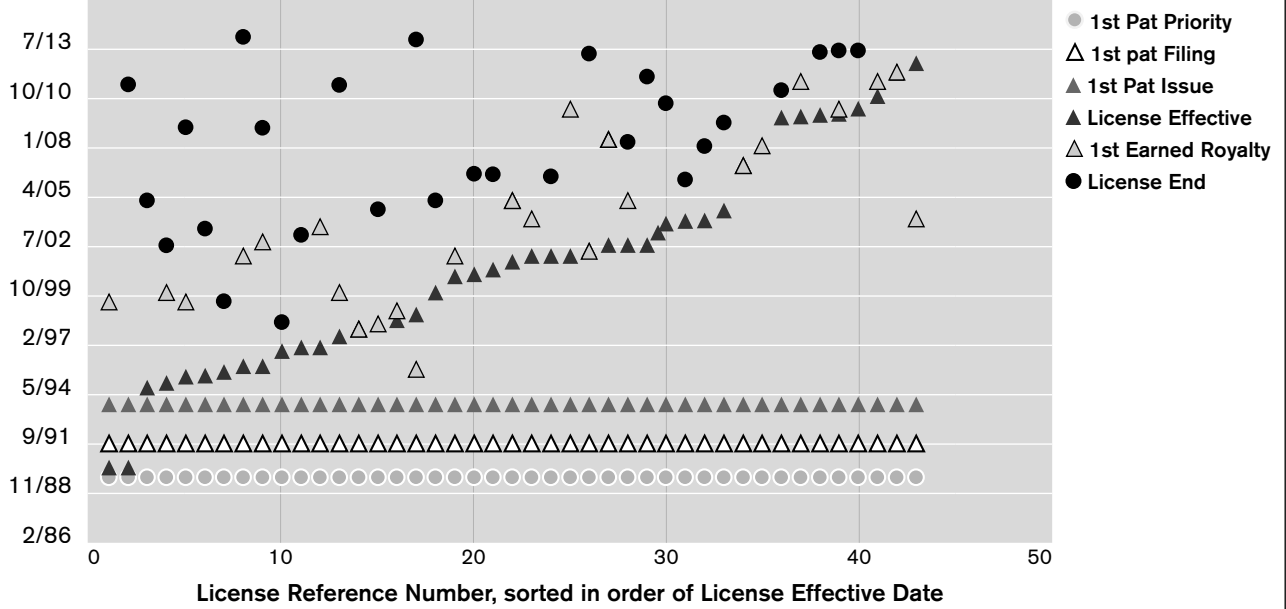
licensees. Another explanation is that AI licensors write less strong diligence provisions and/or enforce their diligence provisions less well.

As might be expected, markedly more licenses associated with products remain active than those that are not associated with products, at both the NIH and the AIs. Considering only licenses to patents licensed one to nine times: 13 percent of AI licenses associated with products ended unforeseeably, whereas 30 percent of the AI licenses not associated with products ended unforeseeably. Showing a similar effect, 31 percent of NIH licenses associated with products ended unforeseeably, and 69 percent percent of NIH licenses not associated with products ended unforeseeably. See Figure 5.

More exclusivity may translate into more pre-patent expiration termination at AIs, though the effect is modest and the number of data points is small, possibly providing evidence for the effect of diligence. At the AIs, 28 percent (12 of 43) of non-exclusive licenses without products are “returned” to the institution before patent expiration, and 35 percent (32 of 92) of licenses with exclusivity (by field of use or all fields of use) are returned before patent expiration. At the NIH however, considering only licenses without products, 69 percent both with (54 of 78) and without (86 of 124) exclusivity are returned, which is harder to interpret. [See Supplementary Figure S5, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjlbn>.]

Another argument favoring exclusivity is that incentivized licensees work faster. The Bradford-Hill criteria supporting causation teach that the putative cause must precede the effect. To investigate time effects, four dates per license agreement were analyzed: 1) the patent priority date of the oldest patent in the license, a

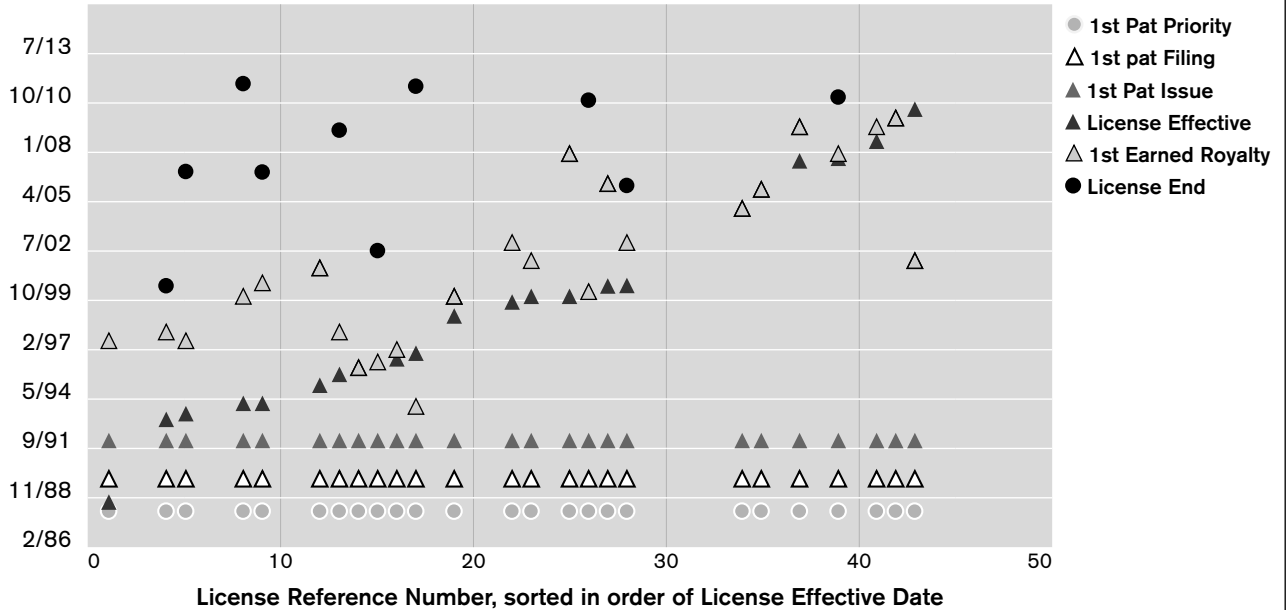
Figure 4A
Timelines for 43 license contracts to the Gallo-Montagnier sextet of HIV related patents



All license data received in September 2007. All product data received in April 2010, but required to be accurate as of September 2007.

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Figure 4B
Timelines for the 25 license contracts to the Gallo-Montagnier sextet of HIV related patents which ever paid an earned royalty on a product sale



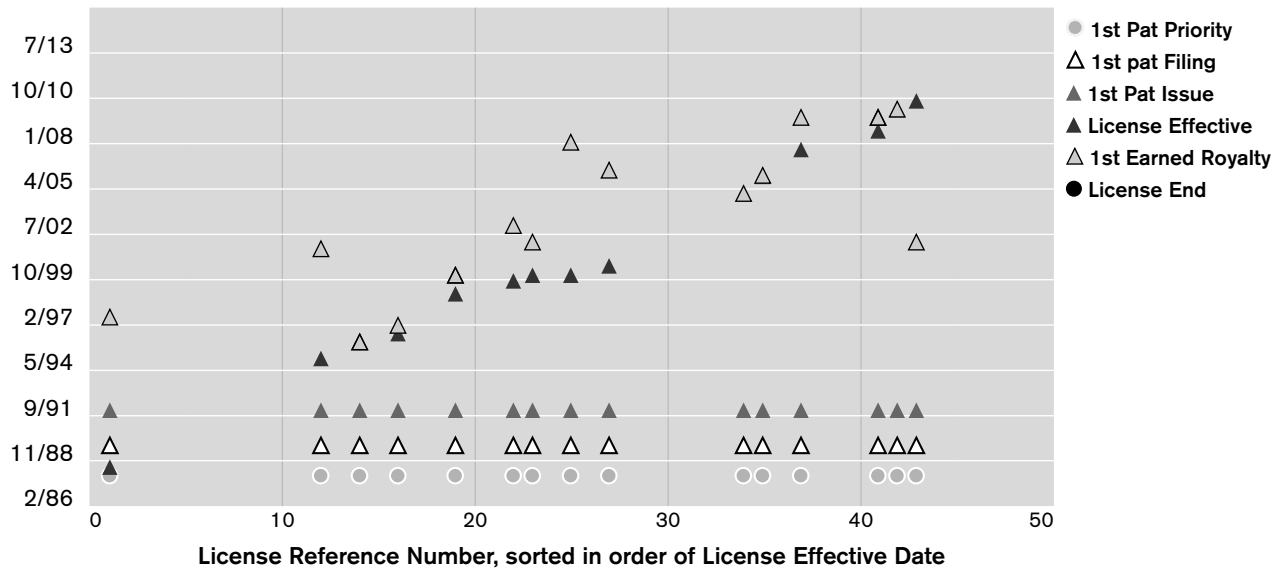
All license data received in September 2007. All product data received in April 2010, but required to be accurate as of September 2007.

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reasonable proxy for invention publication in the bio-tech sector; 2) the earliest patent publication date of the

oldest patent in the license, which is the unambiguous date the invention was published; 3) the date recorded

Figure 4C
Timelines for the 15 license contracts to the Gallo-Montagnier sextet of HIV related patents which ever paid an earned royalty on a product sale, and remain active licenses
9 of the 15 are settlement agreements



All license data received in September 2007. All product data received in April 2010, but required to be accurate as of September 2007.

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as the “License Effective Date,” which for nonsettlement agreements⁸⁵ is often the date the license was signed; and 4) the date the first earned royalties on product sales were received, which is expected, for nonsettlement agreements, to be close to the time the commercial products were sold.

Considering the most comparable groups of licenses, the nonsettlement agreements to patents licensed 1-9 times: timeline analysis [Supplementary Tables S7A and S7B, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjlcl>, and Figure 6A below] may suggest that the process proceeds more quickly overall at the AIs than at the NIH OTT. Note that the points in the figure are the median values in small data sets with large distributions. The graph of median values comparing overall AI and NIH OTT timelines suggests that the process overall proceeds somewhat more rapidly at the AIs than at the NIH OTT ($P=.052$, Fisher’s exact test comparing ≥ 4.5 years to < 4.5 years elapsed time between earliest patent priority date and a reported product sale⁸⁶). However, a statistically significant difference in overall timelines by exclusivity within the AIs ($P=.71$, Fisher’s exact test comparing ≥ 4 years to < 4 years elapsed time between earliest patent priority date and a reported sale⁸⁷) and within the NIH OTT ($P=.43$, Fisher’s exact test comparing ≥ 5 years to < 5 years elapsed time between earliest patent priority date and a reported

sale⁸⁸) was not observed. The null hypothesis can not be ruled out as an explanation.

Figure 6A shows that the median effective date of the licenses with exclusivity precedes receipt of earned royalties (proxy for commercial product sales) at both the AIs and at the NIH. Note the double-sided arrows on Figure 6A. Figure 6A therefore suggests that licenses with exclusivity tend to be executed before product introduction, while non-exclusive licenses are “just in time” licenses, entered into essentially at the same time as product introduction. Licensing before product introduction is more consistent with incentive creation than “just in time” licensing. This result is found to be statistically significant at the AIs ($P=.0007$, Fisher’s exact test, comparing ≥ 1 year to < 1 year elapsed time between the license effective date and a reported product sale⁸⁹), and falls short of statistical significance at the NIH OTT ($P=.15$, Fisher’s exact test comparing ≥ 1 year to < 1 year elapsed time between the license effective date and a reported product sale⁹⁰).

The only groups of licenses with product characterization are the NIH OTT licenses. Figure 6B [See Supplementary Tables S6A, S6B, S6C, at <http://op.bna.com/hl.nsf/r?Open=rkun-8sjlc6>, for the raw data] shows that diagnostics take longer to develop commercially than reagents ($P=.054$, Fisher’s exact test, comparing ≥ 7 years to < 7 years elapsed time between the license effective date and a reported product

⁸⁵ In settlement agreements, the parties may decide to back date the license to capture past sales, and then record a first royalty upon receipt of payment, which occurs significantly after the product was first sold.

⁸⁶ There is a 5.2 percent probability the effect is by chance.

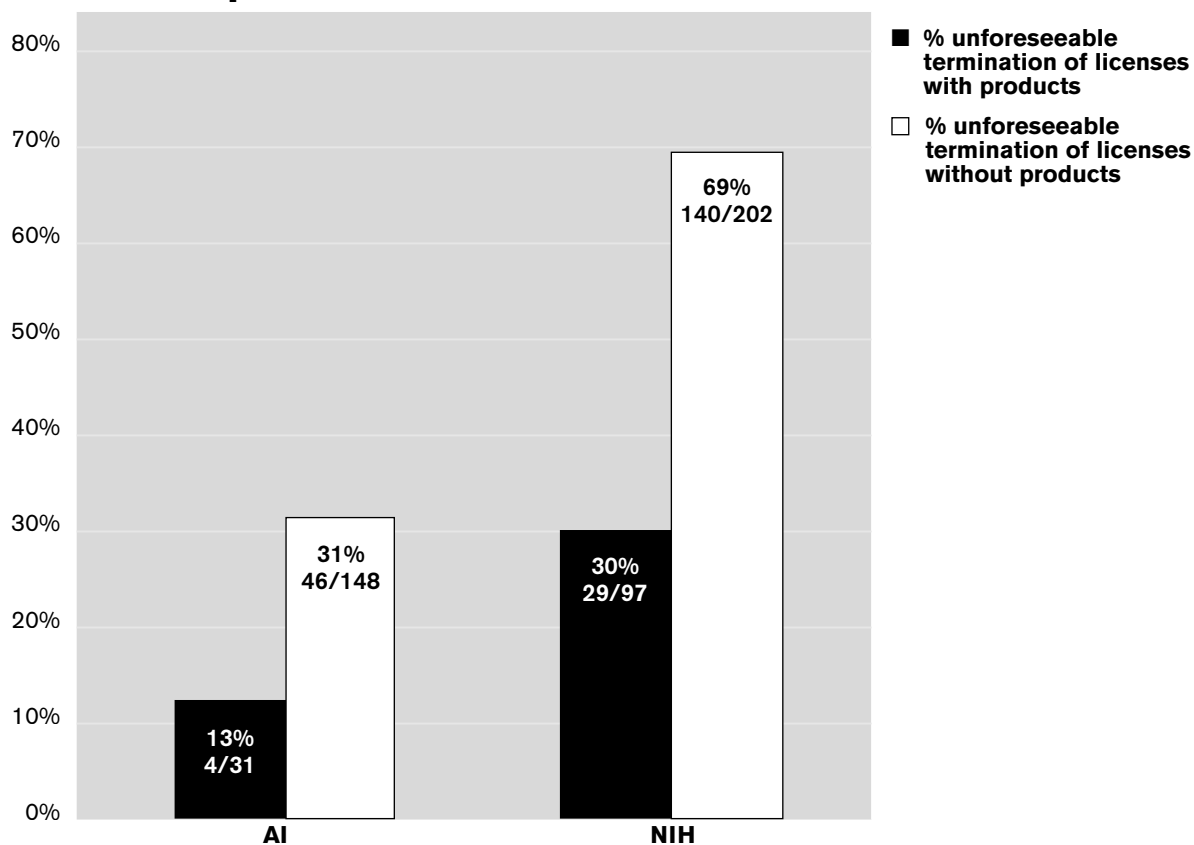
⁸⁷ There is a 71 percent probability the effect is by chance.

⁸⁸ There is a 43 percent probability the effect is by chance.

⁸⁹ There is a .07 percent probability the effect is by chance.

⁹⁰ There is a 15 percent probability the effect is by chance.

Figure 5
Comparison of unforeseeable license termination for licenses with and without products



- Unforeseeable termination for AIs means the license ended for a reason other than patent expiration.
- Unforeseeable termination for the NIH means that the license ended for a reason other than patent expiration or a time limit in the license itself.

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sale⁹¹). This result is considered statistically significant. Figure 6B also suggests that introducing a diagnostic product where the analyte is a nucleic acid may require more time than introducing one where a nucleic acid is not the analyte, however, this time difference is not statistically significant ($P = .214$, Fisher's exact test, comparing ≥ 9 years to < 9 years elapsed time between the license effective date and a reported product sale⁹²). It is notable that of all the 162 products identified by the NIH OTT, only eight were coded "therapeutic," and two of these also were coded "diagnostic." One interpretation is that DNA Patents are indeed mostly associated with diagnostics and reagents, and not with therapeutics, at least at the NIH OTT as of fall 2007.⁹³ The length of the timelines, roughly five years for reagents, and seven to nine years for diagnostics, provides support for that hypothesis, as they are shorter than one might ex-

pect based on the literature⁹⁴ and conventional wisdom for therapeutics. Another possible interpretation is that the NIH OTT's reputation for being chary with exclusivity has discouraged development of more therapeutics based in part on DNA Patents.

It is intriguing, yet perhaps not unexpected, that the overall product development timelines are shortest for reagents, a little longer for diagnostics where a nucleic acid is not the analyte, and longest for diagnostics where a nucleic acid is the analyte, and that this pattern repeats, albeit with longer times overall for settlement agreements. This suggests that making and selling a diagnostic is harder and takes longer than selling a reagent, and that there may be a greater delay associated with selling a diagnostic where a nucleic acid is the analyte, at least during the time period of this study. Table 2 below shows that for the most part, diagnostics for infectious diseases do require FDA approval and do not

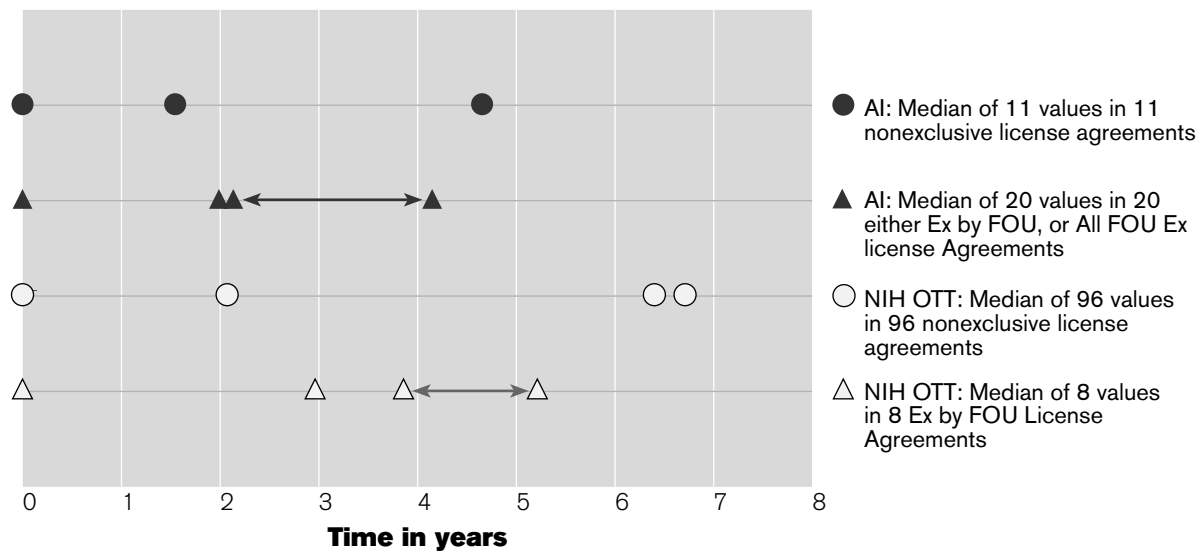
⁹¹ There is a 5.4 percent probability the effect is by chance.

⁹² There is a 21 percent probability the effect is by chance.

⁹³ NIH data were received in 2010 but pertain to licenses negotiated and products that became commercially available at the end of 2007.

⁹⁴ Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg, and Aaron L. Schacht, "How to improve R&D productivity: the pharmaceutical industry's grand challenge," *Nature Reviews Drug Discovery*, Vol. 9, March 2010, pp. 203-214.

Figure 6A
Timelines for AI and NIH OTT Products, associated with licenses with, and without exclusivity



Left most point is earliest patent priority date, followed by, patent publication date, license effective date, and first receipt of earned royalties on product sales.

A BNA Graphic/lsr06g8

use a nucleic acid as the analyte, whereas for the most part, those often characterized as “inborn errors of metabolism,” or at least metabolic phenotypes, and those related to oncology, do use a nucleic acid as the analyte and do not require FDA approval when offered as a service.

The fact that the latter group may take longer to be introduced as commercial diagnostic products hints at the role of insurance companies, as the gate to commercial availability may be less a matter of scientific feasibility or FDA approval than of creating a consensus among clinicians and payers on a standard of care. The SACGHS case study compendium found marked consistency in pricing of roughly \$35-\$40 per amplicon for nucleic acid-based genomic tests, thus also hinting at the importance of the role played by insurance companies.

Summary and Conclusions

The field of use in the license agreement is a far superior predictor of the type of commercial product the patent will cover than the patent claims.

A policy favoring more exclusivity may result in commercial products associated with DNA Patents getting to market faster. It is not possible, from these data, to make an equivalent statement about genomic diagnostic products, as the AI data set did not include the same detailed product characterization as the NIH OTT data. The data do not support direct cause-and-effect assertions regarding exclusivity but do show that licenses with exclusivity tend to be executed before product introduction, while nonexclusive licenses are “just-in-time” licenses. Thus, licenses with exclusivity are more consistent with incentive creation than those without. A larger percentage of AI-managed DNA Patents overall

are licensed, relative to NIH OTT-managed DNA Patents, and the licenses last longer at AIs.

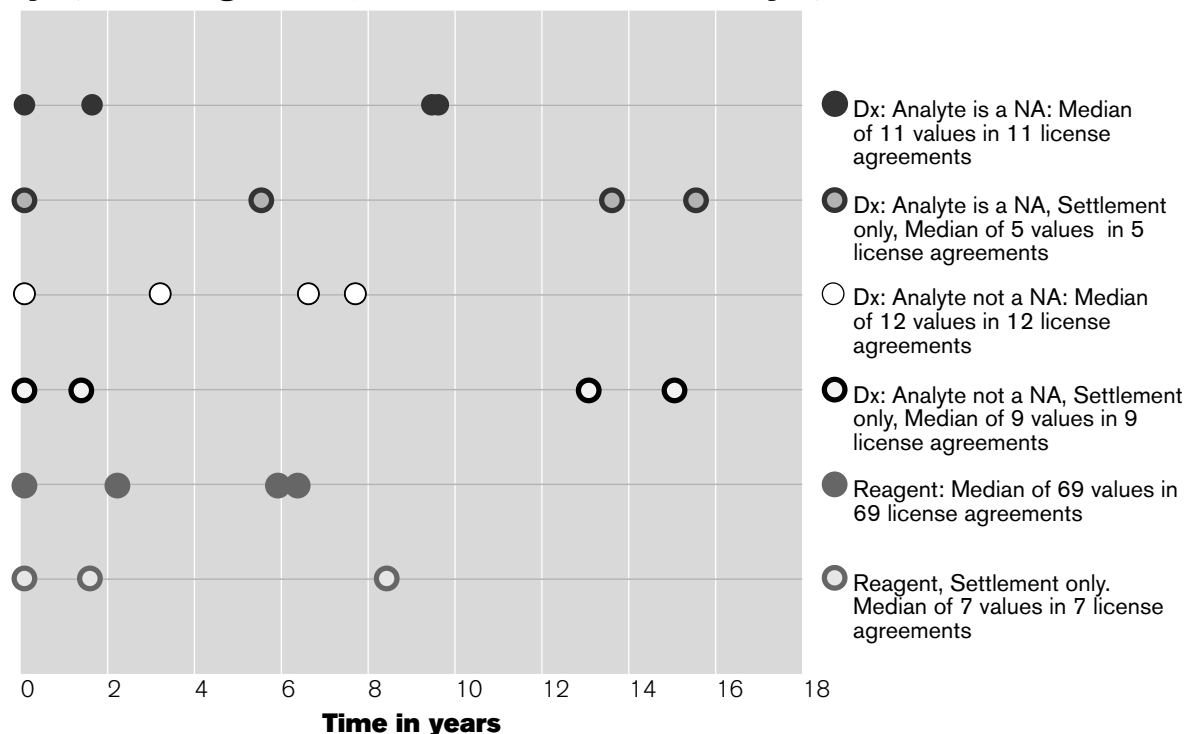
On average, earned royalty-generating commercial products identified by the NIH OTT as “diagnostic” appear to take longer to get to market, perhaps one to two years longer, relative to a proxy date (the date the first patent was filed) for invention conception, than products identified as “reagents.” This suggests that it is harder, on average, to develop a diagnostic than a reagent, and implies that incentives can be useful. The line between easy to develop and hard to develop is not bright. Two trends, targeted therapeutics⁹⁵ and companion diagnostics,⁹⁶ are blurring the distinction between therapeutics and diagnostics, adding to the challenge of determining an optimal scope of exclusivity in license grants.

There is general agreement that proprietary rights lower the perceived risk of investing in products that require time and money to develop. AUTM data show that more than 90 percent of patent licenses to start-ups have at least some exclusivity.⁹⁷ This also is true for start-ups that license AUTM member-managed DNA

⁹⁵ Typically, antibody conjugates, such as Thyrogen or Bexxar.

⁹⁶ Products that help select a suitable treatment, such as OncotypeDx.

⁹⁷ Looking at AUTM data from the 2006, 2005, and 2004 surveys, the most recent years for which such detailed data were gathered, and considering only U.S. universities, hospitals and research institutions, and patent management firms, 695/764 (91 percent), 554/609 (91 percent), and 598/658 (91 percent), respectively, were characterized as “exclusive.” Note that the AUTM Survey characterizes licenses with any exclusivity as “exclusive.” There is no “exclusive, by field of use” reporting category in the AUTM Survey.

Figure 6B**Timelines for NIH OTT Product Types: Reagent, Diagnostic (a Nucleic Acid is not the Analyte) and Diagnostic (a Nucleic Acid is the Analyte)**

Left most point is earliest patent priority date, followed by, patent publication date, license effective date, and first receipt of earned royalties on product sales.

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Table 2
Types of Diagnostic Products

Diagnostic Type	FDA/EMEA Approved?	Nucleic Acid based?	# of distinct sources Fall 2007/# of distinct sources ever
Infectious agents	21/ 29	2/ 29	16/29
Inherited, classic "IEM" and metabolic phenotype, not specialized oncology	0/10	10/10	9/10
Oncology only	4/8	7/8	7/8
Other non oncology inherited	3/3	0/3	3/3
Total	28/50	19/50	35/50

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Patents.⁹⁸ As discussed earlier, OncotypeDx and Macula Risk clearly benefited from patent incentives.

There are more recent biomarker-based diagnostic start-ups, such as Allegro Diagnostics⁹⁹ and SynapDx,

⁹⁸ Figure 5 of *Nature Biotechnology*, 24: 31-39, 2006; see *supra*, fn. 9. Of the 44 licenses to DNA Patents that were granted to start-ups, only one was characterized as non-exclusive, 13 as "exclusive, by field of use," and 29 as "exclusive, all fields of use."

⁹⁹ <http://www.allegrodiagnostics.com/>.

¹⁰⁰ which report exclusive patent licenses on their websites,¹⁰¹ although the scope of the license exclusivity is unknown. Allegro Diagnostics was founded in 2006 to commercialize pulmonary diagnostics for lung cancer, and reports having raised \$9.6 million in venture funding. SynapDx will develop diagnostics for autism spec-

¹⁰⁰ <http://www.synapdx.com/>.

¹⁰¹ See http://www.allegrodx.com/media/06_29_11.php and http://www.synapdx.com/pdf/SynapDx_License_PressRelease_050211.pdf, respectively.

trum disorders, and reports raising its series A round of \$9 million in 2010. These companies did not start with physical science inventions, as Illumina or Helicos did, but with patented inventions on biomarkers, and methods of making diagnoses using the biomarkers, some of which are nucleic acid sequences.¹⁰²

Exclusivity appropriate to the difficulty of developing and thus incentives needed to develop diagnostic tests, combined with appropriate diligence requirements, such as those found in the Nine Points, can align interests and maintain flexibility in the dynamic, evolving area of medical diagnostics and personalized medicine.

Finally, epidemiological tools, such as sensitivity and specificity analysis for predictive classifiers and timeline analysis designed to elucidate causation, have a role to play in the debate on innovation policy and patient access to health care. A study of timelines using patent and product data in the FDA *Orange Book* would be an important test of the applicability of some of the

¹⁰² The likely licensed patent claims can be found by typing the publicly noted inventor names into public patent databases.

methods described here and could yield useful health and public policy information.

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