ABA SECTION OF SCIENCE & TECHNOLOGY LAW

Biotech Briefing Fall 2011

Message From the Biotechnology Law Committee Co-Chair

Welcome to the Fall 2011 issue of *Biotech Briefing*. This issue of the *Biotech Briefing* comes to you after a hiatus in publication, and we are glad to be back. This issue contains two articles on timely topics: whole genome sequencing, and *Stanford v. Roche*. The article on whole genome sequencing was authored by Gary Marchant (Professor of Law at the Sandra Day O'Connor College of Law, Arizona State University) and Rachel Lindor (Research Fellow at the Sandra Day O'Connor College of Law and Mayo Medical School). Sean O'Connor (Professor of Law at the University of Washington) authored the second article on the Supreme Court's recent decision in *Stanford v. Roche*. We thank our authors for their contributions. Please let me know (kcarver@cov.com) if you are interested in contributing to our Winter issue.

☐ Krista Carver
Covington & Burling LLP

The Game Changer: Whole Genome Sequencing

Gary E. Marchant[1] and Rachel A. Lindor[2]

One decade ago the first draft of the human genome sequence was published with great expectations for rapid, unprecedented medical breakthroughs. In fact, DNA sequence data have enabled steady and impressive progress in understanding and treating human disease.[3] Yet, critics argue that practical benefits have been slower and fewer than anticipated, and that hopes are diminishing for identifying blockbuster genes at the root of serious diseases in large numbers of people.[4]

The genomic revolution is about to receive a major kick-start, though, with the advent of whole genome sequencing (WGS), a process that reveals the DNA sequence of an individual's entire genome. Over the past few years, WGS has moved quickly from a future scenario to a current research reality and is now moving into the clinical realm, raising many profound medical, legal, ethical, and social issues. This article provides a brief overview of these issues, after first describing the current status and applications of WGS. The bottom line is that WGS is about to become a major game changer not only for science and health care, but also in more profound and long-ranging ways.

Status of WGS

In 2004, the federal government set a target of $1000 for sequencing an entire human genome, at which point it would be economically feasible to integrate WGS into clinical care. That goal is now within reach. The traditional Sanger method of sequencing DNA base-by-base has been superseded by "next-generation" and soon "third generation" sequencing technologies that are capable of massive parallel sequencing at exponentially reduced cost and time. Several companies are now commercializing these technologies, competing to be the leader in this emerging new industry. This technology push has driven down the cost of sequencing exponentially, from the $100 million required to sequence the first genome to the commercial availability today of WGS for $10,000.[5] The cost of WGS is expected to hit the $1000 goal within

[1] Ph.D., J.D., M.P.P., Professor of Law, Sandra Day O'Connor College of Law, Arizona State University.

[2] J.D., M.D. (pending), Research Fellow, Sandra Day O'Connor College of Law, Arizona State University/Mayo Medical School.

[3] Eric S. Lander, *Initial Impact of the Sequencing of the Human Genome*, 470 NATURE 187 (2011).

[4] Nicholas Wade, *A Decade Later, Genetic Map Yields Few New Cures*, N.Y. TIMES, June 12, 2010.

[5] *E.g.*, Illumina, http://www.everygenome.com.

1-4 years, with many expecting the cost to drop as low as $100 in the years to follow.[1]

WGS likely will have enormous practical implications for both health care and the law. The rapidly falling cost of sequencing is making it increasingly affordable for individuals to have their genomes sequenced. In 2009, for example, fewer than 100 genomes had ever been sequenced, but over 2000 were sequenced in 2010 and an estimated 25,000 will be sequenced this year.[2]

Applications

The dramatically reduced cost and time required for WGS has opened the door to clinical applications. Recent findings suggest we all carry 100 or more rare genetic variants that could significantly increase our risk of specific diseases, most of which would not be detected by existing genetic screens that are limited to more common genetic variants. [3] There are already several noted examples in which an individual with an intractable disease underwent WGS and revealed a rare genetic variant that facilitated life-saving treatment.[4] As the cost of WGS continues to drop, the potential health and preventive benefits of identifying the rare genetic variants we all carry will likely spur greater use of sequencing by individuals, health insurers and providers.

WGS has been especially fruitful in efforts to personalize cancer treatment. Several leading cancer institutes have begun to sequence the entire genomes of tumor cells in order to compare them to patients' healthy cells. This comparative analysis reveals critical genetic changes in the cancer cell that have allowed providers to tailor treatment options to individual patients.[5]

The falling cost of sequencing technology will eventually make sequencing a more efficient method of patient care than traditional genetic testing, which relies on a different test for each disease. For example, personalized medicine is moving health care in the direction of testing for polymorphisms in drug-metabolizing genes prior to prescribing a growing list of drugs. Since the individual gene tests can range in price from several hundred to several thousand dollars, a once-in-a-lifetime WGS for $1000 or less will drive health insurers and payers to adopt WGS in the near future.

Further into the future (but perhaps within the next decade), WGS will be used for an ever-growing and often more controversial set of applications. Many experts predict that all citizens will eventually have their entire genomes sequenced. Researchers will use the sequences of volunteers to look for all sorts of correlations with various traits, including behavioral tendencies and performance outcomes. Parents might start using WGS to select their offspring using preimplantation genetic diagnosis (PGD). Police may seek access to stored genome sequences to assist forensic investigations. Indeed, as the power of ubiquitous gene sequencing becomes apparent, the potential applications are almost limitless.

Legal, Ethical and Social Issues

WGS raises numerous legal, ethical and social issues, both now and in the future, which are briefly summarized below:

Patenting: Over 4000 human genes are currently patented, raising the issue of whether sequencing every gene of an individual infringes those patents and requires thousands of licenses. [6] Although the issue has not yet been resolved, there is a credible argument that sequencing a

---

[1] Andrew Pollack, *The Race to Read Genomes on a Shoestring, Relatively Speaking*, N.Y. TIMES, Feb. 9, 2008.

[2] Radoje Drmanac, *The Advent of Personal Genome Sequencing*, 13 GENET. MED. 188 (2011).

[3] Kelly E. Ormond et al., *Challenges in the Clinical Application of Whole-Genome Sequencing*, 375 LANCET 1749 (2010).

[4] *E.g.*, E.A. Worthey et al., *Making a Definitive Diagnosis: Successful Clinical Application of Whole Exome Sequencing in a Child with Intractable Inflammatory Bowel Disease*, 13 GENET MED 255 (2011).

[5] Boris Pasche & Devin Absher, *Whole-Genome Sequencing: A Step Closer to Personalized Medicine*, 305 JAMA 1596 (2011).

[6] The patentability of human genes is currently being litigated in the context of Myriad's BRCA patents. *See* Ass'n for Molecular Pathology v. PTO, 669 F.Supp.2d 365 (SDNY 2009) (rejecting patents for human genes), *rev'd*, __ F.3d __, 2011 WL 3211513 (C.A.Fed.), 99 U.S.P.Q.2d 1398.

gene and then comparing the sequence to published sequence data to identify the variant an individual carries does not infringe the patent, unlike traditional gene testing that often requires use of a patented gene segment as a probe.

Informed Consent: Traditional informed consent processes, aimed at ensuring research participants understand all of the risks of their participation, are likely not feasible for WGS. Because of the complexity of genetic information and the potential scope of findings, recent estimates suggest that consenting patients to WGS using traditional methods would take 6 hours.[1] The potential ramifications of genetic testing for family members and the likelihood that sequenced genomes will be used for future research also complicate traditional paradigms for consent.

Disclosure of Incidental Findings: The sheer amount of data captured by WGS will drastically increase the frequency of incidental findings—those unrelated to the original purpose of the test but with potential clinical or other significance for patients. There is much debate about if, when, and how these findings should be disclosed to patients. Some argue there is a moral duty to inform individuals of any significant or treatable finding, as is expected for most other clinical testing. Others argue that the 3-4 million variants expected per person and the constantly changing understanding of their significance would make this expectation impossible to meet.[2] Indeed, one estimate suggests that delivering WGS findings under the current paradigm would require five hours.[3]

Confidentiality/Privacy/Storage: As more and more people have their genome sequenced, where will that valuable but sensitive data be stored? Will it be given to the patient, and if so, in what format and with what annotation? Currently, some companies provide genomic data over the internet, but others concerned about online security provide the information only on a hard disk. Will the data be accessible to the patient's medical providers, possibly linked to his or her electronic health record? Will police or private litigants be able to gain access to that data using a warrant or subpoena?

Clinical Laboratories Improvement Amendments (CLIA): Most WGS is currently being done in a research setting, often in non-CLIA certified laboratories that, under CLIA, are not permitted to report back health data to subjects. A problem arises if a researcher identifies a gene variant in a subject's DNA sequence that presents a significant health risk that the subject could take action to mitigate. Would the laboratory be required to retest the sample in a CLIA lab before reporting back the result? Who would pay for this additional cost?

FDA Regulation: An FDA advisory committee recently recommended that the FDA restrict direct-to-consumer genetic testing to tests ordered by a physician. If the FDA adopts this advice, will it also try to restrict consumers from obtaining their own complete genomic sequence?

Liability: The availability of WGS is likely to open many new liability fronts. Physicians may be at risk for failing to warn a patient of a known risk factor present in their genome or for prescribing a drug that the patient's DNA sequence indicates is potentially hazardous or ineffective. In product liability and toxic tort cases, defendants will seek an injured plaintiffs' genome sequence for clues of susceptibilities to alternative causes that may have caused the injury, while plaintiffs will try to use their enhanced genetic susceptibility or induced mutations to prove causation or duty.

Social-Ethical: WGS will reveal enormous information about our individual predispositions and predilections, going well beyond health data to include traits relating to our aptitudes, capabilities, and tendencies. The potential applications of these data are almost unlimited but will have profound implications for education, career planning, sports, criminal culpability, mate selection, and many other areas.

Conclusion

WGS will be a game changer, for our health care in the near term, and much more broadly for our personal well-being and social lives in the longer term. At each step in its rapid

---

[1] Jonathan S. Berg et al., *Deploying Whole Genome Sequencing in Clinical Practice and Public Health: Meeting the Challenge One Bin at a Time,* 13 GENET. MED. 499 (2011).

[2] *Id.*

[3] *Id.*

development, WGS will likely raise a myriad of legal, ethical and social issues, for which we have provided but a cursory introduction here.

Practical Implications of *Stanford v. Roche* for Ownership of University Inventions

Sean M. O'Connor, J.D., M.A.[1]

The discovery and commercialization of biotechnology innovations often rely on collaborations between universities and for-profit firms. The federal government funds much of university life sciences research and, under the Bayh-Dole Act,[2] has some rights to research arising from that funding. Two important strands of invention ownership issues in this web of collaboration arose under litigation that culminated in the recent Supreme Court decision *Board of Trustees of Leland Stanford Junior University v. Roche Molecular Systems, Inc.* ("*Stanford v. Roche*").[3] The first is the question of whether Bayh-Dole trumps any other invention assignment agreements when federal funding was used in any part for the invention. The second is whether a 1991 development in Federal Circuit case law regarding invention assignments is binding federal common law. While the Supreme Court limited itself to the first question—because the petition for certiorari was so limited—some of the justices addressed the second in a concurrence and a dissent. Accordingly, this article focuses on practical implications of the Supreme Court's holding, including the issues it left open.

The salient facts of the case are as follows. Dr. Mark Holodniy became a research fellow at Stanford University in 1988.[4] He executed Stanford's then standard Copyright and Patent Agreement (CPA) which provided that he "'agree[d] to assign' to Stanford his 'right, title, and interest in' inventions resulting from his employment" at Stanford.[5] His work required him to learn and use the polymerase chain reaction technique (PCR) that Cetus Corporation had pioneered. Cetus was already collaborating with Stanford on research in this area, and Holodniy's supervisor arranged for him to learn PCR at Cetus and pursue a substantial part of his research there with Cetus employees. Upon arriving at Cetus, Holodniy executed Cetus' Visitor's Confidentiality Agreement (VCA), which provided that he "'will assign and do[es] hereby assign' to Cetus his 'right, title and interest in each of the ideas, inventions and improvements' made 'as a consequence of [his] access' to Cetus."[6] After nine months, during which the invention at the heart of this case was conceived, Holodniy returned to Stanford to test and refine the invention. He worked with colleagues there, allegedly under federal funding.[7] In 1991, Roche Molecular Systems, Inc. (Roche), purchased all of Cetus' PCR-related assets. Over the next few years it conducted clinical trials on the PCR HIV technique as it had been developed while Holodniy was still at Cetus, and then developed and distributed commercial kits worldwide.[8] In 1992, Holodniy and his Stanford colleagues finished testing and refining the invention. Stanford then obtained invention assignments from them all and filed patent applications on the technique.[9] Three patents ultimately issued, in 1999, 2003, and 2006.[10] In 2000, Stanford approached Roche about taking a license to the Holodniy patents, but Roche responded that it was a co-owner or licensee of the inventions—under the terms of the VCA, some materials transfer agreements, and under common law shop rights—and declined to take a license.[11] Stanford sued Roche for patent infringement in 2005.[12]

---

[1] Professor of Law and Faculty Director, Law, Business & Entrepreneurship Program, University of Washington School of Law. Contact: soconnor@uw.edu.

[2] P.L. 96-517 § 6 (Dec. 12, 1980).

[3] 131 S. Ct. 2188 (2011).

[4] *Id.* at 2192; Trustees of Leland Stanford Junior University v. Roche Molecular Systems, Inc., 583 F.3d 832, 837 (Fed. Cir. 2009).

[5] 131 S. Ct. at 2192.

[6] *Id.*

[7] 583 F.3d at 838; 131 S. Ct. at 2192. Stanford was never able to produce the government funding agreement.

[8] 131 S. Ct. at 2192.

[9] 583 F.3d at 838; 131 S. Ct. at 2192.

[10] *Ibid.*

[11] 583 F.3d at 838.

[12] 131 S. Ct. at 2193.

The district court resolved the case largely in Stanford's favor by adopting a legally recursive timeline of events. First, the court found, there was an agreement to assign inventions that did not yet exist to Stanford under the CPA at some indeterminate time in the future. Second, there was an actual, immediate assignment of inventions (that still did not exist) to Roche (Cetus) under the VCA that, barring the later Bayh-Dole consideration, would have made it impossible for Holodniy to honor his obligation to later assign his inventions to Stanford at their call. Third, the receipt of federal funding by Stanford to actually reduce the now existent invention to practice brought any patents arising from this work under the provisions of Bayh-Dole. And fourth, the filing of patent applications then retroactively stripped Holodniy of any title he had to the invention at any point in time, including when he executed the VCA. Thus, two later in time agreements had the effect of superseding earlier agreements even without any actual modification of the earlier contracts. While the district court did not clearly articulate its views on the interaction of the CPA and VCA, it relied on a view that Bayh-Dole grants the government a right of first refusal to inventions arising under federal funding agreements, and grants the recipient of federal funds, the "contractor" in Bayh-Dole parlance, a "right of second refusal."[1] This would leave the actual inventor—who is generally not a party to the funding agreement—with only a residual interest in the inventions conditional on both the government and contractor electing not to exercise their rights.

On appeal, the Federal Circuit reversed the district court's Bayh-Dole holding and articulated why the VCA trumped the CPA. This left Roche with an ownership interest in the patents and thus deprived Stanford of standing in the case.[2] The court rejected the district court's "right of second refusal" construct for contractors.[3] It adopted another district court's ruling that "'the primary purpose of the Bayh-Dole Act is to regulate relationships of small business and nonprofit grantees with the Government, not between grantees and the inventors who work for them.'"[4] However, the Federal Circuit allowed that if the contractor or its employees have done anything to violate provisions of the Bayh-Dole Act, then the government may be able to void these actions and take title for itself.[5] With regard to the CPA and VCA, the Federal Circuit held that the former had only established a promise to do some act in the future at Stanford's request—essentially a call option—while the latter transferred rights upon its execution. Thus, while Holodniy arguably breached the CPA when he signed the VCA, Stanford had no action against Roche directly and would have to pursue recourse against Holodniy.[6]

Stanford petitioned for certiorari on the Bayh-Dole issue only. The Supreme Court granted certiorari and affirmed the Federal Circuit. In particular, it reaffirmed its earlier holdings that rights in an invention belong to the inventor, absent some express transfer between the inventor and his employer or another.[7] It then rejected Stanford's argument that Bayh-Dole is a "vesting statute" similar to the Atomic Energy Act, in which title to relevant inventions is vested in designated agencies by act of law.[8] Further, it focused on the definition under Bayh-Dole which requires that a "subject invention" (those inventions subject to the provisions of Bayh-Dole) be an "invention *of the contractor*."[9] Under the majority's view, the emphasized portion would be superfluous if *any* invention arising under federal funding were subject to Bayh-Dole. Instead, the Court held that a subject invention is one to which the contractor lawfully has rights or title. Most importantly, the title allocation rules under Bayh-Dole, which leave the inventor with only a conditioned residual interest where neither the government nor the

[1] 487 F.Supp.2d 1099, 1119 (N.D. Cal. 2007).

[2] Stanford continued to have rights to the patents through Holodniy's Stanford research colleagues, who had not signed away their rights to any other party.

[3] 583 F.3d at 844

[4] *Id.* at 845 (quoting Fenn v. Yale Univ., 393 F.Supp.2d 133, 141-2 (D. Conn. 2004)).

[5] By contrast, the *Stanford* district court had held that such actions were automatically void. 487 F.Supp.2d at 1118-9.

[6] The district court and the Federal Circuit also considered Stanford's arguments based on the bona fide purchaser provisions of the Patent Act, 35 U.S.C. § 261, but found them unpersuasive. Discussion of that topic is beyond the scope of this short article.

[7] 131 S. Ct. at 2195.

[8] *Id.* at 2195-6.

[9] *Id.* at 2196 (emphasis added).

contractor elect to take title, only apply to subject inventions.

While the Court was constrained to the Bayh-Dole issue by Stanford's own petition for certiorari, a concurrence and a dissent expressed concern over the Federal Circuit's holding on the VCA issue.[1] Under these views, the majority's holding on the Bayh-Dole issue, combined with the Federal Circuit case law, provides opportunity and incentive for inventors—and contractors—to circumvent Bayh-Dole's title allocation system. For these justices, the Federal Circuit's 1991 ruling in *FilmTec Corp. v. Allied Signal, Inc.*[2] should be revisited. In that case, the court asserted that the assignment of rights in an invention that does not yet exist is an assignment of an expectant interest and grants at most equitable title until the invention is actually made and a patent application filed.[3] However, immediately upon the filing of a patent application on the invention, legal title to the invention rights vests in the assignee with no further action required.[4] Actual assignments of expectant interests must be distinguished from mere obligations to assign rights in the future.[5] The latter are often used when the prospective assignee does not know in advance whether it wants title to the future invention and thus establishes a call option. When the invention is made and a patent application is filed, no transfer of title occurs until the option is called. In the meantime, the inventor may assign any of her rights to third parties, although this sets her up for breach of the option agreement if the holder ever calls it.

The *FilmTec* court did not state whether it was basing its decision on an application of state law—which normally governs contract law interpretation—or establishing a rule of Federal common law. This remained murky though later decisions,[6] until the 2008 decision in *DDB Technologies, L.L.C. v. MLB Advanced Media, L.P.*[7] The Federal Circuit held that invention assignment agreements are governed by federal common law because they are integral to the question of standing in federal patent cases.[8]

The concurring and dissenting Supreme Court justices in *Stanford* seem concerned as to both the rule that federal common law governs invention assignment agreements and that rule's distinction between assignments of expectant interests and obligations to assign. Their concern appears rooted in how Stanford lost control of Holodniy's rights and potentially jeopardized the government's rights in the invention. But, when Holodniy executed the CPA, *FilmTec* had not been decided and the University of California system appears to have believed that "agree to assign" effected an immediate transfer just as "hereby assign" did.[9] This, however, had been an incorrect understanding of the law, although the California state courts may not have cleanly addressed the issue until 1997. Once *FilmTec* was decided in 1992, though, all employers were on constructive notice that they should use the "hereby assign" language if they wanted to lock in a title transfer. If they continued not to use it, then they were either ignorant of the law or selecting the risk of the option agreement.

The question is why some universities—including Stanford—continued using the "agree to assign" language. It could be that at least some used it knowing full well about *FilmTec*. In these cases, the university may have decided to forego the "agree to assign" language because it did not know at the time of a researcher's hire whether all, or which, of her future inventions should be university property. Another argument may have been that the university cannot take title to things that do not yet exist. A third argument may have been based on a confusion of the federal tax exempt rules

---

[1] *Id.* at 2199-2205 (J. Sotomayor concurring, JJ. Breyer and Ginsburg dissenting).

[2] 939 F.2d 1568 (Fed. Cir. 1991).

[3] *Id.* at 1572.

[4] *Id.*

[5] *Id.* at 1573.

[6] *See* Speedplay, Inc. v. Bebop, Inc., 211 F.3d 1245 (Fed. Cir. 2000); IpVenture, Inc. v. ProStar Computer, Inc., 503 F.3d 1324 (Fed. Cir. 2007).

[7] 517 F.3d 1284 (Fed. Cir. 2008).

[8] *Id.*

[9] *See* Shaw v. The Regents of the University of California, 58 Cal.App.4th 44, 53 (Cal. 3d Dist., 1997) (rejecting University's argument that an agreement to assign had a "contemporaneous and 'complete transfer of plaintiff's right to the University'" because University had mistakenly relied on two earlier cases in which the assignment agreement in question used "hereby agree" in addition to "agree to assign").

prohibiting the assignment of expectant interests by the entity to others with the permissible assignment of expectant interests from an employee or contractor to the entity. All three of these are simply misunderstandings of the law. The first potentially remains a problem, but has three straightforward solutions. First, universities can use the "hereby assign" language in assignment agreements and then simply assign back inventions as needed. Second, universities can craft a scope of expectant interests to be immediately assigned that captures inventions that will be made under arrangements where the university must have rights, such as government funding agreements. Third, universities can institute a "supremacy clause," such as that upheld by the Delaware Court of Chancery in *Cephalon, Inc. v. Johns Hopkins University*,[1] in which employees must have a clause in their consulting agreements stating that the outside entity agrees that the employee is under an obligation to assign her inventions to the university and that this obligations is senior to any invention assignments the outside entity might impose. The challenge with this approach is that it is only as good as the diligence of employees in implementing it. Further, employees may not realize that assignment language may be in other kinds of agreements, such as the VCA in *Stanford*.

In the end, *Stanford* may be more important for what the Supreme Court did not decide than for what it did. The purported reliance on Bayh-Dole as a backstop to assignment problems should never have been seen as solid. But many universities' longstanding reliance on "agree to assign" language—and the failure of Stanford to petition for certiorari on the *FilmTec* issue—may leave them still hesitant to accept *FilmTec* as binding law. However, until some other circuit or the Supreme Court decides differently on the rule, it should be treated as the law of the land. Given the solutions to the perceived problems of instituting "hereby assign" language above, universities should no longer shy away from it for those reasons alone. Of course, universities may want to explore what rights they really need to acquire, and then have the courage of their convictions to let the others remain with their inventors.

[1] 2009 WL 4896227 (Del. Ch. 2009).

Biotechnology Law Committee Leadership

Chairs:
Eileen Smith Ewing
Krista Hessler Carver

Vice-Chairs:
Sofya Bakalova
Vid Mohan-Ram

Section of Science & Technology Law Officers:
Chair: Eric Y. Drogin
Chair-Elect: Lucy L. Thomson
Vice-Chair: Julie A. Fleming
Secretary: Hugh B. Wellons
Budget Officer: Jorge L. Contreras
Assistant Budget Officer: William B. Baker
Delegates to the House of Delegates:
Ellen J. Flannery
Bonnie E. Fought
Immediate Past Chair: Stephen S. Wu
Past Chair Liaison: Thomas J. Smedinghoff

Copyright 2011 American Bar Association. The contents of this publication may not be reproduced, in whole or in part, without written permission of the ABA. All requests for reprint should be sent to: Director, Copyrights and Contracts, American Bar Association, 321 N. Clark St., Chicago, IL 60654, FAX: 312-988-6030, e-mail: copyright@americanbar.org.

Editorial policy: *Biotech Briefing* endeavors to provide information about current developments in law, science, medicine, and technology that is of professional interest to the members of the Biotechnology Committee of the ABA Section of Science & Technology Law. Materials published in *Biotech Briefing* reflect the views of the authors and do not necessarily reflect the position of the ABA, the Section of Science & Technology Law, or the Editor(s).