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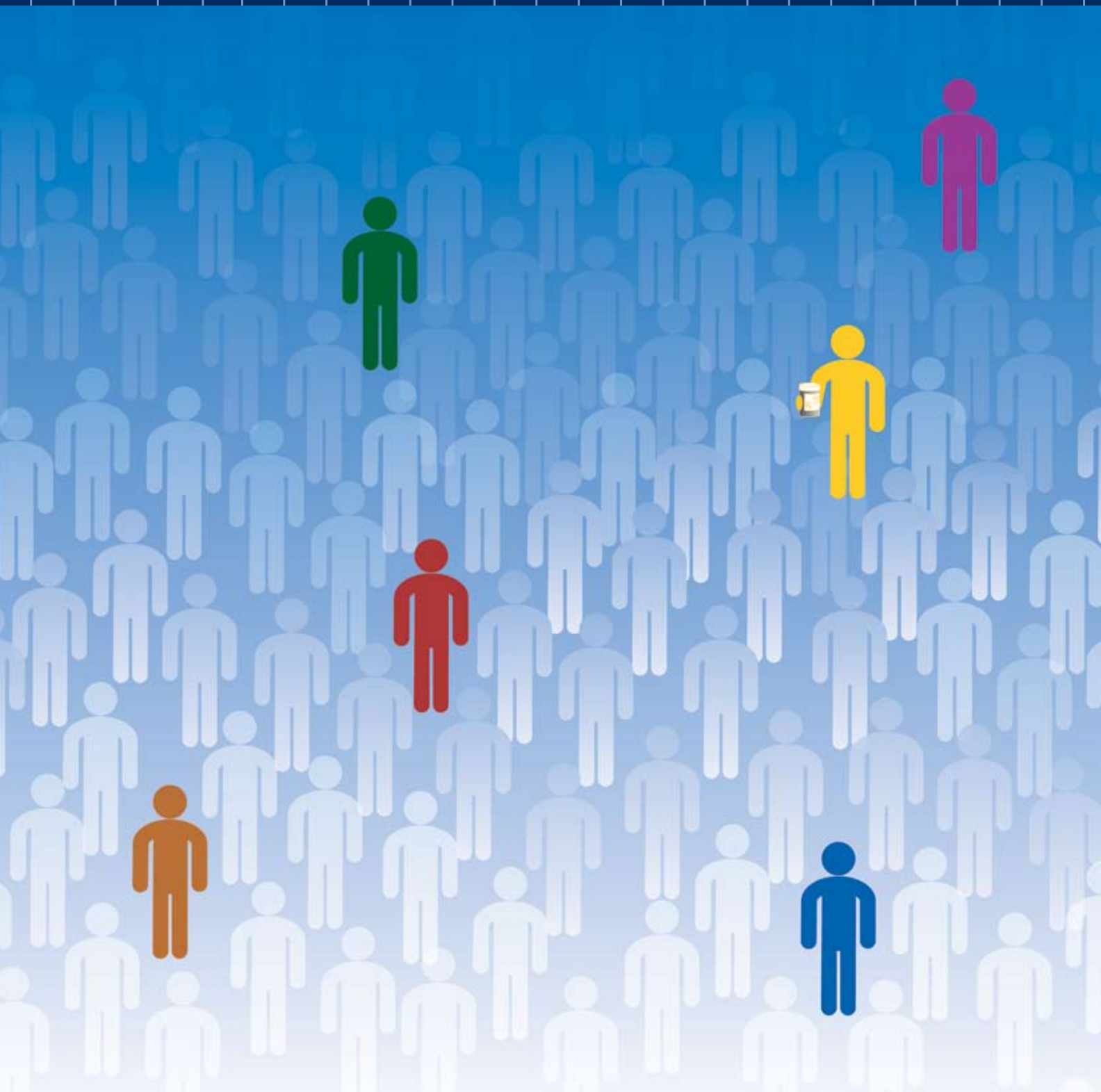

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Planning for the other shoe to drop – Future echoes of *LabCorp. V. Metabolite*

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Personalized medicine improves the quality of medical care and can help contain health care costs. In one aspect, personalized medicine is used to identify those patients likely to benefit from a particular therapy. Familiar examples of this implementation include using HIV phenotyping and genotyping assays to determine the effectiveness of anti-retroviral therapy and guide selection of anti-retroviral drugs, and HER-2 amplification assays to identify breast cancer patients likely to benefit from Herceptin therapy. In another aspect, subtyping patients enrolled in clinical trials and analyzing differences among responsive and non-responsive populations allows identification of drugs that work only in subsets of patients to determine which patients may be more likely to suffer adverse drug reactions. An individual's expression profile, phenotype or genotype may be useful for predicting onset, outcome or response to therapy for a variety of diseases, including cancer, viral infection (e.g., HIV) and heart disease. Early identification of at-risk individuals can optimize treatment regimens for patients leading to better outcomes and reduced costs.

In some cases a skilled physician can, by simple inspection of a test result, evaluate risk or determine an appropriate course of treatment. The use of HIV phenotyping or genotyping or HER-2 amplification assays to guide treatment decisions illustrates how simple correlations (e.g., HIV phenotype with drug resistance or HER-2 amplification with response to Herceptin therapy) are used to reach medical conclusions based on the results of an assay[1]. In other cases, more complex models are needed to interpret the medical significance of a test result. For example, protein expression and dimerization profiles can be used to differentially diagnose and predict disease risk or disease outcome and sometimes this can be done by mere inspection, but could also require constructing sophisticated models using training sets obtained from characterized patients or other quantitative analysis of the expression values.

Patents traditionally have provided effective protection for companies that invest the time and money needed to develop diagnostic tests. This year, the United States Supreme Court agreed to review (but later dismissed) *Laboratory Corporation of America Holdings v. Metabolite Laboratories, Inc.* 548 U.S. ___, 126 S. Ct. 2921 (2006). *LabCorp* raises provocative questions as to the proper scope of protection for inventions that rely on simple correlations between an assay and a prognosis or diagnosis. Although the Court's dismissal left the law unchanged for now, the case heralds changes that personalized medicine companies should consider in developing their patent strategy.

The facts of the case are as follows. Metabolite licensed a patent[2] based on the discovery of a correlation between high levels of the amino acid homocysteine and deficiencies of two essential vitamins, folate and vitamin B12. The patent included claims directed to a specified way of measuring homocysteine (i.e. a "homocysteine assay" claim) and also included and also broadly claimed a method of diagnosing a vitamin deficiency according to the correlation (i.e., an "assay and correlate" claim):

> *A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of: assaying a body fluid for an elevated level of total homocysteine; and correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate*[3].

Legal Perspectives

Initially, LabCorp paid royalties to Metabolite pursuant to a license, but then stopped after switching to an assay that was purportedly outside the scope of the Metabolite's assay claims. However, since the method of diagnosing claim was not limited to any particular assay format, Metabolite sued LabCorp for inducing infringement by providing assay results to doctors along with literature explaining the correlation between homocysteine and the vitamin deficiencies. At the trial, Metabolite argued that the correlating step necessarily is infringed by recognizing that an elevated homocysteine level would indicate a likely vitamin deficiency, once the natural relationship between homocysteine levels and the vitamin deficiencies became known. The "correlating" therefore would occur automatically in the mind of any competent physician. At the District Court level, the jury agreed, and Metabolite was awarded damages and an injunction. *LabCorp* slip op. at 6.

LabCorp appealed to the Federal Circuit and argued that if the method claim was construed so broadly as to cover all homocysteine assays, it must be invalid under § 112 of the patent laws[4] because, among other things, the specification taught only a few types of assays and failed to precisely define the types of activities that would constitute "correlating" according to the method of the patent. The Federal Circuit rejected LabCorp's section 112 arguments and upheld the jury's verdict. Slip op. at 7.

LabCorp requested that the Supreme Court of the United States hear the case. In its request LabCorp advanced a new theory under which Metabolite's assay and correlate claim could be found invalid. According to their theory, such a broad claim provided Metabolite with a monopoly over a basic scientific fact or "law of nature" (i.e., the relationship between homocysteine levels and vitamin deficiencies). Laws of nature are not eligible for patent protection according to § 101[5] of the patent laws.

The Supreme Court asked the Solicitor General to comment on whether it should hear the case. Pointing to the absence of any record from the lower court regarding this new "law of nature" argument, the Solicitor recommended that the Supreme Court not take the case. Against that advice, though, the Supreme Court did agree to hear the case and in stating their reasons why they agreed to do so they set the issue out as "whether a patent instructing a party to 'correlate test results' can validly claim a monopoly over a basic scientific relationship used in medical treatment such that a doctor infringes the patent by looking at a test result and thinking about that relationship?" Some two months after hearing oral argument, the Court issued its decision, which anti-climactically dismissed the case (citing its own "improvidence" in taking the case) without actually coming to a decision on the merits[6].

Eight justices took part in the decision[7] and three signed on to a dissent authored by Justice Breyer[8]. Justice Breyer argued that the Court should have decided whether Metabolite's "assay and correlate" claim was invalid on the merits because it claimed a "law of nature." Justice Breyer summarized the Court's precedential decisions establishing that laws of nature (such as, E = mc2), natural phenomena (e.g., electromagnetism) and abstract ideas (e.g., algorithms) are excluded from patent protection. Justice Breyer explained that these exclusions further the patent system's Constitutional mandate to "promote the Progress of Science and Useful Arts"[9] by assuring that no monopoly is granted that ***preempts*** all uses of a basic scientific fact. Slip op. at 2-3 According to Breyer, the correlation claims did, in fact, preempt a basic biological principle. He also noted that allowing Metabolite's broad "assay and correlate" claim to stand might inhibit doctors from using their best medical judgment and could contribute to health care costs. Slip op at 14.

In these authors' opinion, the Court's initial decision to hear *LabCorp* and Justice Breyer's dissent signals a renewed focus on the eligible subject matter requirement of 35 U.S.C. § 101. This may reflect the Court's view that the patent system needs adjustment so that it better promotes technological progress, especially in areas of biomedical research[10]. Adjusting the patent system could mean either allowing only narrower claims (i.e., less preemption), thus minimizing freedom to operate barriers encountered by the health care system or allowing broader claims (i.e., more preemption), thus maximizing the protection afforded by the patent system to personalized medicine companies or balancing those competing interests.

Companies operating in the personalized medicine space need effective patent protection to protect their research and development invest-

ments at the product stage. However, allowing broad claims could arguably preempt all uses of basic biological discoveries. Promoting technological progress requires the patent system to balance these competing objectives by granting claims that are broad enough to provide meaningful protection but narrow enough to encourage others to develop further innovations.

Moving forward, we can expect astute litigants to use the § 101 preemption argument set out in the *LabCorp* dissent to challenge the validity of these and other types of claims useful for protecting personalized medicine innovations[11]. It therefore is critical for personalized medicine companies to develop and execute patent strategies that anticipate the possibility that such challenges eventually may succeed. At greatest risk are claims such as Metabolite's simple assay and correlate claim. A comprehensive set of dependent claims calling out assay techniques and correlation methods can provide valuable backup protection should the broad claim be found invalid under § 101. Claims covering "theragnostic" technologies (i.e., structured to recite obtaining a test result and choosing a treatment course according to that result) should be less vulnerable to § 101 challenges given the inclusion of another step which necessarily limits such claims so that they can not fairly be said to preempt a law of nature. And if possible, claims should be sought that cover the technology used to obtain patient data (such as, e.g., claims directed to probes, assays, or kits). By planning for the possibility that Justice Breyer's dissent may anticipate a coming change in the interpretation of § 101, personalized medicine companies can minimize negative impacts on their patent estate.

FOOTNOTES

1. See, for example, Journal of the American Medical Association, August 16, 2006-Vol 296,. No. 7 which can also be found at www.jama.com), and Persons DL, Bui MM, et al., "Fluorescence in situ hybridization (FISH) for detection of HER-2/neu amplification in breast cancer: a multicenter portability study," Ann Clin Lab Sci. 2000 Jan;30(1):41-8.

2. U.S. Patent No. 4,940,658.

3. Claim 13, U.S. Patent No. 4,940,658.

4. 35 U.S.C. 112, paragraphs 1 and 2 set out the requirements for enablement, written description and definiteness that a patent specification must satisfy to support valid claims.

5. 35 U.S.C. § 101 states "whoever invents or discovers any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

6. In addition to the parties' own briefs, numerous "friends of the court" briefs were filed by organizations and institutions that recognized the significant implications of the issues at hand. This briefing, in Justice Breyer's view, should have allowed the Court to reach a decision on the merits of LabCorp's "law of nature" challenge. Slip op. at 9-10.

7. Chief Justice Roberts recused himself from the case.

8. Justice Stevens and Souter joined Justice Breyer's dissent.

9. U.S. Const., Art. I, § 8, cl. 8.

10. Consistent with this interpretation is the Supreme Court's unanimous decision in Merck KGaA, v. Integra Lifesciences I, Ltd., et al. 545 US 193 (2005) which diminished patent protection by expanding the scope of 35 U.S.C. § 271(e) (which establishes a safe harbor exemption from patent infringement liability) to include certain preclinical activities.

11. In a recent litigation (Ariad Pharmaceuticals, Inc. Mass. Institute of Technology, Whitehead Institute for Biomedical Research, and President and Fellows of Harvard College v. Eli Lilly & Co., U.S.D.C., D. Mass., Civil Action No. 02-11280-RWZ) Lilly used a § 101 argument to challenge the validity of Ariad's claims directed to methods of inhibiting NF-_B-driven activity, based on Lilly's interpretation that the claims read on the naturally occurring regulation of NF-_B-driven gene expression within cells, and so covered a law of nature. See, e.g., Smith (2006), "Ariad v Lilly, Part II: The next big patent battle" (http://money.cnn.com/2006/08/04/news/companies/ariad/index.htm).