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Via Email to: genetest@uspto.gov

RE: Genetic Testing Study

Dear Mr. Vishnubhakat:

I want to thank you for the opportunity of providing the views of myself my views and my company, Bio-Reference Laboratories (BRLI), on genetic diagnostic testing. I hope that my views will assist the USPTO in preparing a balanced report for Congress on the subject, as required by the America Invents Act (AIA). I am aware of the USPTO's more specific wish to seek comments on the issue of independent second opinion genetic diagnostic testing, where patents and exclusive licenses exist that cover primary genetic diagnostic tests; on the relationship of patents to medical care and practice; on the rights of innovators; as well as on costs and insurance coverage. I hope to address these topics in this letter.

Some of the views I express here have already been presented during my testimony before the House Judiciary Subcommittee on Courts, the Internet and Intellectual Property, in connection with its hearing on "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing" on October 30, 2007.

Since that testimony in 2007, the situation regarding the exclusive licensing of gene patents has become far more compelling, creating a new appreciation of personalized diagnostics fueled not only by the rapidity of gene discovery and new clinical correlations but also the availability and cost effectiveness of new sequencing technologies. The old ways are simply no longer applicable and will surely stifle innovation, progress and patient care.

Bio-Reference Laboratories, Inc.

I am the founder and CEO of BRLI, a publicly traded company with headquarters in Elmwood Park, New Jersey. We are the fourth largest clinical laboratory in the United States; we provide national service in certain specialized areas and we are a full service laboratory in the New York Metropolitan area. For almost 25 years, I have also been an attending physician on the medical wards of Columbia University's College of Physicians and Surgeons' New York-Presbyterian Hospital.

BRLI is a full service clinical laboratory. This means that we analyze blood, urine and tissue samples for a whole host of conditions, including diabetes, HIV/AIDS and hepatitis, to name a few. We have specialty capabilities in the areas of oncology and genetics. We employ more than 3,000 individuals and serve physicians across the country who send us the samples to test. Over the past twenty years, BRLI has grown substantially. In 2011 BRLI's revenues totaled nearly $570M, up from two hundred thousand dollars in 1987 when we began operating as a clinical laboratory; we have enjoyed an 18 year run where we have a 20% compound annual growth rate (CAGR) in revenue. Our other financial metrics and growth are equally impressive.

A few years ago, I was making rounds with the interns when a patient was presented whose heart muscle was defective. She had a condition known as hypertrophic cardiomyopathy. A significant number of people with this condition are susceptible to sudden death syndrome. I asked the medical student to tell me the options for treating this patient and discovered for the first time that we could diagnose the condition by using a genetic test. In the past, our ability to make an exact diagnosis was limited; using data from an EKG and evaluating the shape of the heart using an echocardiogram, we hoped to have clues to the severity of the condition. But, as I learned at that time, with proper genetic testing, a much more accurate diagnosis could be made and the risk of sudden death could be properly evaluated and even reduced. That impressed me, and I became a firm believer in the role of modern genetic testing as part of our clinical practice. It didn't take me long, however, to run head-on (and repeatedly) into severe and continuing obstacles to achieve such results, brought about by the existence of exclusively licensed patents on genetic diagnostic tests.

Summary of My Views

At the outset, I want to make it clear that that it is neither my philosophy nor my intent to attack the U.S. patent system, or the question of eligibility for patenting of genes or of genetic diagnostic methods. I leave it to others, such as the U.S Supreme Court in its recent case *Mayo Collaborative Services et al v Prometheus Laboratories* 566 U.S.__(2012) or the Court of Appeals for the Federal Circuit in its decision *AMP et al v USPTO v Myriad Genetics* (Fed. Cir. 2011), to evaluate and qualify the legal eligibility of diagnostic methods, including genetic diagnostic methods.

However, I wish to provide you here with my clear opinion that, in certain fields of endeavor such as genetic diagnostic tests and especially second opinion genetic tests, exclusivity rights may be doing more harm than good. While historically, patents, which confer legal monopolies of limited duration, have benefited society in numerous ways, such as by increasing innovation, in the case of genetic diagnostic testing that is patent-protected and exclusively licensed, the public health has been adversely affected.

It is my view that, while patents might still be issued in my field (within the qualifications and limits set forth by the courts in the *Mayo* or *AMP* or other cases), the *exclusive licensing* of genetic associations, meaning the naturally occurring correlation of specific gene

sequences/mutations to certain clinical conditions, should be barred or at least severely curtailed or qualified.

BRLI's Experiences with Patented Genetic Testing

I became personally familiar with the issues of patenting diagnostic genetic tests when in 2006, BRLI purchased GeneDx, a laboratory in Gaithersburg, Maryland, that does DNA sequencing to diagnose rare genetic disorders. In addition to diagnosing genetic disease outright, GeneDx has the ability to test for human genes that are associated with certain diseases or that make a person highly susceptible to a certain disease. My company was excited by the opportunity to participate in the forefront of modern medicine and at the same time take advantage of an important business opportunity.

Unfortunately, however, the ability of GeneDx to offer these genetic tests has been severely restricted by gene patent holders or their exclusive licensees, such that GeneDx, as well as other clinical laboratories, may not provide tests without the threat of being sued for infringing gene-related patents.

The patent holder of a gene patent, usually a university where the original research was conducted, controls the commercial use of the gene. This means that a laboratory cannot analyze the gene for mutations in order to diagnose the presence of a disease or condition, such as breast cancer or muscular dystrophy, without permission of the patent holder. In contrast, in cases where the university grants licenses to multiple laboratories to conduct the diagnostic tests, the public interest and technological advancement are generally promoted through the competitive process.

Let me provide several examples of the problems my company has encountered in trying to do its business. In one case, shortly after we acquired GeneDx, one of our customers, a geneticist, asked for a diagnosis for a rare skin disorder. While we were in the process of sequencing the gene in order to make a diagnosis, we received a letter from another laboratory claiming that within the sequence we were analyzing was another sequence associated with hearing loss. We were told that this hearing loss gene area was patent protected and that we could not proceed further without infringing the patent. The laboratory would not accept a fee or royalty from us to conduct the genetic test, but said that the patient would have to submit DNA to them for testing; they would just re-do our existing work at full cost to the patient to confirm what we had already done.

Another notable example of the problem involve the multiple genes and mutations associated with Long QT Syndrome. The LQT story is described in detail in Appendix F to the *Report of the Secretary's Advisory Committee on Genetics, Health, and Society: Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* (2010; "Report," obtainable at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf). Long QT Syndrome is a disorder of the heart's electrical system that is characterized by irregular heart rhythms and risk of sudden death.

The discovery of LQT Syndrome genes was partially funded by the NIH. Numerous U.S. patents were obtained on the genes and multiple mutations within them, and the patent holder (the University of Utah) granted an exclusive license to one laboratory, DNA Sciences, to develop and offer the diagnostic test for the genes. However, DNA Sciences never developed a genetic test for this disorder. Meanwhile, GeneDx *did* develop testing and made it available to the public. DNA Sciences sued GeneDx for infringement, and would not issue GeneDx a sub-license to offer testing. DNA Sciences was sold to another company. GeneDx contacted the new company and requested a license. The new company refused. GeneDx asked simply to be allowed to offer the test only so long as the new company was getting their test ready, so that there would be testing available to the patients and their families in the interim. The new company refused. The new company was then purchased by yet another company, which started offering the test through PGxHealth.

Thus there was a full 2-year period during which genetic testing for LQT Syndrome was not available for this disorder which kills children and young adults. I am aware of at least one patient, Abigail, who during this time developed an arrhythmia. If testing were available, the cause of Abigail's arrhythmia would have been diagnosed and the correct therapy been instituted. However, Abigail died suddenly at age 10 from her undiagnosed LQT syndrome.

My company GeneDx was eventually able to obtain separate licenses from the University of Utah for additional genes and mutations involved in LQT syndrome. The result was (and remains) that the licensing field is split: GeneDx has rights to test for some genes and PGxHealth has rights to some others. This remarkable situation is described in the Report's Appendix F as "unstable," (see page F-34) and is, in my view, close to ridiculous.

The problem of exclusive licensing extends to many other genetic diseases, aside from LQT genes. One well-publicized example is the BRCA1/BRCA2, the genes whose mutation results in a predisposition to breast cancer, ovarian cancer and even prostate cancer. These genes were also discovered with the help of funding from the National Institutes of Health. There are multiple patents in this portfolio, including many owned or co-owned by the University of Utah. The University of Utah has granted an exclusive license to its owned or co-owned patents to one company to develop, use and commercialize the diagnostic tests for BRCA1 and BRCA2.

In addition to BRCA1 and 2 and Long QT Syndrome genes, many providers have discontinued or have been prevented from providing genetic testing for other diseases.

The Role of Open Competition in Genetic Testing

I have a strong underlying belief that competition in diagnostic testing is critical to protection of the public health. Right now, except when blocked by exclusive licenses, clinical laboratories compete. We compete on service—getting back the results in a timely manner and in a way that contains clinically useful information to the physician and perhaps the

patient. We compete on quality—we have to get the right result; if we do not, then we will suffer the consequences – the loss of business. We compete on price--we know that if we are more efficient we can get more business. We need to compete fully and across the board on technology. We need, for example, to be able see if there is one area of the human genome that has been associated with one condition or disease that might have new or further meaning when combined with another area of the human genome. This robust competition protects the public. When a gene test is the exclusive province of a single laboratory because of an exclusive licensing agreement, that laboratory does not have to compete on any of these factors. The absence of competition leads to substandard quality of tests, inadequate marketing of or information about tests, as well as to excessive pricing, making the tests unaffordable and unavailable to thousands of individuals.

It is my belief that the exclusive licensing of genetic diagnostic patents is creating a serious public health problem. As the number of genes that are discovered to be associated in some manner to a certain disease keeps increasing, so will the problems. It is clear that while the function of many genes has already been discovered, many correlations between mutations in these genes and diseases still remain to be discovered. I expect that such discoveries will accelerate in the next few years, and that the number of established correlations will grow exponentially. And, since the numbers of discovered genetic correlations will grow, so will the numbers of patents and the number of exclusive licenses for diagnostic tests. Such a plethora of patents will decrease competition, produce intractable thickets, and in a worst (but easily foreseeable) case scenario will seize up entire fields of research and development.

The More Limited Role of Patent Protection in the Diagnostic Industry than in the Pharmaceutical Industry

This brings me to another significant problem caused by exclusive licenses: innovation is stifled. When an exclusive license is granted, research on finding new genes that will enhance the clinical significance of the original discovery is brought to a halt. I do not have a problem if the discoverers of such correlations obtain patent protection for the diagnostic applications of these correlations (always as qualified by the *Mayo* and *AMP* decisions, of course, so that the patents do not preempt the entire natural correlation or "law of nature" as the courts call it). I understand that the research enterprise needs financing and involves risks. Patent protection is a time-proven method of trying to control such risks.

In the case of genetic diagnostic correlations, however, it is my view that the risks are not as high nor the uncertainties as deep as is the case in the discovery of new drugs. I know that getting a new drug from discovery all the way through approval by the FDA may cost up to or more than $1 billion, and involve a decade or more of work and uncertainty. Exclusive patent protection is critical in order to fund such high risk and highly regulated endeavors.

In contrast, in the case of the discovery of genetic correlations to diagnosing disease or disease predisposition, the investment in time and money, the uncertainty, and the regulatory hurdles are not nearly as onerous as in the case of drugs. For example, a service laboratory like

my company could enter the market quickly at only a small fraction of the cost of what would be needed in the pharmaceutical industry. Allowing companies like mine, that can quickly put a diagnostic test on the market and provide competition to other laboratories in the same area, will be extremely beneficial to the public health.

There is a fundamental difference between the situation of drug companies and diagnostic laboratories. Given the huge costs of drug development, denying patent rights or exclusive licensing for drugs, formulations or methods of use could have serious consequences for the willingness of companies to undertake the needed research in the first place. Without solid patent protection, the companies could see no way to recoup their enormous investment. But in the area of gene patents for diagnostic tests, efforts to identify new genes and their correlation with disease would not seriously be discouraged by the absence of exclusive patent rights for several reasons. The costs of discovery are not comparable to those for drug development. Furthermore, because there are other ways of gaining royalties from the gene identification--for example development of drugs for the diseases themselves--the loss of some royalties from non-exclusivity on lab tests is not likely to have a serious adverse impact on the incentives to identification.

Another major difference between drugs and genetic diagnostic tests is found in the very nature of the two technologies. In the case where a drug is patented by one pharmaceutical company, its competitors are not prevented from continuing their research into the *same disease* with the expectation that they can develop different drugs that will avoid the patent holder's patent. The disease itself is not patented, as it obviously cannot be since it is a natural phenomenon. Thus, there are a potentially unlimited number of drugs of different compositions and structures that might be tested and proposed for treating the same disease.

In genetic diagnostics, in contrast, for a given disease, such as Long QT Syndrome, we are dealing with one or at most a handful of genes and their correlations. Once these are in exclusive hands for the average life of a patent, say 18 years, neither I nor others can enter the field and use the patented genes to find other genes or improve the tests that correlate to the same disease. In fact, since my work is primarily commercial in nature, were my researchers to do commercially relevant discovery research with patented genes, I understand that such research would constitute patent infringement of the rights of the exclusive holder. See, *Roche Products Inc., v. Bolar Pharmaceutical Co. Inc.*, 733 F2d 858 (Fed. Cir. 1984). The public does not benefit from such a situation.

I am therefore in favor of a regime where a company like mine can obtain a non-exclusive license from the holder of the patent or obtain a non-exclusive sublicense from the licensee of the patent. If I can demonstrate that my test would be better, faster, provide fewer false negatives or positives, fill a niche, cost less to the public or perhaps complement the test already offered by my competitor then the public will benefit greatly by my entry.

I am not asking for a free ride; all I am asking for is the ability to compete fairly and benefit the public and my company. In the area of genetic testing, exclusivity is a formula for mediocrity.

The NIH and Major Academic Institutions Disfavor Exclusive Licensing of Patented Genetic Diagnostic Tests

Many institutions, including the National Institutes of Health (NIH), major universities, and the Association of University Technology Managers (AUTM) already believe that the best practice is to strictly limit the grant of exclusive licenses to extraordinary circumstances.

More particularly, the NIH-recommended policy is to restrict the licensing of genomic inventions to non-exclusive approaches "whenever possible." A non-exclusive licensing approach "whenever possible" favors and facilitates making broad enabling technologies and research uses of inventions widely available and accessible to the scientific community. See, "Best Practices for the Licensing of Genomic Inventions: Final Notice" (70 Fed. Reg. 18413, 18415, April 11, 2005), at http://www.ott.nih.gov/pdfs/70FR18413.pdf (last visited 23 March, 2012).

Similarly, AUTM, the Association of University Technology Managers came out in 2007 with their recommendation of a consensus recommendation by about a dozen major U.S. research universities, entitled "In the Public Interest: Nine Points to Consider in Licensing University Technology." This policy addresses the need for commercial arrangements to be cognizant of the public good. http://www.autm.net/Nine_Points_to_Consider.htm (last visited 23 March 2012). It has been endorsed by close to 100 universities or academic associations, the most recent one in February 2012. See: http://www.autm.net/source/NinePoints/ninepoints_endorsement.cfm (last visited 23 March 2012).

Second Opinions and Genetic Testing

All of the concerns I have expressed above regarding exclusivity and genetic testing apply with equal force and even more to obtaining second opinions. The whole point of obtaining a second opinion from another laboratory is to confirm the first result. This provides both the patient and the physician reassurance before recommending and embarking on a major life changing and sometimes threatening procedure, such as surgery or highly toxic therapy in the case of cancer.. Laboratory tests are subject to errors even in the best of cases: Samples may get confused, readings may be erroneous]. It is therefore long standing good medical practice for a physician to request a second test before initiating drastic medical procedures.

If there is no licensed laboratory other than one, and it refuses to grant sublicenses, then physicians and patients are stymied in their conclusion that a decision on proper medical treatment is based on repeatable and reproducible test results. This is yet another clear example of how exclusivity leads to bad medicine.

Conclusions

I am not an expert of how the problem of exclusive licensing in genetic diagnostic testing can be overcome. I understand, however, that there are many possible solutions.

For example:

- The USPTO could encourage the Congress to strengthen the march-in provisions of the Bayh-Dole Act in cases where diagnostic tests have been developed using federal funds. March-in has never been used and is, to many observers, as good as non-existing.

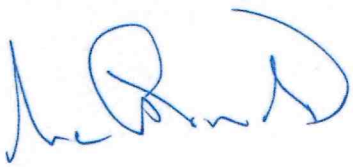
- The USPTO could recommend that Congress enact specific legislation tailored to genetic diagnostic tests, even those that have not been developed suing federal funds. Such legislation could require judges who traditionally design equitable remedies in infringement litigation to consider the harm caused by exclusive licensing to the public health and, if such harm is found, to obligate the patent holder to grant a sublicense so as to promote the public health. This is an approach that is fully consistent with the U.S. Supreme Court's opinion in the *eBay* case, which set forth the need to consider the public interest before automatically granting permanent injunctions.

- A further - and perhaps less onerous - solution is for the USPTO to propose legislation that would create an exemption for second medical opinions from the exclusive licensing of patents that have been obtained through federal funding.

- Symmetrically, the USPTO could recommend legislation that would force judges to consider the public health before enjoining a laboratory that wishes to offer a second opinion test, even when the patented test has not been discovered using public funds.

I have valued this opportunity to share my views on the serious public health consequences of exclusively licensed patents for diagnostic gene testing. I most respectfully urge the USPTO to recommend to the Congress a remedy to the problems I have described.

Very Truly Yours
BioReference Laboratories, Inc.



By: Marc D. Grodman, MD, CEO