Statement of Dr. Marc Grodman,
CEO of Bio-Reference Laboratories, Inc.

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"

October 30, 2007

Mr. Chairman, members of the subcommittee, I want to thank you for the opportunity of testifying on a critical issue of public health. I also want to congratulate the subcommittee for its leadership in scheduling this hearing on the important topic of the impact of gene patenting in genetic testing.

My name is Marc Grodman. I am the founder and CEO of Bio-Reference Laboratories (BRLI), a publicly traded company with headquarters in Elmwood Park, New Jersey that is the largest independent regional clinical laboratory in the Northeast, and that also provides national service in certain specialized areas. 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 almost 1700 individuals and serve physicians across the country who send us the samples to test. Over the past twenty years, BRLI has grown substantially. This year its revenues will total more than a quarter of a billion dollars, up from two hundred thousand dollars in 1987.

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.

At the outset, I want to make it clear that that I am not here to attack the entire U.S. patent system, or even the patenting of genes or gene sequences *per se*. I am also not here to challenge the rights of universities under the Bayh-Dole Act of 1980 ("Bayh-Dole") to profit from the commercialization of their discoveries. 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. What I am saying is that the exclusive licensing of genetic associations, meaning of specific gene sequences or mutations in relation to certain clinical conditions, should be barred.

I would like to focus my remarks on two points: (1) explaining how the grant of exclusive patent licenses for conducting genetic diagnostic tests runs contrary to the public health; and (2) proposing a practical and simple remedy for this problem, which involves the Bayh-Dole Act of 1980.

I became personally familiar with the issues when in 2006, BRLI purchased GeneDx, a wonderful laboratory, not far from here in Gaithersburg, Maryland, that does DNA sequencing, analyzing each base pair of the chromosomes, to diagnosis 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.

How has this problem arisen?

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 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.

Indeed many institutions, including the National Institutes of Health (NIH), major universities, and the Association of University Technology Managers (AUTM) believe that the best practice is to limit strictly 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 October 25, 2007).

Similarly, AUTM recently came out 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, published on March 6, 2007 addresses the need for commercial arrangements to be cognizant of the public good. http://www.autm.net/ninepoints_endorsement.cfm, last visited October 26, 2007.

I have to confess to a strong underlying belief—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 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 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.

Let me give you several examples of the problems my laboratory 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 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.

We have experienced another notable example of the problem involving genes associated with Long QT Syndrome. 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 these genes was partially funded by the NIH. Numerous U.S. patents were obtained on the genes and the patent holder (the University of Utah) granted an exclusive license to <u>one</u> laboratory to develop and offer the diagnostic test for the genes.

We have consulted with Dr. Wendy Chung, a highly respected physician and research scientist at Columbia University's New York-Presbyterian Hospital, who has informed us that there have been serious quality problems which continue, generally unresolved, in connection with the LQT Syndrome tests. A key problem relates to inaccurate or incomplete testing. Thus, tests done by the exclusively licensed clinical laboratory failed to detect mutations that were found in the same patients who were tested by Dr. Chung's research laboratory. One such case involved a five year old child who was at very high risk of sudden cardiac death. An incorrect test could have had fatal consequences for the child. An incorrect diagnosis in the child would also have left over 20 other mutation carriers in her family at risk for sudden cardiac death. A system that allows only one laboratory to conduct a genetic test creates other problems as well. Dr. Chung has also informed us that the turn around time for the test is lengthy, and can take as long as six to eight weeks. Finally, the price of the test to the public is currently $5,400 even though a competitive laboratory could offer the test for about a quarter of the price. I am submitting as Appendix A to the subcommittee a written statement by Dr. Chung that describes in greater detail the problems with the Long QT syndrome test.

The University of Utah awarded an exclusive license to DNA Sciences for genetic testing in several genes associated with LQT. 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. Thus there was a full 2-year period during which genetic testing 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 arrythmia. If testing were available, the cause of Abigail's arrythmia would have been diagnosed and the correct therapy been instituted. However, Abigail died suddenly at age 10 from her undiagnosed LQT syndrome.

In sum, we have tried, with no success, to sublicense the Long QT genes from the laboratory with the exclusive patent rights so that we could offer the test to the public. I am convinced that if we had the rights to perform this test, we could do a better job and do it less expensively so that the test would be more widely available.

This problem extends to many other genetic diseases aside from LQT genes. One well-publicized example of this problem has to do with 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.

To begin with, there were several problems with the BRCA1 and BRCA2 tests, according to information we have received from Dr. Chung , which is contained in her statement to the subcommittee. For example, for many years, the testing procedures did not include genomic deletions and rearrangements. As a result, there were a number of mutations that were not detected by the test offered until 2006, meaning that the tests were not as comprehensive as they could have been if other companies and researchers had been permitted to create a better test. Furthermore, the laboratory's insistence on testing blood only has restricted the test unnecessarily in instances in which there is no blood but only other genetic material. The cost of the test, which is still high--approximately $3,000-- poses a problem for people who are uninsured or live in states in which Medicaid does not reimburse the cost.

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. I am submitting as Appendix B to the subcommittee a statement provided to me by Dr. Katherine Matthews, a neurological pediatrician at the University of Iowa, describing the serious problems she has encountered previously with the exclusive licensing of gene patents in the area of neurological disorders. Many of these problems are similar to those described by Dr. Chung in her statement.

It is my strong 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.

There is another significant problem caused by exclusive licenses: innovation is stifled. As Dr. Chung's statement demonstrates, 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. 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 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 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.

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.

Fortunately, I believe that the Bayh-Dole Act of 1980 offers a ready solution to these problems that requires no legislation at all.

The Bayh-Dole Act was enacted more than twenty years ago to encourage the commercialization of patents obtained through federal funding by allowing the universities sponsoring the research to hold the patent. Nonetheless, Congress understood that this patent monopoly, based on taxpayer funding, could be misused--and Congress specified a remedy for

the misuse. Thus, the Act empowers the federal agency financing the research to "march in"--and provide licenses to other interested parties--when, for example, the "health or safety needs" of the American people are not being "reasonably satisfied" by the patent holder or its exclusive licensee.

The march-in rights are clearly spelled out in Bayh-Dole (35 U.S.C. § 203 (a)(2)):

> (a) With respect to any subject invention in which a small business firm or nonprofit organization [e.g. a university] has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made [e.g. NIH] shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder, to require the contractor, an assignee, or exclusive licensee of a subject invention [e.g. in the case of the Long QT exclusive licensee] to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such
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> (2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees...

Bayh-Dole applies because most of the research leading to gene patents have been funded by the federal government.

I am aware that the NIH has never exercised its "march in" powers. I also know that it has denied three formal requests to "march in," although none of those instances involved diagnostic genetic tests.

In its opinions on two of those requests (Norvir™, manufactured by Abbott Laboratories, decided July 29, 2004; and Xalatan™, manufactured by Pfizer, decided September 17, 2004), the NIH indicated that the cases rested essentially on complaints about pricing alone, and asserted that "march in" rights were not designed for "controlling" drug prices. In addition, because in both instances the FDA had approved the drugs as safe and effective and no evidence had been presented by the requesters that march-in would alleviate health or safety needs not met by Abbott or Pfizer, the NIH declined to act. As I will demonstrate below the situation with genetic diagnostic tests is entirely different from that of these drugs.

The third denied request involved a 1997 petition from Baxter Labs that the NIH initiate march-in proceedings in a litigation between two competing products for separating stem cells. See, *Johns Hopkins University v Cellpro Inc.,* 152 F3d 1342 (Fed. Cir., 1998). The NIH found

no health and safety needs at issue because the difference between the products was just one of "convenience of use." The NIH found that Baxter had taken appropriate steps to reasonably satisfy "health or safety needs," and did not initiate proceedings.

None of these cases, I believe, poses any obstacle to NIH's use of "march in" powers to ensure that the public's "health and safety needs" are met by diagnostic genetic laboratory tests. In fact, the exercise of march-in rights would be especially appropriate in cases involving diagnostic gene testing. Opening up the licensing process to more than one diagnostic testing laboratory will have the highly desirable benefits outlined above with respect to improved quality, wider public availability and, incidentally, lower cost to the public.

There is a fundamental difference between the situation of drug companies and diagnostic laboratories, as I have pointed out previously. Given the huge costs of drug development, breaking up exclusive patent rights for drugs 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.

In addition, breaking up exclusive licenses need not provide a windfall for my company or any other company. The Bayh-Dole section of the patent law contemplates expressly that the marching-in agency arrange that a license or sublicense be given to a responsible applicant "upon terms that are reasonable under the circumstances." See 35 U.S.C. § 202(a). This clearly envisions the calculation of a reasonable royalty – not a royalty free license. There is plenty of

precedent for reasonable royalties in other areas of the patent law, such as 35 U.S.C. § 154 (a "reasonable royalty" to be charged to a party who has been on notice of pending patent claims that later issue) and 25 U.S.C. § 284 (after losing an infringement lawsuit the infringer has to pay damages no less that a "reasonable royalty"). The courts have developed a lengthy jurisprudence on what is a "reasonable royalty" for damages for patent infringement. See for example *Georgia-Pacific Corp. v. U.S. Plywood Corp.*, 318 F. Supp. 1116 (S.D.N.Y. 1970) (using 15 factors to determine a "reasonable royalty" such as the nature of the invention, other established royalties for the same patent, other comparable royalties, the custom of the industry, etc.).

Finally, calculating reasonable royalties is a well known exercise to patent-savvy universities and to the NIH's Office of Technology Transfer, both of which have licensed out their own extensive portfolios of patents in the last few decades.

Bayh-Dole vested the government with the responsibility of ensuring that government funded technology licenses protect the best interests of the public. In light of the foregoing, I believe that this committee should require that the that NIH enforce the "march in" provisions of Bayh-Dole in appropriate cases involving diagnostic genetic testing, including the ones outlined above. This is a feasible and indeed necessary way to ensure that the public's health and safety needs are met more widely with regard to DNA diagnostic and susceptibility testing. If the NIH is unwilling or unable to enforce the law as written, then Congress should review whether the power to enforce Bayh Dole should be placed in the hands of another federal agency. The NIH cannot be permitted to let Bayh Dole's march in provisions become dead letter law. The NIH must implement the law, not nullify it.

I have deliberately not discussed in detail other obvious remedies. The subcommittee is clearly aware that there are legislative solutions, such as the bill that was proposed by former Rep. Lynn Rivers. In my opinion, there is no need for a study to document further a problem that is already well known in the field of genetic diagnostic testing.

I have valued this opportunity to share my views on the serious public health consequences of exclusive patents for diagnostic gene testing. I most respectfully urge the subcommittee to adopt a remedy promptly to the problem I have described.

Appendix A

Statement of Dr. Wendy Chung
Submitted in Connection with the Statement of Dr. Marc Grodman,
CEO of Bio-Reference Laboratories, Inc.

The House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in connection with a hearing on Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing

October 25, 2007

Mr. Chairman, Members of the Subcommittee,

Thank you very much for the opportunity to submit this statement which accompanies the Statement submitted by Dr. Marc Grodman, CEO of Bio-Reference Laboratories, Inc.

My name is Wendy Chung, MD, PhD. I am a clinical and molecular geneticist and am director of Clinical Genetics at Columbia University. I am director of the fellowship program in molecular genetics and cytogenetics at Columbia University and direct both a clinical and research molecular genetics laboratory. I am the Herbert Irving assistant professor of pediatrics and medicine at Columbia University. I have been conducting research in human genetics for the last 17 years in the areas of obesity, diabetes, breast cancer, pulmonary hypertension, inherited arrhythmias, congenital heart disease, and spinal muscular atrophy.

In recent years, there has been groundbreaking research in human genetics that has identified the genetic basis for over 2200 human diseases. Genes have been identified for nearly all types of human disease including susceptibility to breast cancer, colon cancer, Parkinson disease, Alzheimer's disease, stroke, coronary artery disease and myocardial infarction, arrhythmias, diabetes, and macular degeneration. These conditions are not rare diseases, but are common conditions from which the majority of Americans will suffer at some point in their lives. Importantly, for many of these conditions, there are effective preventive measures that can be taken if patients know they are at risk. Therefore, genetic testing for these conditions plays a crucial role in allowing patients to assess diseases for which they are at risk, quantify the level of risk, and determine the interventions that will be most effective given the molecular basis of their disease predisposition.

Clinical testing is now available for over 1,180 of these genetic disorders, but in approximately 20% of these cases, only one laboratory is available to perform such testing, and genetic testing is often expensive ($1000-$5400) with long turn around times (approximately 2 months), and often ambiguous results. The provision of inexpensive, clinically useful genetic testing has been stifled in part based upon the issuance of patents for genes and provision of exclusive licenses that allow only a single laboratory to perform clinical genetic testing.

As significant as our previous advances in human genetics have been, within the last year alone, there has been an explosion in the identification of multiple genetic risk factors for many more diseases including inflammatory bowel disease, myocardial infarction, asthma, diabetes, and obesity. These advances were made using a genetic technique called genome wide association studies which will likely continue to identify many additional genetic risk factors for common diseases. To continue translating these genetic discoveries into improved health and quality of life, it is critical to ensure that affordable, interpretable clinical genetic tests will be available to all Americans.

A significant obstacle to providing this effective genetic testing to patients has been the issuance of patents on human genes and the issuance of exclusive licenses to use these genes for diagnostic purposes to a single laboratory. Neither one alone, but issuance of BOTH gene patents AND exclusive licenses in combination result in a monopoly in the provision of genetic

tests. It should be noted that the majority of genes for human diseases do not have both gene patents and exclusive licenses granted for genetic testing. However, there are a few notable examples for which this has occurred that have had detrimental results for the public good which we will discuss below.

Many of the genes for human diseases have been discovered in part or in whole in laboratories within universities and medical schools, funded in large part by the National Institutes of Health. Under this system, the patent holder controls the commercial use of the gene. In many cases where the university or medical school grants licenses to multiple companies, the public interest and technological advancement are promoted through the competitive marketplace. In those cases, however, where the patent holder on the gene grants an exclusive license to a single laboratory to develop and market diagnostic tests for that gene, the monopoly on the test generally leads to unfavorable consequences. The resulting monopoly in genetic diagnostic testing has many of the same effects as monopolies in other sectors. If there is only a single provider for a medical genetic testing, there is no competition or market force. This leads to substandard quality of the tests, inability for physicians to independently confirm a test result, lack of innovation and test improvement, slow turn around times for testing, and excessively high prices that often make these tests unavailable to many patients and unnecessarily increases the cost of health care provision by third party payers.

There are two especially noteworthy examples of this problem with gene patents and exclusive licenses.

The first example is for hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2, the research on which was partially funded by the NIH. As the patent holder, the company refused to issue licenses to any other laboratories, commercial or academic, to provide a comprehensive diagnostic test for BRCA1 and BRCA2. That company had relied exclusively upon sequencing technology for 10 years to screen for mutations in these genes, a technology that is expensive and able to detect some but not all mutations in these genes. Large deletions, insertions, and re-arrangements in BRCA1/BRCA2 cannot be detected by this methodology and were known to be a cause of mutations (Walsh *et al.*, *JAMA 295*: 1379, 2006). It was only after considerable pressure from the scientific community that the company added methods to detect these deletions, insertions, and re-arrangements in 2006, over 10 years after they first introduced clinical genetic testing, and barred anyone else from performing the tests. In a competitive marketplace, this delay never would have occurred.

Test result interpretation provided by the company has been problematic. As of 2005, approximately 1,433 BRCA1/BRCA2 genetic tests had been reported out by the company to have "variants of unknown significance" which leaves the patient and the physician not knowing whether or not the patient is at increased risk for breast and/or ovarian cancer. These variants of unknown significance are reported disproportionately in minority populations (African Americans, Hispanics, and Asians) because we have less information about the normal genetic variation in minority populations who are less likely to participate in research studies unless diagnostic laboratories proactively gather this information. Rather than developing the necessary databases of normal genetic variants in multiple ethnic groups, scientifically analyzing the conservation of these nucleotide positions across other species, correlating these variants with

the personal and family histories of the patients tested, and/or performing biological assays to functionally assess these variants, the company simply continues to report out ambiguous results because there is no incentive for them to improve the quality of the data interpretation since they face no competition in the market. Furthermore, until recently, all these data were held exclusively by the company so there was no ability for scientists to conduct these experiments themselves for the benefit of the public.

The company is willing to perform genetic testing only on blood samples and has not developed the ability to perform genetic testing on paraffin embedded tissue from previous cancer specimens although this testing is routinely performed in research laboratories. In many cases, the family member with either breast or ovarian cancer is deceased and the only source of genetic material for testing is a tumor sample that was previously removed. Testing an affected family member is necessary for accurate interpretation of a negative result in other unaffected family members. A negative genetic result in the daughter of a BRCA1 or BRCA2 mutation carrier reduces the daughter's risk of cancer to that of the general population while the cancer risk for a daughter with a negative genetic result of a mother who had early onset breast cancer but was negative for BRCA1 or BRCA2 remains substantially elevated over the general population. Again, without competition, the company has had no incentive to develop genetic testing from sources other than blood, cruelly leaving families at risk with no remedy.

The cost of BRCA1/BRCA2 testing has remained substantial, costing approximately $3000 from the time it was first offered 12 years ago. The cost could have been reduced by offering targeted rather than comprehensive testing for specific populations in which founder mutations account for a large fraction of all mutations. This has been offered for Ashkenazi Jews in the US, but for no other populations. For the first seven years, many insurance companies did not cover genetic testing for BRCA1/BRCA2 or required a lengthy preauthorization process that discouraged many patients from pursuing testing. Some of my patients died during that preauthorization process, and then the families were not able to get their affected family member tested to guide their future medical care. In addition, for the first eight years, the testing was not covered by Medicare, and for the first ten years and still in many states is not covered by Medicaid. This has created enormous disparities in access to the BRCA1/BRCA2 diagnostic tests due to the high cost which has continued to increase over the years to the current cost of $3200.

The second notable example has been for genetic testing for Long QT Syndrome which is associated with fatal arrhythmias of the heart and sudden death. These results can be prevented by avoiding triggers such as heart rates that are too fast or too slow or startling sounds during sleep, taking medication, and having a cardiac defibrillator implanted. Importantly, the therapy for each patient is based upon his or her molecular genetic defect. There are now 9 molecular subtypes of Long QT syndrome, and the triggers for arrhythmias and the most appropriate medical therapy depends upon which gene is mutated, a fact that can only be determined by genetic testing. A medication that is commonly used for Long QT syndrome, beta blockers, which decrease the heart rate, are the first line drug for Long QT1 and Long QT2, but actually increase the risk of arrhythmias in Long QT3 which is more appropriately treated with medications such as mexiletine or flecainide.

The discovery of these genes for Long QT syndrome was partially funded by the National Institutes of Health. Patents were obtained on many of the first Long QT genes by the University of Utah, which granted an exclusive license to one laboratory to develop and provide a diagnostic test for the genes. DNA Sciences, the first commercial laboratory to offer testing, forced two other laboratories to cease and desist offering genetic testing for Long QT syndrome on the basis of their exclusive licenses. DNA Sciences subsequently went out of business, and for a period of time patients were unable to get any genetic testing for Long QT syndrome because the license holder was not performing testing. The licenses were subsequently purchased by Clinical Data Systems which is again the only laboratory licensed to offer genetic testing for Long QT syndrome. Many of the same problems that the medical community has experienced with BRCA1/BRCA2 testing have been repeated with Long QT syndrome testing because there is a monopoly on the testing. I describe them below.

Although the number of genes for Long QT syndrome has increased from 5 to 9 over the time that clinical testing has been made available, there has been no increase in the number of genes analyzed by the exclusively licensed laboratory, even though this would improve the testing sensitivity and would be clinically important.

Most concerning is that the company has rendered genetic testing results to me that have several times been inconsistent with independent genetic data obtained in my laboratory For most patients there is no ability to independently confirm these results since there is no other clinical laboratory performing this testing., There are instances where I have independently performed genetic testing in my research laboratory and then sent samples to the company for independent confirmation prior to initiating medical therapy based upon their genetic test results and then found inconsistencies. One case would have had devastating effects for a 5 year old patient and her family since she carries two mutations (usually only one mutation is necessary for Long QT syndrome) and has a particularly malignant form of Long QT syndrome associated with nearly 100% mortality in childhood without intervention. Furthermore, because the mutation was inherited from both her mother and father, 20 other mutation carriers in her family are at risk for sudden cardiac death would have been missed had we not independently confirmed the correct result. In a competitive environment, where there is another laboratory offering this test, this situation would never exist. That company has also incorrectly reported genetic variants as disease associated because they have misinterpreted the scientific literature. There are many Long QT genetic variants that are associated with prolongation of the QT interval only upon exposure to certain medications that prolong the QT interval, but otherwise do not cause problems if patients do not take medications that prolong the QT interval. Patients carrying these variants should avoid such medications that prolong the QT interval, but do not have a high risk of sudden cardiac death if they do not take these medications. The company also reports some of these drug induced Long QT variants as independent Long QT mutations, leading many cardiologists to pursue overly aggressive intervention with medication and implantable defibrillators.

Similar to genetic testing for BRCA1/BRCA2, the company reports out "Class II variants of unknown significance" in approximately 5% of their test reports. These variants of unknown significance are reported disproportionately in minority populations (African Americans, Hispanics, and Asians) and is often extremely anxiety provoking and often leads to prophylactic

implantation of a defibrillator. Rather than developing the necessary databases of normal genetic variants in multiple ethnic groups, scientifically analyzing the conservation of these nucleotide positions across other species, correlating these variants with the personal and family histories of the patients tested, and/or performing biological assays to functionally assess these variants, the company has not improved the test interpretation. Furthermore, the database of genetic variants is not publicly available, so there is no opportunity for scientists and physicians to attempt to interpret the genetic test results themselves beyond the information they have on their patient and the information in the scientific literature, leaving patients and physicians wondering if the patient really has Long QT syndrome or what treatment would be beneficial. Plainly, the exclusive license stifles scientific research and creates a barrier to medical progress.

The company is only willing to perform genetic testing on blood samples and has not developed the ability to perform genetic testing on paraffin embedded tissue tissues although this testing is routinely performed in research laboratories. Unfortunately, many of the cases that require testing are cases of sudden death, particularly sudden infant death syndrome (SIDS) in which the autopsy is normal. In such cases, usually the only tissue available for testing after the autopsy is paraffin embedded tissue. For families to obtain closure on the cause of death of their loved one and prevent similar deaths in other family members, it would be important to be able to perform genetic testing on fixed tissues.

The current cost of genetic testing for Long QT syndrome is $5,400 and is not routinely covered by most insurance companies without a lengthy preauthorization process that frequently takes 3-12 months to complete. Furthermore, testing is not covered at all by Medicare or Medicaid. The actual cost of the testing without the cost of the licensing fees could be 25% or less of the existing price and would be accessible to many more patients if it were correctly priced in a competitive market.

In summary, when genetic testing is performed by a single laboratory, the quality of the genetic testing and interpretation of results suffer, and the price of the testing remains artificially elevated to the detriment of patients who could take preventive measures to preserve their health if provided with accurate information to determine their risk of life threatening diseases.

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Appendix B

Statement of Dr. Katherine Mathews

Submitted in Connection with the Statement of Dr. Marc Grodman, CEO of Bio-reference Laboratories, Inc.

Before the House Judiciary Subcommittee on Courts, the Internet and Intellectual Property

"Stifling of Stimulating – The Role of Gene Patents in research and Genetic Testing"

Dated: October 26, 2007

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Mr. Chairman, Members of the Subcommittee,

Thank you very much for the opportunity to submit this statement which accompanies the Statement submitted by Dr. Marc Grodman, CEO of Bio-reference Laboratories, Inc. My purpose in submitting testimony today is to provide first hand information about how the lack of competition among clinical laboratories offering specific genetic tests affects the quality of care that patients receive. I hope that my testimony will help in your consideration of questions concerning the role of gene patents in genetic testing.

I am a pediatric neurologist with expertise in neurogenetics and neuromuscular disease. In my clinical practice, genetic testing is often the most efficient, cost effective and/or accurate way to make a specific diagnosis. There is a choice of laboratories that offer the testing for some of these genetic tests. In this case, the University of Iowa Pathology Department has worked with clinicians such as me to choose the laboratories that provide the best service, most accurate and thoughtful results and are most cost effective. (This is also our approach to choosing reference laboratories for non-genetic diagnostic tests.) However, as you have heard, other genetic tests are available from a single commercial laboratory which has exclusive rights to the use of that gene in clinical testing. If a single laboratory has excessive costs, poor service or consistently inaccurate or incomplete results, I have few options. I can cease to offer the genetic test to my patients, or I can continue to accept suboptimal information for those patients who can afford the testing.

In my own case, after experiencing a consistent and unremitting pattern of laboratory and administrative errors that negatively impacted my care for patients, and after hours on the phone trying to correct or identify the basis of the problems, I notified one laboratory in writing in 2005 that I would no longer be sending them samples for one type of disease. Unfortunately, because the laboratory in question has exclusive rights to the testing for this disease and other diseases I deal with commonly, I have had to continue using them on occasion, and the problems have continued. In my management of a patient with one of these diseases, whenever I feel that not making a specific genetic diagnosis is a medically acceptable option, I explain to the patient that the only source of genetic testing has been unreliable and difficult to work with in my experience. Therefore I recommend that we forgo genetic testing at this time.

I will attempt to outline the problems that have led to this approach and present some typical examples.

Case 1.

This case (and several others presented here) involves inherited peripheral neuropathy, or Charcot-Marie-Tooth disease. Neuropathies are caused by loss of function of the nerves going to the limbs and typically result in weakness of the ankles, lower legs and hands; absent reflexes; and decreased sensation in the feet and hands. There are many reasons a person might have neuropathy (such as diabetes). One subset of the neuropathies is inherited and there is an ever-increasing list of specific genes that are associated with inherited neuropathies. The inherited neuropathies as a group are called Charcot-Marie-Tooth disease, or CMT, and each genetic cause is given a specific number/letter designation, such as Charcot-Marie-Tooth type 1A, CMT1A. It is often helpful to make a specific genetic diagnosis to allow accurate genetic counseling to a family as the different subtypes are inherited differently (illustrated in Case 4 below). Arriving at a specific genetic diagnosis also prevents unnecessary, expensive and sometimes painful testing looking for other, non-genetic causes of neuropathy.

An adopted child was referred for increased falling and the physical findings indicated this was likely a neuropathy. She also had several other medical problems, making the diagnosis more complex. The most common reason for a child to have a neuropathy is that it is inherited (CMT as discussed above). I ordered genetic testing for CMT1A, the most common form of CMT. The test was called "not interpretable" and a second sample was requested. One month after the first sample, the second was sent. Five months after the original test and 4 months after the second, after several phone calls from the family asking about the results and numerous phone calls to the laboratory, the report was released. The diagnosis of CMT 1A was highly likely. This whole process was surprising, as genetic testing for this disease has been available for more than 10 years, many laboratories used to offer the testing (before the exclusivity restrictions were enforced), and interpretation of test results is usually extremely straightforward and available within 2 weeks (which is what the family had been told by me).

In phone calls with this lab, we were told that the reason for the difficulty with this case was that the laboratory had recently changed the way they performed the test, and were finding a small number of patients (such as this one) whose results they had not expected. The laboratory didn't have a back up approach in place to assist with interpretation (such as repeating the test, using the previous or one of several other possible technologies) and apparently had not tested this technique to identify such potential problems prior to implementing the change clinically. Furthermore, the several month delay before the lab director would complete the report suggests that the lab director lacked sufficient understanding of the genetics of this disease to interpret the results. Finally, the lab director did not appear to have contacted an expert in the field for assistance. This case left the family involved very unhappy, and gave me very little confidence in the laboratory.

Case 2.
A 47 year old woman and her adult children were referred for genetic counseling. She has progressive ataxia (unsteady gait) resulting in significant disability, as do many of her family members. The clinical diagnosis is spinocerebellar ataxia (SCA) and there are more than 20 different genetic causes of SCA. The different genetic causes are clinically indistinguishable, so genetic testing is required for a specific diagnosis. This patient had genetic testing done by a previous neurologist. The report showed that most of the SCA genes were normal, and one (SCA8) was interpreted as "borderline". The report states that it could not be determined if this borderline result was associated with disease. However, the objective results (as opposed to the interpretation) of the genetic testing for this patient were also listed. The SCA8 result was 99; with normal being up to 50 in the literature, and up to 70 in this lab's own report. Clearly, 99 was in an abnormal range rather than a borderline range. There was no explanation for this discrepancy in the comments or interpretation of the report. This information is critical to provide accurate counseling to the children of the patient. Therefore, the neuromuscular nurse called the lab, where the director agreed that the interpretation did not make sense. The lab requested a second sample, which they will test at no charge to clarify the diagnosis. (Results are still pending.)

While the response to our concerns was very appropriate and helpful in this instance, errors in interpretation of this magnitude are outside of what is expected for a clinical laboratory. Most physicians only read the "Interpretation" section of a genetic test report. They rely on the expertise and knowledge of the laboratory director.

Case 3.
This case was sent to me by a colleague at a different university. A great deal of detail was included in the summary and I was told that the entire situation is documented in the medical record. This case involves a disease called CADASIL that typically causes strokes and migraines in young adults. Brain MRI is quite abnormal in the disease, but the abnormality is not specific for CADASIL. This is an autosomal dominant disease, meaning that if a person is affected, their children have a 50% chance of having the same disease and other family members are affected. Genetic testing is the easiest and generally most accurate way to make the diagnosis. The disease is steadily progressive with recurrent strokes resulting in significant disability, dementia and in some cases, premature death. There is no specific treatment.

A middle aged man had some transient neurologic abnormalities, migraines and an abnormal MRI of the brain. Genetic testing for CADASIL was sent. The laboratory identified change in Notch 3, the CADASIL gene. The report stated that this was a known disease-associated mutation. The interpretation was confusing to my colleague because the DNA variant should not have led to a change in the protein. (Some amino acids can be coded several ways by the DNA, so a DNA change does not necessary cause a protein change, and without a protein change, disease is quite unlikely.) My colleague called the laboratory director to discuss this unusual situation. The lab director stood by the result and insisted this was CADASIL. Because of the suspicion that this was NOT in fact CADASIL, both of the gentleman's parents were tested (neither of whom had any symptoms relevant to CADASIL) and the mother had the same genetic variant. In her case, the same laboratory reported this as a "known polymorphism", meaning that it was a benign variant not associated with disease.

Ultimately a biopsy was performed to see if the man had other typical findings of CADASIL. None were found. Finally, the same laboratory was sent another sample from the patient. The lab identified the same variant that had been found previously and found in the patient's mother, and this time it was called a known polymorphism. The patient's ultimate diagnosis appears to be multiple sclerosis, treatment for which was delayed by one year due to this error. The bill to the family for all the genetic testing was approximately $10,000. The emotional cost was huge. There was no acknowledgement on the part of the laboratory that there had been an error, despite multiple phone calls regarding this case from the physician involved.

Case 4.

A 33 year old man was seen for clarification of his diagnosis and genetic counseling. He has Charcot Marie Tooth disease, but the type was unknown. He has a young son and wondered if the child could inherit his problems with weakness. His mother and several other relatives were similarly affected. Testing for CMT1A was normal. We then sent testing for CMTX. This is one form of CMT that is inherited in an X-linked fashion (carried on the X-chromosome). If this man has CMTX, then he could not pass it on to a son, since he would only give his son a Y chromosome. If this family has another form of CMT, the risk to his son would be 50%. This was an issue of grave concern for this man as he felt that his life had been significantly impacted by CMT. The CMTX report interpretation read: "This individual possesses a sequence alteration in the coding region of the Cx32 gene which cannot be interpreted as either disease associated or benign polymorphism, and therefore the result is indeterminate". The specific nucleotide change was also listed on the report. By reviewing the nature of the amino acid change, and databases listing the structure of this gene in many lower species, we were able to come to a conclusion that this change is highly likely to be disease causing. We confirmed this be discussion with a research expert in the field and have given appropriate counseling to the patient for CMTX.

Case 4 is one example of a case where the result is "indeterminate". Any time a mutation or alteration in a gene is identified, whether in a research laboratory or a clinical laboratory, the first question to be answered is whether it is simply part of the genetic variability that contributes to making us each an individual, or does it change the function of something essential, leading to disease. There are several approaches that can be taken to try to answer the question. The simplest is to look at the medical literature to see if the change has been reported in other people with the same disease or in the general population. If it is unreported, then one can examine additional information (computer database searches and basic biochemistry), as described in case 3, to make the best possible determination about whether or not the change is disease-related. In a research laboratory, several increasingly complex steps can be taken to clarify the nature of the genetic variation.

Clinicians rely on the genetic testing laboratory director to do the database searches and use their knowledge of biochemistry and physiology to examine the effects of the potential mutation and give the clinician the best possible guidance about whether it is disease-causing or benign. Clinicians generally have neither the time nor the expertise to do that level of analysis. This kind of support is generally viewed as part of the cost of the test (above and beyond the simple technical examination of the DNA). Most genetic testing laboratories in my experience offer this kind of service. If a laboratory fails to provide this service, I generally try to find an alternative laboratory to work with on future patients.

The problem of indeterminate test results is illustrated in Case 4, but I could have presented many more cases. Two similar cases from another institution were recently presented at the Symposium on Neurogenetics at the 2007 Child Neurology Society meeting and were contrasted with reports from a laboratory that provided detailed analysis of genetic variants.

In summary, the lack of choice in laboratories offering genetic testing, as a direct result of the patenting of genes and granting of exclusive contracts, is unusual in medicine and deleterious to patients and practitioners alike. It has led to my limiting my diagnostic testing in some cases, and accepting suboptimal test results in others. It has led to uncounted phone hours attempting to sort out errors and problems, without the simple recourse of choosing a different laboratory. It contributes to unnecessary health care expense. I feel that my ability to provide the best possible care to my patients is compromised by the current situation in genetic testing. Many of my colleagues in clinical genetics and neurology around the country share my concerns.

We are moving into an era when some treatments for genetic diseases will be based, at least in part, on the specific genetic mutation that caused the disease (example: PTC 124 is currently in trials for Duchenne muscular dystrophy and cystic fibrosis patients with point mutations and premature stops). If genetic testing becomes a prerequisite for best therapy, and each of these genetic tests is "owned" by a single, for-profit company without competition, I see no incentive to optimize service and accuracy, or to minimize costs to the patient, resulting in further escalation of health care costs and even greater clinical impact of errors in genetic testing.

Thank you very much for your attention to this issue.

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