COLUMBIA UNIVERSITY
College of Physicians and Surgeons

Department of Pediatrics
Division of Molecular Genetics
1150 St. Nicholas Ave. Room 620
New York, NY 10032
212.851.5315 Tel
212.851.5306 Fax

www.cumc.columbia.edu

March 24, 2012

Saurabh Vishnubhakat, Attorney
Advisor, Office of Chief Economist,
United States Patent and Trademark
Office, Mail Stop External Affairs, P.O.
Box 1450, Alexandria, VA 22313–1450.

RE: Genetic Testing Study

Dear Mr. Vishnubhakat:

I want to thank you for the opportunity of providing my views 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.

I am a board certified clinical and molecular genetic who care for patients with hereditary disorders. My patients depend critically on access to accurate molecular diagnostic testing to determine the cause of the disease in their family to allow for appropriate risk stratification, prevention, and treatment of disease. Without access to accurate genetic testing, their lives and those of their family members are at risk, and they are unable to make informed reproductive decisions to potentially minimize the risk of genetic diseases to future generations. Because genetic diseases affect all organ systems and patients of all ages, there is no are of medicine that my practice does not touch. Furthermore, as genetic testing becomes increasingly comprehensive (including whole genome and whole exome sequencing) and increasingly adopted across all areas of medicine, these issues need to be addressed and resolved to allow for high quality patient care.

At the outset, I want to make it clear that I am a plaintiff in the case *AMP et al v USPTO v Myriad Genetics* (Fed. Cir. 2011) and believe that the information content of genes should not be patentable. The consequence of patenting of many human genes has led to exclusive rights for only a single laboratory to perform genetic diagnostic tests and have prevented the option for patients to obtain second opinions. The effect of these exclusive licenses has been adverse for patients. It has had the effect of increasing the cost of testing, limiting access for patients, stifling innovation to improve the testing methods and sensitivity of testing by providing comprehensive testing of all relevant genes, and does not allow patients to obtain critical second opinions if they or their providers believe there may have been an error in testing. This last point is critical. Errors in genetic diagnostics labs can occur due to sample switching errors, numerous technical problems with assay design, errors in informatics processing of the data, and simple human errors of reviewing the data. Finally, there can be differences in opinion about interpretation of the same primary genetic data, and some labs have more or less sophisticated methods to interpret pathogenicity of novel genetic variants and go to various degrees to follow up novel variants to allow for accurate interpretation of these results. In my own experience as a clinical

geneticist, I have detected errors by even the best clinical diagnostic laboratories when I compared the results on the same patient from my research laboratory to those of the clinical diagnostic lab. I have identified errors due to all of the sources I listed above, and my independent analyses have served to improve the methodology and accuracy for all patients served by these labs. However, these improvements were only possible because of my ability as an academic researcher to do what most other physicians cannot do-provide a true second opinion. Unfortunately, in one case, my second opinion was provided only after my 5 year old patient died of sudden death from his genetic cardiac condition which could have been prevented if I had had accurate genetic test results. Accurate genetic testing is absolutely critical for good patient care, and cross laboratory validations are a routine part of the quality control and quality assurance we routinely practice throughout medicine but cannot ensure for genes with exclusive licenses.

It is my view that, while patents might still be issued in my field, 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.

The problem of exclusive licensing extends to many genetic diseases, and one well-publicized example is the BRCA1/BRCA2, the genes whose mutation results in a predisposition to breast cancer and ovarian cancer. These genes were 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. Myriad Genetics has the exclusive license to perform genetic testing for BRCA1 and BRCA2 in the United States. Myriad charges patients $3600 for genetic testing although the cost in Canada and Europe is half that amount. Innovation has been stifled, and testing for many years incorporated only sequencing methods even though deletions/duplications/re-arrangements were known to be another important source of mutations because there was no competition to improve the sensitivity of the test. Thus there have been many women who received false negative test results because they had only sequencing based assays or limited testing for complex rearrangements. The number of genes included in the test has never been expanded beyond BRCA1 and BRCA2 even though we now know of at least 12 additional genes for hereditary breast cancer and another 5 for hereditary ovarian cancer. Finally, most disturbing is that Myriad does an extremely poor job of interpreting any but the most obvious loss of function alleles as either pathological or benign. Instead, they frequently issue reports of missense variants (single amino acid substitutions) as variants of uncertain significance and fail to provide the scientific community with access to the variant database to help with accurate interpretations. This has the end result of significantly increasing anxiety among many patients who have truly benign polymorphisms but are led to believe they may have pathogenic disease causing mutations. I had one family in which three sisters all pursued prophylactic mastectomies and oophorectomies based upon their genetic test results that were years later re-interpreted to be normal genetic variants but originally classified as variants of uncertain significance. At the other end of the spectrum, there are women who have not pursued aggressive enough means of cancer surveillance and prevention because they did not accurately assess their cancer risk based upon variants of uncertain significance. Women in other countries do not face the same problem as women in the US due to availability of multiple labs performing the same testing.

Competition in diagnostic testing is critical to protection of the public health. Labs compete on service (turnaround time, ease of test interpretation), quality, and price. 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 and excessive pricing, limiting its clinical utility.

It is my belief that the exclusive licensing of genetic diagnostic patents is creating a serious public health problem. As the number of genes associated with disease increases and as genetic testing is integrated more fully into medical decision making, so will the problems for genes with exclusive licenses.

There are many possible solutions to the problem of patenting of genes and exclusive licenses for genetic diagnostic testing. This could be decided by the Supreme Court if it agrees to hear *AMP et al v USPTO v Myriad Genetics.* However, a legislative solution is another alternative. The USPTO could propose legislation that would create an exemption for second medical opinions from the exclusive licensing of patents or recommend legislation that would force judges to consider the public health before enjoining a laboratory that wishes to offer a second opinion test for a gene that is patented and has an exclusive license. Either solution would offer an improvement for patients.

Thank you for the opportunity to share my views on the serious public health consequences of exclusively licensed patents for diagnostic genetic testing.

Sincerely,

Wendy Chung, MD PhD
Herbert Irving Assistant Professor of Pediatrics and Medicine
Director of Clinical Genetics
Columbia University