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To: Deputy Under Secretary Lee and Deputy Commissioner Hirshfeld

Re: Comments on the 2014 Interim Guidance on Patent Subject Matter Eligibility

We appreciate you inviting comments on the 2014 Interim Guidance on Patent Subject Matter Eligibility. We have taken issue with some of the details laid out in this guidance document and have provided our comments for your consideration.

The Supreme Court ruling, *Association for Molecular Pathology v. Myriad Genetics*, threatens the foundation of our patent system. Patents are designed to only be held on technology, not nature. Human understanding of nature is what we call science. Applying the understanding of that science is a technology. In this specific case, Myriad Genetics has filed a patent on naturally occurring genes. This is a patent on nature, not a patent on technology.

The 2014 Interim Guidance on Patent Subject Matter Eligibility, specifically in regards to Section III Sample Analyses Example 2, should be revised. In this example, it is rationalized using the guidance structure outlined in this document that complimentary DNA (cDNA) represents a patentable substance because it is "markedly different" than its natural counterpart found in nature. This logic is founded in the Supreme Court ruling, *Association for Molecular Pathology v. Myriad Genetics*, in which the courts found that cDNA was distinct from the actual gene it was derived from.

If Claim 1 in this example states that an isolated gene is not patentable, then we would argue that for this exact reason cDNA is not patentable in Claim 2. This is simply a naturally edited version of the original DNA sample. Additionally, the claim that cDNA doesn't exist in nature is just not true because cDNA is just DNA, indistinguishable and structurally the same. cDNA is routinely made by retroviruses found in nature (such as HIV-1), further proving that cDNA in general is a natural product. If processes didn't exist in nature to create what scientists have called cDNA, and Myriad Genetics engineered a technology to create cDNA, then we would encourage Myriad Genetics patent the technology on how they created the cDNA, but still not patent the product cDNA from that technology.

If the PTO does not agree with what we believe to be a common sense position on this issue, we would at least like the distinction to be made that cDNA produced from non-spliced mRNA is not patentable. This DNA is both structurally and functionally equivalent to the isolated gene it was derived from. If an amplified copy of a gene from a DNA polymerase is not patentable (an isolated gene), then an amplified copy produced from a reverse transcriptase should not be patentable either. This should be made clear in your guidance document because not all mRNA derived from genes undergoes a splicing step and cDNA made from non-spliced mRNA is the equivalent of an isolated gene.

We disagree with the precedent that this section of the guidance was derived from, *Association for Molecular Pathology v. Myriad Genetics*. Allowing such patents to exist will stymie research and make it difficult to use a technique such as RT-PCR for research and discovery, something that is absolutely routine in many molecular biology labs. Our position on the impact such a practice would have is consistent with a recent analysis of this debate

published in the Journal of Law and the Biosciences[1]. The consequence of allowing such patents can lead to a monopolization of data derived from the research studying these particular DNA sequences. This can potentially make it more difficult for the health benefits of such scientific research to make its way down to the people who need it.

Over the next 10-20 years, the Patent and Trademark Office (PTO) is going to have to make many important decisions regarding the ownership of biotechnologies that will, on the surface, appear different than the natural products they are derived from. Allowing something like cDNA to be patentable is the equivalent of saying an unwrapped present is markedly different than the gift-wrapped version. They might appear structurally different, but they are truly the same thing. It is important that the PTO set precedents now to ensure that in the near future individuals and corporations are not allowed to take ownership of products of nature. The current guidance suggested here falls short of protecting products of nature from ownership.

The procedure of cDNA creation is simple and well understood in the field. It allows one to convert mRNA into DNA through the activity of a reverse transcriptase. This enzyme uses mRNA as a template and constructs an exact copy of this template using deoxyribonucleotides instead of ribonucleotides. This is what makes DNA different from RNA. Since mRNA is an RNA copy of the gene comprised of DNA, this reverse process simply converts the RNA message back into a double stranded DNA molecule. In the absence of a splicing step, where the introns of the mRNA are cut away, the DNA produced from a reverse transcriptase reaction with mRNA is the exact version of the DNA the mRNA was made from. Calling it cDNA doesn't make it any different.

Since the purpose of DNA is information, the point here is that the full gene and the cDNA contain the exact same information regardless of the fact they might be structurally different at different stages of this process. A gene with all of its introns and exons placed into a plasmid and transformed into a cell will produce the exact same final mRNA message as an edited version of this gene containing only the exons (e.g. cDNA). Both the gene and cDNA produced the same product and therefore both of them are functionally identical even if they are structurally different. Calling this a markedly different substance is a personal judgment not founded in scientific logic.

A major issue we have is that according to your guidance, the cDNA produced from mRNA from a particular gene is patentable even if there is no splicing step. The argument that a splicing step somehow makes this process unique is a technicality that ignores the reality of what is taking place. Yes, the cDNA produced from a spliced mRNA is technically different from the DNA of the gene being studied, but the reality is that it is not markedly different. The full gene and the cDNA have the same function in the lab – the exons are what the researchers are studying. This is why they created the cDNA in the first place and why they want the patent.

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[1] A, Bakshi, Gene patents at the Supreme Court: Association for Molecular Pathology v. Myriad Genetics. J Law Biosci 2014: Isu007v1-Isu007.
http://jlb.oxfordjournals.org/content/early/2014/05/02/jlb.lsu007.full.pdf+html

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The distinction being drawn here is one not consistent with the biochemical theories of the cell. If you used something like the patented technology CRISPR-Cas9 system to remove the introns from gene of interest, you would be left with the exact version of the cDNA you made from the reverse transcriptase reaction. Suggesting that the removal of the intron sequences all of a sudden makes the cDNA unique ignores the fact that the cell, which utilizes this splicing process, considers the gene to be the actual final mRNA sequence and not the sequence found in the actual genomic DNA. The splicing step is simply a form of regulatory control for the cell. The cDNA that this guidance document suggests is patentable is the gene from the genomic DNA and represents the same thing as an isolated gene. The gene, to many in the field, is not the entire intron and exon sequence, it is the part of the DNA that contains the actual sequence that codes for the protein of interest, all of the exons combined.

Life is composed of incredibly complex biochemical phenomena that have been evolved by the forces that drive nature. The last 50+ years have been remarkable for the fields of science that study these phenomena because we have finally begun to identify and understand some of these marvelous biochemical processes that are fundamental to all life. Unfortunately, the ability to continue to explore this world is being compromised because ownership is being granted to products of nature.

Thank you very much for your consideration of our comments.

Sincerely,

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Charles Mueller obtained his PhD in Biochemistry from the University of Maryland. His dissertation was on the study of DNA repair enzymes. His work involved RT-PCR, which is a standard technique in the molecular biology field to check expression levels of mRNA from a particular cell source by converting mRNA into cDNA. He is currently a Research Associate at the Potomac Institute for Policy Studies where he creates policy recommendations based on science and technology.

Jennifer Buss is a PhD in Biochemistry from the University of Maryland. Her dissertation research focused on genetic engineering for expression in different cell lines, relying on cDNA clones, PCR to make mutations, and plasmids to isolate genes and express proteins. She is currently a Research Fellow at the Potomac Institute for Policy Studies.

Kathy is a PhD in Biochemistry from the University of Maryland. Her dissertation research focused on spectroscopic determination of protein-DNA complex conformations through molecular biology, spectroscopy, and in vitro biochemistry. Kathy is a Research Associate and CReST Fellow at the Potomac Institute for Policy Studies.

Brian Barnett has a B.S. in Neurobiology & Physiology. He completed an undergraduate thesis that investigated the biological and behavioral components of an animal model of ADHD. He is currently a Research Assistant at the Potomac Institute for Policy Studies.