Impact of Advances in DNA Sequencing Technology on Genetic Diagnostic Testing

By Kevin E. Noonan -- February 20, 2012

Dr. Ellen Jorgensen of Genspace, one of the witnesses at the U.S. Patent and Trademark Office's first hearing regarding the advisability of permitting "second opinions" for patented genetic diagnostic tests without patent infringement liability, advocated "at-home" or "do-it-yourself" DNA testing as a solution (*see* "USPTO Holds First Hearing on 'Second Opinion' Genetic Testing"). This proposal raises a significant number of questions, particularly with regard to the potential for harm to the public due to errors that might arise from such "at-home" genetic diagnostic testing or whether precautions in interpreting results would be taken concerning the emotional consequences of finding a genetic mutation in an individual's BRCA genes.

However, the saliency of any technical objections to the idea must be considered to be significantly reduced by an announcement from Oxford Nanopore Technologies at the Advances in Genome Biology and Technology Conference at Marco Island, FL last week: a disposable gene sequencing machine the size of a standard USB thumb drive and capable of providing a complete genomic sequence for about $900. Terming the business model for the device "pay-as-you-go" sequencing, the chief technology officer of the company, Clive G. Brown stated that the new device eliminates the need for expensive ($50,000 - $750,000) machines currently in use for gene sequencing, and touted the use of the device for bedside genetic testing, biological field work, and food safety (*e.g.*, for identifying pathogens *in situ* in real time).

The basis of the device is so-called "nanopore" sequencing (explained in greater detail for the interested in "The $1,000 Genome: The revolution in DNA sequencing and the new era of personalized medicine" by Kevin Davies). Briefly, the technology employs alpha-hemolysin, a bacterial membrane "pore" protein, stabilized with cyclodextrin, to measure changes in electrical current as each base moves through the pore after exonuclease cleavage. The devices take advantage of parallel processing on a chip and computer analysis of the data to create the linear sequence. Initially each chip will contain 2,000 pores with machines using chips having 8,000 pored being developed for release in 2013. While the sequencing capacity ("tens of thousands bases per read") is higher than with competing machines, so is its error rate (4%). This level of error would preclude use of the device for genetic diagnostic sequencing, for example.

But machines and methodologies will get better, which raises the possibility that DNA sequencing soon may be within the reach of the consumer (much like accurate blood glucose determinations are now done with devices requiring nothing more than a pinprick of blood). Under these circumstances, much of the current patent protection (and the IP protection model underlying it) for genetic diagnostic testing may become obsolete. First, determination of an entire sequence does not *per se* infringe gene-specific DNA or method claims unless gene-specific primers are used (and even these claims are subject to some reevaluation; *see* "Caught in a Time Warp: the (In)validity of BRCA1 Oligonucleotide Claims"). This is one reason why the majority of the claims at issue in the Myriad case (*i.e.*, claims to isolated

genes) are not infringed by the practice of genetic diagnostic methods and why even if the plaintiffs and their ACLU masters prevail, the women will have no remedy. Thus, the only direct infringer using these "mini-sequencer" devices would be the consumer, and unlike situations where suing consumers has been successful (like music file-sharing), the individual damage from any specific consumer defendant's infringement would be minimal. While the damage to the patent-holder might be large cumulatively, it is unlikely that a patentee could successfully sue consumers as a class. Inducement to infringe might also be challenging to prove since it is unlikely that Oxford Nanopore Technologies will provide instructions relating to any particular gene with specificity. In any event, the identity of disease-related mutations is (and might continue to be) in the public record and so the consumer herself would remain the only infringer.

It may also be expected that Oxford Nanopore Technologies will provide information on genetic counselors to be consulted to assist the consumer to interpret the meaning of her deduced nucleotide sequence. These genetic counselors will be practicing a method involving comparing the deduced consumer sequence with the canonical "normal" sequence, and should not be infringing any valid claims. This is because the Federal Circuit unanimously held in *AMP v. USPTO* (the "*Myriad*" case) that mere "comparison" claims do not satisfy the *Bilski* test and are thus invalid. In addition, under this scenario the issue of "joint infringement" would arise, because the consumer would produce the sequence and its interpretation relating to inherited propensity for disease would be performed by the genetic counselor. Unless the Federal Circuit dramatically changes the jurisprudential landscape in deciding the *McKesson* and *Akamai* cases *en banc*, infringement would not lie against either Oxford Nanopore Technologies or the genetic counselors.

The development of such an eventuality provides yet one more impetus for genetic diagnostic testing to avoid patents as a protection for the technology, and to use instead trade secret protection and other means that avoid disclosure. These prospects make it even more imperative, perhaps, that whatever actions are taken by the Office, Congress, or the courts regarding genetic diagnostic testing be done cautiously and in a limited fashion. Otherwise, we may find that we have imposed impediments to future technologies, just as progress in the technologies we intend to regulate make the regulation obsolete. Certainly this can't be the kind of progress the Founders had in mind.

An Oxford Nanopore Technologies video showing on the company's technology works can be viewed below:

http://www.youtube.com/watch?v=_rRrOT9gfpo&feature=player_embedded