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# Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics

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Obtaining patents on human genes or gene fragments has been a heated issue in scientific and legal circles for several years. Opponents of such patents have advanced arguments on at least three different grounds, including moral,<sup>1</sup> legal,<sup>2</sup> and social.<sup>3</sup> Although there has been some indiscriminate criticism of all types of human gene patents,<sup>4</sup> thoughtful commentators have targeted patents on diagnostic genetics as a particularly troublesome area. However, rather than wait for the more complex issues to be resolved by the medical, legal, and ethics communities, this article suggests a pragmatic solution for making patented diagnostic genetic tests available to health care providers and their patients.<sup>5</sup>

## Problems Associated with Patents on Diagnostic Genetics

Diagnostic genetic tests (such as the BRCA-1 breast cancer test) are used to identify a specific genetic mutation or specific mutations in an attempt to assess the risks of a particular disease. There are often multiple mutations correlated with a particular disease; such diseases are referred to here as *polymutational* diseases. An important inquiry to be addressed before performing any genetic testing is to determine which mutations are significant for diagnosing the disease or for identifying a carrier, and therefore, which mutations should be considered *standard* when performing such testing.

In 2001, the American College of Medical Genetics (ACMG) set an example of how to determine which mutations of a disease are significant and should be tested.<sup>6</sup> The particular disease focused on by the ACMG was cystic fibrosis (CF), specifically, how to identify carriers of CF.<sup>7</sup> The ACMG recommended a standard set of mutations that includes all CF-causing mutations with an allele frequency of  $\geq 0.1$  percent; this recommendation results in a panel of 25 mutations.<sup>8</sup> CF represents a good example of a disease in which a medical organization has officially proposed a standard panel of mutations for the industry to use.<sup>9</sup> In addition, the ACMG over the past decade has issued policy state-

ments with recommendations for the significant mutations to be employed in and genetic testing of a variety of other diseases including Alzheimer's disease, breast cancer, Canavan disease, colon cancer, Factor V Leiden, fragile X syndrome, newborn hearing screening, Prader-Willi and Angelman syndromes, and uniparental disomy genetic testing.<sup>10</sup>

Standard panels for the genetic testing of many other diseases could, and most likely will, be set by the scientific community and medical organizations in the next years. In fact, there may already exist diseases that have a few mutations that are routinely tested for and recognized informally as the standard but have yet to be officially endorsed by a medical organization. For example, Tay-Sachs disease has a recognized panel of targeted mutations that are tested by many different labs.<sup>11</sup>

The criteria for selecting the mutations, that is, whether it is an allele frequency  $\geq 0.1$  percent or  $\geq 10$  percent, may vary from disease to disease. The number of mutations that are part of the standard panel also may vary, as are the cases of CF (*e.g.*, 25) and Tay-Sachs (*e.g.*, 6). Nevertheless, the creation of an official standard panel, or even the recognition of an informal panel, addresses the problem of knowing which mutations to include when performing tests.

Problems immediately arise, however, if several of the chosen mutations, SNPs, and mutational diagnostic tests have been patented by different parties. Two widely discussed troublesome consequences of patenting are exclusivity<sup>12</sup> and stacking.<sup>13</sup>

The first occurs either when patent holders reserve market exclusivity for themselves or exclusively license them to third parties such as reference laboratories, as they are, of course, entitled to do by their patent rights. For example, Athena has been given an exclusive license from Baylor University for Charcot-Marie-Tooth disease (CMT1A), from Duke University for Alzheimer's disease (Apo-E), and from the University of Minnesota for Spinocerebellar Ataxia (SCA1).<sup>14</sup> Myriad Genetics has secured an exclusive license from OncorMed for the second patent on the breast and ovarian cancer gene (BRCA2).<sup>15</sup> In contrast, the patent covering the most common allele for cystic fibrosis is not exclusively licensed but rather is broadly licensed and made available by the University of Michigan, as is evidenced by the

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numerous references to clinical labs offering the genetic test for this allele.<sup>16</sup> Exclusive licensing approaches are said to inhibit clinicians who are interested in using genetic diagnostic methods to aid their patients with a disease<sup>17</sup> and to hinder the development of medicine by preventing or delaying others from identifying new mutations for that disease.<sup>18</sup> For example, in the case of the genetic test for hereditary hemochromatosis, 30 percent of US laboratories stopped developing or no longer offered the test at all, once the patents on the genetic testing were awarded.<sup>19</sup>

The second potential consequence is patent stacking. This results from having to seek and obtain licenses from a variety of different patent holders in order to broadly test a given genetic disease.<sup>20</sup> Such a licensing program can become prohibitively expensive as a result of both transactional costs and multiple royalties and has even been referred to as a "nightmare."<sup>21</sup> Many diseases can be correlated to a genetic variation, such as a nucleotide sequence permutation, known as single nucleotide polymorphism (SNP), within an individual's makeup.<sup>22</sup> Recent studies by the SNP Consortium and the International Human Genome Project Sequencing Consortium have identified more than 1.4 million SNPs in the human genome, with an average of one in every 1.9 kb.<sup>23</sup> The use of specific SNPs in diagnostics or of the probes useful for their detection has been the subject of many patents over the years. In order to accurately study or test for a particular disease that is correlated to multiple patented SNPs or SNP fragments, it may be necessary to obtain a license from each of several patentees of the multiple SNP-based tests. This is a classic example of patent stacking. The transaction costs of investigating and obtaining multiple licenses to multiple mutations, SNPs and diagnostic tests in such a situation can quickly become prohibitive.

Currently, genetic testing is available for more than 300 diseases or conditions in more than 200 US laboratories, with the potential development of tests for another 325 diseases.<sup>24</sup> One can quickly see that the problems of exclusivity and stacking arising out of multiple patents on SNPs, for example, will become worse as the technology matures.

The problems of license exclusivity and patent stacking appear particularly acute in the area of multiplex arrays. This technology, which has been applied diagnostically, provides the ability to simultaneously detect genes or proteins that are expressed in a single tissue at a given point in time. In fact, in April 2003, the FDA issued a draft of nonbinding recommendations to provide guidance for preparing and reviewing pre-market approval submissions for such multiplex tests.<sup>25</sup> For example, if an array manufacturing company wants to

develop a chip using proprietary platform technology (e.g., Affymetrix's GeneChip<sup>26</sup>) in a test for cystic fibrosis, it may first have to obtain a license from the patentees of several of the 25 mutations that are part of the ACMG standard panel.

Several solutions have been proposed to address the concerns arising out of patenting of diagnostic genetic tests. For example, it has been proposed that the US Patent and Trademark Office (USPTO) should apply the existing statutory requirements for patentability more stringently to the field of genomics or that the Court of Appeals for the Federal Circuit, the most specialized patent court in the United States, should apply its non-obviousness standards as stringently to human gene patents as it does to other advancing fields of technology.<sup>27</sup> Other proposed solutions include compulsory licensing<sup>28</sup> or legislative exemptions for diagnostic testing.<sup>29</sup>

This article suggests that the use of patent pools is reasonably likely to make patents pertaining to the diagnosis of polymutational diseases available to those who wish to make the subject inventions available to the industry at reasonable, non-discriminatory royalties.

This article first discusses the general legal concept of a patent pool and analyzes its applicability to genetic diagnostics using the published Antitrust Guidelines issued from the US Department of Justice (DOJ) and from the Federal Trade Commission (FTC). It concludes by discussing the commercial incentives available to patent holders in genetic diagnostics that might motivate them to join a patent pool rather than go at it alone.

### Patent Pools

A patent pool is an arrangement in which "two or more patent owners agree to license certain of their patents to one another and/or third parties."<sup>30</sup> Patent pools structured and implemented in various forms<sup>31</sup> have been used in a variety of industries ranging from sewing machines and aircraft to radio and software.<sup>32</sup> Depending on their structure and implementation, some patent pools have been found to be anti-competitive and objectionable,<sup>33</sup> while others have been found to be pro-competitive and acceptable.<sup>34</sup>

In 1995, the DOJ and the FTC provided guidance to businesses and their advisors in structuring pro-competitive arrangements by issuing the *Antitrust Guidelines for the Licensing of Intellectual Property*.<sup>35</sup> Section 5.5 of the *Antitrust Guidelines* (hereafter Pool Guidelines) addresses patent pools (and cross licensing) and suggests criteria to be used in determining when a patent pool is pro-competitive and therefore probably acceptable and when it is anti-competitive and probably unacceptable.<sup>36</sup>

Critical to the structuring and implementing of patent pools are the definitions of *complementary*, *competing*, *blocking*, and *essential* patents. *Complementary* patents are for “technologies that may be used together, and not substitutes for each other.”<sup>37</sup> Two different patents each on a different SNP for the same disease would be complementary. *Competing* patents cover technologies that substitute for each other.<sup>38</sup> A patent on a SNP and another one on an antibody might be competing technologies to diagnose the same disease. A *blocking* patent “block[s] another if [the latter] can not be practiced without infringing on the basic patent.”<sup>39</sup> A patent on an isolated gene and all its fragments might be blocking to all genetic testing for a disease. *Essential* patents have been defined as ones having “no technical alternative” and useful “only in conjunction with other pooled patents.”<sup>40</sup> An example would be a patent on the critical SNP or the gene correlated to the disease.

The Patent Pool Guidelines provide guidance in structuring patent pools by stating that patent pools may be pro-competitive by:<sup>41</sup>

- Integrating complementary technologies;
- Reducing transaction costs;
- Clearing blocking positions;
- Avoiding costly infringement litigation and
- Promoting the dissemination of technology.

However, patent pools may be found to be anti-competitive if they:

- Constitute methods of fixing prices or allocating customers and markets;
- Exclude or drive competitors from the market or reduce innovation; or
- Discourage the participants from engaging in research and development.<sup>42</sup>

Patent pools approved after the introduction of the Guidelines include Motion Pictures Coding Experts Group technology (MPEG\_2),<sup>43</sup> Digital Versatile Discs (DVD-3),<sup>44</sup> DVD-6,<sup>45</sup> and for Third Generation (3G) mobile telephony (patent platform).<sup>46</sup> In each case, the DOJ applied the Patent Pool Guidelines in considering whether to pursue an enforcement action against the patent pool. In particular, the DOJ decided *not* to pursue an enforcement action against the MPEG\_2 patent pool for several reasons:<sup>47</sup>

1. The pool included only complementary and essential patents;
2. The offered licenses were non-exclusive;
3. An independent expert was used to label a patent “essential”;
4. All licensees were promised equal access;
5. Members could still develop alternative technologies; and
6. The efficiency of licensing was increased.

The DOJ Business Review Letters for the MPEG-2, DVD-3 and DVD-6 pools, and the 3G patent platform suggest the additional following criteria for structuring and implementing future pro-competitive patent pools:

- The patents in pool must be valid, essential, and complementary, not substitutive as determined by an independent expert;
- Any grant-back provisions should obligate licensees to grant back to the pool “essential patents” on a non-exclusive basis, at a fair and reasonable royalty.

The pools should not enable the licensors to unreasonably:

- Aggregate competitive technologies or set a single price for the pooled technologies;
- Disadvantage competitors in downstream product markets;
- Collude on prices outside the scope of the pool; or
- Impair innovation in the development of rival products or technologies.

The successes and failures of these recent patent pools serve as a valuable heuristic tool in the creation of patent pools for diagnostic genetics. Any proposed diagnostic genetics patent pooling agreement should adhere to the Patent Pool Guidelines and the suggested DOJ criteria. Once established, the proposed pool documents should be submitted to the Antitrust Division of the DOJ for a business practice review<sup>48</sup> and to the FTC for an advisory opinion.<sup>49</sup>

## Application of Guidelines and Criteria

This section discusses application of the patent pool guidelines and criteria suggested by the Patent Pool Business Letters to diagnostic genetics of polymutational diseases.

### What Patents Should Be Included in the Pool and Who Decides?

**1: Only essential and complementary patents.** Whether a patent is essential or not will depend on the mutation or mutations claimed and their diagnostic value. If there are multiple patented fragments or SNPs that cover different segments of a gene involved in a particular polymutational disease and only a small number have some degree of diagnostic value, then these would be considered essential for the patent pool. A pool for the diagnostic genetics of this disease should only contain these patented fragments or SNPs.

**2: Any blocking positions should be included.** If, for example, a company were to have a dominating patent on a purified gene involved in breast cancer including all fragments that hybridize to it, it would be critical to include that patent in the pool so that any problems caused by blocking later patents on valuable SNPs can be eliminated. If the blocking patent is not included, the pool may not cover the essential patents and may be anti-competitive.

**3: No aggregation of competing patents and setting a single price for them.** Consider diagnostically useful genes or gene fragments  $X_{1a}$  and  $X_{1b}$ , which cover a similar area of genetic material and which are owned by different patentees. Allowing both patents into the pool could run the risk of the two patentees colluding on the price for the license. This type of situation is less likely to happen in the application of a patent pool to diagnostic genetics of a polymutational disease because there should not be two patents on the same area of genetic material; if there were multiple ones, only one should be selected.

**4: Only valid and unexpired patents in the patent pool.** There ought to be a mechanism to vet patents of dubious validity. It is relatively easy to mandate that, if a member's only patent expires or is invalidated by a third party, it is necessary for that member to replace the invalid or expired patent with a new patent that meets the patent pool criteria in order to remain as a member of the pool.<sup>50</sup> However, absent an invalidation event, the pool participants might agree that, if prior art or argumentation not previously considered by the USPTO is brought to one the members' attention, the pool has the responsibility of either obtaining an opinion of counsel that the patent remains valid and enforceable, requesting reexamination of the patent before the USPTO, or both.

**5: An independent expert(s) is required.** The formation of an independent committee of experts consisting primarily of representatives from commercial and clinical institutions, as well as attorneys who are experts in biotechnology patent law and antitrust law, is recommended. The committee's tasks will include selecting the patented genes, fragments, or SNPs considered complementary, essential, and/or blocking to the patent pool. The committee may treat recommendations issued from a consensus-setting body such as the ACMG as establishing a "standard" to be implemented in deciding which patents are essential and complementary but not substitutive.

### What Terms, Including Pricing, Should the Pool Offer?

**6: The pool should promote the dissemination of technology.** A patent pool should not restrict innovation. Several ways to accomplish this are:

1. Licenses offered to the patent pool by its members should be non-exclusive so that individual members may still offer outside individuals a separate license to their essential patent or patents. This will, in effect, help prevent the anti-competitive effects of "tying" or requiring multiple licenses to be taken when only one is desired.<sup>51</sup>
2. Assure non-discriminatory pool licensing on the same terms and conditions to all would-be licensees.<sup>52</sup>
3. Allow for receipt by the pool of a narrow grant-back clause from the licensees.<sup>53</sup>

Under such a grant-back clause, the licensee agrees to offer back to the patent pool a non-exclusive license to any of its own essential improvement patents at a fair and reasonable royalty.<sup>54</sup> A successful grant-back clause will be narrowly drafted so that it encompasses only those essential future patents of the licensee that are commensurate with the technology of the patent pool license.<sup>55</sup> This agreement prevents the licensee from extracting the benefits of the patent pool while holding out its own essential patents.<sup>56</sup>

**7: Do not disadvantage competitors' downstream markets that use the pooled technologies as inputs.** The DOJ approved the MPEG and DVD patent pools partly because each proposed pool had limitations to prevent foreclosure of competition in the downstream market.<sup>57</sup> These pools had a "reasonable" royalty which was a "tiny fraction" of downstream product prices or "small relative to the total costs of manufacture."<sup>58</sup> The determination of how "small" or "reasonable" a royalty is has

been inconsistent because of the lack of standard royalty rates and multiple interpretations of "reasonable."<sup>59</sup> It has been suggested that a percentage cap should be implemented for pools so that the royalties do not grow to be excessive over time. This is so because, even though a royalty may have been "small" or "reasonable" at the beginning, the cost of producing the downstream product decreases with time.<sup>60</sup> The MPEG and DVD pools had non-discriminatory licensing for all parties, including competitors.<sup>61</sup> In the case of genetic testing, the pooled technology may represent the genes or gene fragments that are predictive for a particular disease. Licensing should be non-discriminatory to manufacturers or users of downstream products, such as arrays or devices that incorporate the pooled patents for one disease.

**8: Pool members must be prohibited from colluding on prices outside the scope of the patent pool license.** A patent pool on diagnostic genetics should discourage collusion among the licensors or licensees in any market.<sup>62</sup> In the MPEG\_2 patent pool, the DOJ noted approvingly that confidentiality provisions existed that prohibited the patent pool licensors and licensees from exchanging competitively sensitive information.<sup>63</sup> Also, the DOJ acknowledged that, because the royalty rates were to be reasonable, it was unlikely that they could be used to facilitate collusion of prices for downstream products.<sup>64</sup>

Application of the enumerated guidelines and criteria to the diagnostic genetic testing of polymutational diseases will lead to pro-competitive patent pools. These, in turn, will reduce transaction costs by avoiding lengthy due diligence opinions and separate licensing deals and avoid costly infringement litigation or premature abandonment of worthy projects.

### **Patent Pools in Diagnostic Genetics Versus Genomics**

Several commentators have raised the potential problems with forming patent pools in the broad field of genomics,<sup>65</sup> suggesting that the genomics industry is too disperse, does not have common goals,<sup>66</sup> advances too quickly, making it difficult to identify the "essential" patents for a patent pool,<sup>67</sup> and noting that, if there are a large number of required patentees, the pool may run afoul of antitrust laws.<sup>68</sup> While application of a patent pool to all of genomics would be difficult, if not impossible, if a patent pool is limited to diagnostic genetics for a given disease, it could circumvent several, if not all, of these problems.

The diagnostic genetics industry is not as diverse as the overall genomics industry. The genomics industry works with and patents at least three kinds of genes, *i.e.*,

those encoding therapeutic proteins, sequences with diagnostic information, or receptors useful in high throughput screening for drug discovery. These three areas are different commercially, and the value of patents in one varies dramatically from the value in the others.<sup>69</sup> The goals of the players in these three arenas are also very diverse.

In contrast, the field of diagnostic genetics is commercially more focused and, when further limited to individual diseases such as breast cancer or CF and to diseases that have a consensus statement on standard mutations, is ideal for a patent pool. Unlike the varied genomics industry, the players in the market for disease-specific diagnostic genetics, regardless of whether or not they are a commercial enterprise or a non-profit entity, have a clear common goal: to provide accurate tests and analytic devices so as to minimize false negative or false positive results for a given disease.

The alleged difficulty of identifying essential patents in genomics because of rapidly advancing technology would not be a problem with a patent pool in diagnostic genetics. Diagnostic genetic technology for a given disease is less likely to advance so rapidly as to overlook essential patents. In addition, an independent expert/committee will have as one of its responsibilities the duty of actively seeking and identifying such patents; and if a mutation or gene that has a significant predictive value for a given disease is identified, it is most likely to be quickly known to the relevant scientific community and a potential standards-setting body such as ACMG.

Finally, the number of patentees that would be part of a patent pool on diagnostic genetics for a given disease would not become as large as fearfully predicted for all of genomics. The only members of a diagnostic genetics patent pool for a given disease would be those patent holders who have essential and complementary patents on specific genetic permutations (such as SNPs) that, according to a consensus-like statement defining the panel of standard mutations, result in a greater likelihood of accurately diagnosing that particular disease.

Any patent pool on diagnostic genetics would be best applied to diseases that are detected by multiple genetic variations on either a single gene or multiple genes, such as polygenic diseases. Examples of such diseases include Alzheimer's, cystic fibrosis, spinocerebellar ataxia, myotonic dystrophy, hereditary breast/ovarian cancer, and hereditary hemochromatosis. On the other hand, certain known diseases such as Huntington's or Canavan, which are caused by a single nucleotide change, may not be suited for a patent pool. In most of the single mutation cases, there will be only one patent owner for the genetic variation.

