How Genetic Variant Libraries Effectively Extend Gene Testing Patents: Implications for Intellectual Property and Good Clinical Care

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Genetic testing for inherited cancer susceptibility is an increasingly valuable tool in medical oncology. The identification of mutations in the *BRCA1* and *BRCA2* genes, for example, leads to specific clinical recommendations for screening or surgery that can improve survival.¹ However, genetic testing can also identify variants of uncertain significance (VUS), changes in the genetic code that have an unknown effect on disease risk. Roughly 7% of women tested for *BRCA1* and *BRCA2* have one of these variants.² Test results with VUS increase, rather than decrease, uncertainty for the patient in a situation with particularly high stakes and present a challenge to the clinician in devising appropriate responses.

The interpretation of VUS is difficult, requiring information on population frequency and ethnicity, detailed pedigrees, cosegregation in families, co-occurrence, sequence conservation, and functional analysis when available. Cosegregation is the process of tracking a VUS through a family to identify specific patterns. A finding that the VUS appears in all those with breast and ovarian cancers but not in older patients who are cancer free, for example, indicates that it cosegregates with disease, suggesting it is deleterious. Co-occurrence refers to finding a deleterious mutation of either *BRCA1* or *BRCA2* in trans with a VUS (ie, a deleterious mutation in one allele and VUS in the other allele of the same gene). This result offers strong reassurance that the VUS is a benign polymorphism. To make these determinations, large amounts of testing data must be linked with family information and clinical history.²⁻⁴

In the United States, a single company—Myriad Genetics (Salt Lake City, UT)—conducts all *BRCA1* and *BRCA2* testing because it holds a patent on the underlying genes. Most patients who have undergone *BRCA* testing have voluntarily provided Myriad with their family and clinical histories. The exclusive testing rights granted by the patent along with the provision of patient information has enabled Myriad to create an extremely valuable database⁵ on the clinical significance of VUS for breast and ovarian cancers. However, the aggregation of this information at a single firm may increase the cost and reduce the quality of testing. We highlight the positive and negative implications arising from the

creation of such a VUS database and suggest legal reforms to address these issues.

Gene Patents and Data Aggregation

Human gene patenting has generated considerable public debate and remains the subject of ongoing litigation,⁶ challenging its validity. A federal appeals court upheld these patents in July 2011, and the US Supreme Court is considering whether to review the decision.⁷

Patents support innovation by granting the innovator a monopoly for a limited period of time. Patent holders can then charge higher prices to recoup investments. In exchange, patents also require disclosure of relevant information at expiration to permit future innovation, competitive market entry, and lower prices.

For gene patents, there is an unintentional secondary benefit: concentration of testing within a single organization. The aggregated test data, when linked with family histories and outcomes, permit interpretation of variants and their clinical meaning, such as whether a variant is associated with an increased cancer risk. Without patents or some other mechanism to promote concentration, testing would be distributed across multiple companies, hampering the sharing and linking of VUS data with clinical outcomes. This secondary benefit from the concentration of testing is increasingly important and would require significant resources to duplicate absent a patent or other mechanism that permits data aggregation.⁸

Intellectual Property and Clinical Value

There are two general ways a company can exploit the value of its information. One is to hold a patent, so other firms cannot use it. The other is to keep that information secret, so other firms cannot find it. The information held by Myriad has important clues to the nature of individual VUS, but the company has not made these generally available to clinical communities. The VUS database is effectively a trade secret that confers economic advantage by making testing with Myriad much more informative than testing elsewhere—because other firms would not have access to its interpretation of VUS. Is this advantage fair, and is it good for society?

The Myriad VUS database illustrates both an additional value and cost of patents. The benefit is the accumulation of clinically valuable information. The cost is that the patent, in effect, becomes self-sustaining, as the information takes on increasing and irreproducible value over time. The database thereby creates a barrier to competitive entry after patent expiration. Myriad will continue to enjoy an advantage over potential competitors because of its ability to classify VUS when other testing centers will not have sufficient data to do so. Indeed, Myriad has acknowledged that it will rely on its “vastly superior information” to try to maintain market dominance after its patents expire.⁶ Alternatives to patent-linked databases exist, but their value is restricted, because data deposition is voluntary. For example, the National Human Genomic Research Institute established the Breast Cancer Information Core (BIC) database in 1995 to provide a VUS repository for *BRCA1* and *BRCA2*.⁹ However, the information it contains holds less value because data submission is not required, and Myriad, which holds the largest aggregation of test results, does not contribute data to it at this time. The ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) Consortium is an ongoing international effort to categorize *BRCA1* and *BRCA2* VUS¹⁰ reported to the BIC and other databases.¹¹

In summary, gene patents can facilitate accumulation of data with immense individual and social value, derived in part from their origin in a sole source. The social cost is that such databases can extend monopolistic power indefinitely. This dilemma calls for a reconsideration of the nature of gene patents, an outcome that will not result from court rulings that simply address gene patent validity.

Approaches to Reform

Law and public policy should encourage aggregation of data for clinical care and research, whether or not a single entity has patent protection for the underlying tests, and they should facilitate reasonable access. These goals should reflect two principles: one, appropriate incentives and regulations should ensure that test information can be linked with outcomes and family histories, encourage ongoing analysis of these linked data, and ensure dissemination to those with a legitimate need for the information; and two, proprietary interests of private entities should be respected, and they should be compensated for the cost of collecting information and facilitating shared analyses.

Vehicles for implementing shared policies may exist in three laws that presently bear on genetic tests. Amendments to these laws could encourage the aggregation and dissemination of test data regardless of the ultimate legal disposition of gene patents. First, the Health Insurance Portability and Accountability Act could place an affirmative obligation on genetic testing laboratories to maintain results in an accessible form with appropriate confidentiality safeguards and to provide access through a formal application process. Second, the Federal Food, Drug, and Cosmetic Act could grant the US Food and Drug Administration explicit authority to regulate all genetic tests and require, as a condition of test approval, that laboratories maintain and aggregate results and link them with related patient information to share with a central clearinghouse. And third, the Clinical Laboratory Improvement Amendments, under which the Centers for Medicare and Medicaid Services certify clinical laboratories, could condition approval

to conduct genetic tests on agreement by laboratories to collect and aggregate results and facilitate appropriate outside access. The cost of these requirements could be supported through an excise tax on genetic tests or by allowing firms a period of exclusive use of the data followed by a requirement to make the information available to outside qualified researchers, clinicians, and other companies.

These approaches depart from the current regulatory treatment of patient information, which focuses primarily on safety, efficacy, and privacy. The suggested reforms, in contrast, impose an affirmative obligation on data compilers to use and disclose information. Although the traditional concerns of test regulation remain fundamentally important, making full use of the secondary benefits of clinical knowledge and experience has become a crucial additional goal for public policy.

A more activist approach to the legal treatment of scientific information finds precedent in the Bayh-Dole Act, which similarly seeks to balance proprietary rights and public benefit. This law grants private parties the right to obtain patents on discoveries from research funded by the National Institutes of Health in return for an obligation to actively attempt to develop commercial products based on these discoveries. It responded to the emergence of the science of bioengineering and the desire of Congress to promote the realization of its full potential. Genomics represents a similarly dramatic transformation in medical science that calls for a comparable rethinking of the applicable legal framework.

In conclusion, private genetic testing companies hold one of the keys to the future of genomic medicine in the results they collect. However, existing law permits them to maintain this information on a proprietary basis and to limit access to clinicians and researchers who could use it to improve clinical practice and advance the scientific understanding of genetics for a range of illnesses certain to grow in the years ahead. This legal anomaly must be addressed if the full potential of genomics is to be effectively realized.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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