

genetest

From: Greenspan, Bernard <bgreenspan@prometheuslabs.com>
Sent: Monday, March 26, 2012 3:23 PM
To: genetest
Cc: Rea, Teresa; Graham, Stuart; Purvis, Sue
Subject: Genetic Testing Study

Introduction: The Fallacy of the Problem

Prometheus Laboratories is seriously concerned that the USPTO might endorse, or that Congress might enact, changes to the current patent law that would allow performance of any diagnostic testing in a manner circumventing either patent holder rights or negotiated license agreements. We believe that such actions are contemplated in response to an ambiguously defined problem having no factual data to substantiate the need for change. It has been proffered that there is a resounding need for second opinion genetic diagnostic testing and that patents and exclusive licensing are impediments to fulfilling this need. But caution must be taken, because legislative actions in response to a need based on unsubstantiated premises can lead to severe unintended consequences.

We analyzed over 300,000 orders in our database for genetic diagnostic tests and tests with a genetic component. The incidence of repeat measurement requests was 0.33%, including those which may have originated from a second physician requesting the test without knowledge that a previous measurement was made for the patient. Thus, in our experience, there is little demand or need for repeat measurements from physicians or patients. With such a low incidence rate, a legislative solution hardly seems to be needed.

We are troubled by the application of the terminology “second opinion” to genetic diagnostic testing. Application of this terminology to diagnostic testing draws an analogy to the subjective realm of physician diagnoses or selection of the course of treatment for a particular patient with a particular clinical condition. This only obscures the underlying issues. It is generally accepted that a patient or an insurance company will want additional opinions on a recommended course of therapy prior to adopting it, especially when that therapy is expensive, invasive, or involves significant risk. In the case of treatments based on genetic measurements, one might still pursue a second opinion, but it would be on the recommended course of therapy rather than on the accuracy of the test results. Discussions with physicians have indicated that when an inherited (“germline”) mutation is in question, additional measurements on the patient’s relatives would yield far more useful information than repeating measurements on the individual patient.

In the cases of somatic mutations, it has been shown that repeated measurements do not necessarily bring additional certainty. Gerlinger and coworkers (2012) characterized intratumor genomic heterogeneity using multiple samples from the same tumor tissue. Their work demonstrates that repeated measurements can yield different results and begs the question, how many repeat measurements would a doctor or patient request in order to ascertain what they believe to be the correct or true result?

Repeatability of Genetic Measurements

The correlation of genetic mutations or single nucleotide polymorphisms, with diseases, or their contribution to the development of particular pathologies, is a powerful and potentially life-saving discovery, whether the polymorphisms are predictive on their own or in correlation with other biomarkers. What may not be fully appreciated is the fact that the genetic sequence of the target polymorphisms, once identified, will become well-characterized and reproducible. Indeed the data must be well characterized and reproducible, both to secure patent rights and to demonstrate clinically meaningful results to the physicians who rely on them. Modern gene sequencing technologies are designed to very accurately detect and report the presence of very specific sequence changes.

Yet assertions are being made that a second, independent measurement of a genetic test would yield a different or more reliable result. There is no evidence to support this, and, in fact, there are data available showing that exactly the opposite is true. The cystic fibrosis transmembrane conductance regulator (CFTR) gene has been linked to inherited cystic fibrosis (CF). The genetic test measures 12 mutations within the CFTR gene. Richards and colleagues (1993) studied 122 CF patients, 131 relatives of CF patients, and 211 individuals with no family history of CF. They reported, "In a blind study comparing the analysis of 12 mutations responsible for cystic fibrosis in multiplex products amplified with DNA from both blood and buccal cell samples from 464 individuals, there was a 100% correlation of results for blood and cheek cell DNA." Thus, even in this complex analysis of 12 mutations, the same samples measured by two completely different methods yielded identical results.

Why then are there some results in genetic diagnostic testing that are reported as inconclusive? It may depend on whether the mutation is germline or somatic. It may be a function of the computational methods used to correlate the signals from the assay with the diagnostic results from clinical data used to develop the test. It could also be a function of the size and diversity of the

population sampled in development. And, some genetic-associated diseases are also influenced by environmental factors. Seddon and colleagues (2009) reported on the correlation of genetic and environmental factors in age-related macular degeneration (AMD). They concluded, “Factors reflective of nature and nurture are independently related to prevalence and incidence of advanced AMD, with excellent predictive power.” In those instances, whether correlated or not, environmental factors are not always incorporated into clinical testing. But, for germline mutations, the mutational status remains constant, regardless of environmental factors.

Prior to commercial acceptance of a diagnostic test, all of the known variability factors would have been published and vetted in the scientific and clinical communities. Key opinion leaders and clinicians take this information under advisement when prescribing, interpreting, and charting an individualized therapeutic course for each of their patients. A second measurement of an inconclusive result is not expected to be different from the first test if the data are processed in the same way. Reliance on a single diagnostic measurement is not how medicine is practiced, and elimination of uncertainty or inconclusive measurements will come only from further scientific research and discovery, not from repeated measurements of the same test on the same patient.

Quality Control for Diagnostic Testing

Within the diagnostic testing environment, strict internal quality controls are applied to each measurement to ensure that validated results are reported. Should a particular measurement fail the internal quality indicators, a repeat test is run. If the quality of the sample provided is not sufficient for the test, an additional sample is requested. These repeat measurements and additional samples are measured without extra cost to the patient or the payer. This is done to ensure the quality and scientific integrity of the results reported back to the physician.

On top of this, government regulations and accreditation programs provide oversight for testing laboratories. The Centers for Medicare & Medicaid Services (CMS) regulates all clinical laboratory testing performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments or CLIA. Commercial laboratories offering diagnostic tests must undergo licensing through CLIA. In addition, diagnostic testing laboratories are also accredited by the College of American Pathologists (CAP) or other accrediting bodies. These accreditation programs involve routine inspections and proficiency testing to assure accuracy and precision of test results.

Thus, in this highly regulated and validated environment, the likelihood of a repeated genetic measurement producing a different answer is as small as the error rate in the measurement technique itself – virtually zero. A second measurement, or as it has been inappropriately named, a second opinion, is fully expected to give the same result, whether performed at the same or a different laboratory. If a second measurement does not yield the same result, the problem is a quality issue, not a patent or access issue.

Ross and coworkers (2008) published a review of seven commercialized multigene predictors of breast cancer (not including the Myriad Genetics test). The purpose of the study was to assess the cost-benefit of multigene breast cancer predictors, and in their conclusions they implore experts in the field to raise questions on the reliability of the statistical data associated with the tests. They indicated that such tests can be easily misused or employed in the wrong clinical setting, and result in “misleading reassurance about test-driven decisions.” All of these concerns are important and underscore the need for quality control as discussed above. And, repeating such a test, even with the highest degree of accuracy, may not yield additional useful information.

Access and Cost

A second testing laboratory, if established, would have to develop and comply with systems duplicating the innovator laboratory. The results would not be expected to be different and, as such, a second measurement will only add cost to the overall health care system without yielding new information. It is not clear who would be expected to pay for this cost.

When a company launches a new diagnostic test, physicians will order the test, and payers will pay for the test based on the strength of its supporting scientific data. When the lab submits a claim for the test to the insurer, information may be requested from the innovator, the payer may do their own research and evaluate the scientific merit and benefit to the patient, and the payer may even request specific patient information to determine the need for the test.

An insurance company’s decision on whether to pay for a new test depends upon whether they feel there is sufficient, validated clinical evidence that the test will add benefit to the patient and that it is within the scope of coverage for the plan in which the patient is enrolled. Apart from the scope of the patient’s plan, the reimbursement is determined by virtue of the merit of the scientific evidence for the test, including any uncertainties as previously discussed.

While it is often asserted that patents limit access to, and insurance coverage of, diagnostic tests, in reality just the opposite is true.

Patents and exclusive licenses are required for an innovator to secure the funds needed to generate the scientific evidence that a test is valid and beneficial to patients. These clinical studies are very expensive, often costing in the range of 1 to 10 million dollars each. Only when this evidence is available will insurance companies cover and pay for these tests.

Taken the other way, a lack of patents and reliance on studies funded by government or other non-profit organizations would be very unlikely to produce sufficient validated clinical evidence to support commercialization and reimbursement coverage.

Patient access to diagnostic tests is as important to commercial laboratories as it is to the patients. For this reason, our company offers a patient assistance program to provide for those truly in need. This ensures that access to important therapeutics and diagnostics is not necessarily limited by a patient's out-of-pocket liability or financial hardship.

Limitations on Patents and Compulsory Licensing

It is difficult to envision an enforceable patent system in which a non-patent holder or licensee could perform a second laboratory measurement without infringing, but would infringe by performing a primary measurement. How would the patent holder ever be able to determine whether the confirming laboratory is also performing primary testing measurements? Who would monitor and police such a system? And, at what costs? Current patent laws place the burden of stopping infringement squarely on the shoulders of the patent holder. Monitoring and distinguishing non-infringing activities from infringing activities will only add costs and redirect resources from new developments.

The laboratories performing the second measurements will generally not be innovators themselves, and thus will not be willing to front the costs associated with the original clinical validations or the increased costs of monitoring for possible infringement. Would the innovator of the test also be required to turn over to the secondary laboratory all of its proprietary validation information? Would it also have to surrender the intellectual property embodying the computational methods used to arrive at the reported results? Indeed, what would limit the scope and amount of proprietary information taken?

A legislative carve-out, or a taking of intellectual property, is not the means to achieve the outwardly-professed goal of second measurement tests as a means to drive the cost down. Access, costs, and reimbursement are entirely separate issues from patent rights.

Finally, the effects on research and development of new and innovative tests created by a carve-out to allow non-licensed parties to avoid infringement will be far reaching. Established companies, university technology transfer offices, and job creation by startup ventures will be faced with the proposition that they will lose the proprietary benefits of their patents and discoveries. Robust intellectual property rights are the cornerstone of a robust economy in which companies and investors are assured of their ability to control and profit from the significant investments, often in the tens of millions of dollars, required for the clinical validation and commercialization of their technologies. Any steps taken to weaken those rights, while having a pre-supposed short-term gain in access to current technology, will result in long-term reduction of investments needed to commercialize future innovations, thus creating a decrease in access to future technologies.

The argument that patents inhibit research and development is misplaced. Referring to the work of Ross and colleagues (2008) cited above, none of the tests cited in their review would have been developed and commercialized were it not for a robust patent system. And, the mere existence of multiple diagnostic and prognostic tests further refutes the argument that any one particular patent or group of patents is inhibiting innovation or that any one particular test should be subjected to compulsory licensing or a patent carve-out.

The USPTO needs to rely on actual data and documented experience and take a firm stand against dismantling patent and licensing rights; we urge that Congress re-focus the discussion on the correct aspects of health care access and reimbursement.

References

Gerlinger, Marco, et al. (2012) Intratumor heterogeneity and branched evolution revealed by multiregion sequencing, *New England J. Medicine* **366**(10):883-892.

Richards, Brenda, et al. (1993) Multiplex PCR amplification from the CFTR gene using DNA prepared from buccal brushes/swabs, *Human Molecular Genetics* **2**(2):159-163.

Ross, Jeffrey, et al. (2008) Commercialized Multigene Predictors of Clinical Outcome for Breast Cancer, *The Oncologist* **13**:477-493.

Seddon, Johanna, et al. (2009) Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables, *Investigative Ophthalmology and Visual Science* **30**(5):2044-2053.

This email message is for the sole use of the intended recipient(s) and may contain confidential and privileged information. Any unauthorized review, use, disclosure or distribution is prohibited. If you are not the intended recipient, please contact the sender by reply email and destroy all copies of the original message.