Technology that makes use of cell-free fetal DNA (cfDNA) circulating in maternal blood may offer important benefits to women who seek noninvasive prenatal testing early in pregnancy. The features of this technology that distinguish it from existing diagnostic tests—lack of procedure-related risk of miscarriage and early timing of use—have driven research and development of broadening clinical applications and stimulated increasing media and consumer attention (1).

Government agencies and foundations that promote public health have funded a substantial portion of the research leading to patents in this field, and at least four U.S.-based biotechnology companies are vying to introduce cfDNA testing and potentially expand the $1.3 billion prenatal testing market in this country (2). Here, we discuss how the restrictive patenting and licensing strategies used by some academic institutions and commercial firms threaten the translation and intended benefits of this technology.

While the clinical applications of cfDNA-related technology may be promising and profitable, the intellectual property (IP) landscape is uncertain. The U.S. Patent and Trademark Office and the European Patent Office have granted numerous patents related to cfDNA technology, but it is unclear whether the validity of these patents can be upheld or whether their claims overlap. As the exclusive licensee of many of these patents, including one particularly broad patent, Sequenom may be in a position to dominate the market for this testing (http://www.genomeweb.com/sequencing/sequenom-says-competitors-will-have-license-ip-noninvasive-t21-detection-tests). In one public statement, the company announced (http://www.elsevierbi.com/-/media/83A DA2E2C73945A2A154DA385FCF0E48) that, “with a dominant and growing IP estate, we expect that Sequenom, to the exclusion of others, may have the freedom to decide which of many technologies to employ in the commercialization of noninvasive prenatal genetic testing.” A monopoly on this IP could limit intended benefits of the technology and may provide yet another example of how patenting and licensing practices can frustrate the successful translation of publicly funded research. Undesired consequences may include inflated prices, decreased availability, constraints on the autonomy of patients and health-care providers, and limits on further validation or development of this testing.

**IP LANDSCAPE**

In 2005, Sequenom acquired an exclusive license to U.S. patent 6,258,540 and its foreign counterparts in specific countries including the United States (http://www.genomeweb.com/sequenom-licenses-prenatal-dx-patents-isis-innovation-0). Under the umbrella of this patent and others in its portfolio, which cover broad methods and applications of noninvasive testing using cfDNA, the company has developed and marketed tests for fetal sex (http://www.reuters.com/article/2010/02/16/sequenom-shares-idUSGE61F0G520100216), RhD blood type (http://www.news-medical.net/news/20100205/Sequenom-CMM-launches-SensiGene-Fetal-RHD-Genotyping-test-for-pregnant-RhD-negative-women.aspx), and trisomy 13, 18, and 21 (http://sequenom.investorroom.com/index.php?s=43&item=326). Shortly before Sequenom planned to introduce its first cfDNA test for trisomy 21, however, the company became entangled (http://www.genomeweb.com/node/915825?emc=el&foo20;=m=375651&foo20;=l=1&foo20;=v=0769a1d85) in highly publicized accusations of data mishandling and securities fraud, and release of the test was delayed.

Meanwhile, academic researchers pushed forward plans to develop cfDNA technology, and numerous relevant patents were solicited and granted (see Table 1 and table S1 for major U.S. patents and applications, respectively). Sources of support for the research that led to these patents include the U.S. National Institutes of Health, the National Science Foundation, and the Wellcome Trust. Many of the resulting patents have been assigned or licensed to either Sequenom or competing biotechnology companies, such as Verinata Health, Natera, Ariosa Diagnostics, and Ravan. Some firms have introduced clinical trisomy testing using cfDNA via physician referral; others are already offering cfDNA tests for fetal sex and paternity directly to consumers (3). Indeed, as envisioned by policies to enhance commercialization of academic research, such as the Bayh-Dole Act in the United States, university scientists were instrumental in founding or providing critical scientific support for these firms (Table 1 and table S1). However, an unintended consequence of such policies may be that the companies block each other’s translational pathways.

It is unclear whether any of these more recent patents describe claims that overlap with those of U.S. patent 6,258,540 and counterpart patents. In addition, it is uncertain whether the development or provision of cfDNA tests by other entities infringes upon this patent or others in Sequenom’s growing patent estate. Thus far, Sequenom has pursued lawsuits or issued warnings to at least three of its competitors to cease marketing of cfDNA tests using techniques that Sequenom claims are covered by its IP rights (http://www.genomeweb.com/sequencing/verinata-licenses-quake-patent-setting-stage-ip-tussle-sequenom). The company has recently announced plans (http://seekingalpha.com/article/268259-sequenom-s-s-ceo-discusses-q1-2011-results-earnings-call-transcript) to expand its team, build new facilities, and strengthen its ties to insurers, vendors, and other partners in an effort to become the primary provider of cfDNA testing (http://www.genomeweb.com/sequencing/sequenom-says-competitors-will-have-license-ip-noninvasive-t21-detection-tests). Furthermore, Sequenom has granted the rights to use its proprietary methods for noninvasive RhD blood typing to only one New York–based corporate laboratory (http://www.analytica-world.com/en/news/61386/sequenom-and-lenetix-enter-agreement-to-develop-and-commercialize-rhesus-d-prenatal-diagnostic.html), while the rights to the trisomy 21 test have...

**A MONOPOLIZED MARKET**

Given the emergence of a highly competitive market for the development and provision of cfDNA tests, it is clear that several biotechnology firms are confident that their commercial products or IP can remain secure despite Sequenom’s public assertions. However, if any of Sequenom’s key patents is enforceable, this competition may collapse. Notably, in November 2006, the validity of one of Sequenom’s broadest patents, European patent 994963 (the counterpart of U.S. patent 6,258,540), was upheld in a European court in response to a challenge by one of its competitors, Ravgen (http://www.freshnews.com/news/65791/sequenom-benefits-favorable-ruling-european-patent-office-opposition-proceeding).

The implications of a monopolized market for cfDNA testing may be far-reaching. As demonstrated by examples such as the BRCA gene patents currently controlled by Myriad Genetics or Genentech’s broad Cabilly patents for recombinant antibody production, the restraints created by a monopoly position over a laboratory procedure can have detrimental ramifications for clinical practice and research (4, 5). The inability of new companies to enter the market can lead to inflated prices, decreased access for consumers, and diminished ability on the part of health-care professionals to provide appropriate care or pursue confirmatory testing (6, 7). Moreover, attempts by other institutions and companies to improve the features of testing, develop related technologies, or study genetic contributors to human health or disease may be severely limited (8). For example, a recent study by Verinata Health researchers suggested that its algorithm for analyzing cfDNA is superior to the one used by Sequenom in detection rates for trisomy and technical practicality (9). If Verinata Health or other companies are prevented from developing more accurate tests, patient care may suffer.

Other signs of negative consequences can already be seen. The current price of Sequenom’s trisomy 21 test is $1900, which is likely beyond the reach of most women and particularly the uninsured. Sequenom anticipates that insurers will cover the majority of costs, leaving insured patients to pay an expected $235 (http://sequenom.investorroom.com/index.php?s=43&item=310). Even though the price of Sequenom’s RhD test is substantially less—$250 before insurance—some providers in the United States have reported shipping patient samples overseas to the United Kingdom—where testing can be performed under a narrow legal exception to one of Sequenom’s patents and often free of charge—rather than have insurers or uninsured patients pay for the test (3).

Exclusive licensing and active patent enforcement often occur even when publicly funded research generates the IP for diagnostic genetic technologies. The stranglehold on clinical practice and research that could emerge with restrictive IP strategies runs counter to the objectives of public funding agencies and could obstruct the realization of the promised benefits of this technology (10). Although protection for some of the initial patents will expire in the coming few years, new patents in the cfDNA research area continue to be issued at a steady pace. Regulatory agencies, funders, and technology transfer offices must pay attention to the downstream

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**Table 1. Major U.S. patents pertinent to cell-free fetal DNA testing.** Patents and applications are provided to the best of our current knowledge.

<table>
<thead>
<tr>
<th>Number</th>
<th>Name</th>
<th>Inventor</th>
<th>Assignee</th>
<th>Issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,258,540</td>
<td>Noninvasive prenatal diagnosis</td>
<td>Lo et al.</td>
<td>Isis Innovation Limited</td>
<td>2001</td>
</tr>
<tr>
<td>6,492,144</td>
<td>Methods for detection of nucleic acid sequences in urine</td>
<td>Umansky et al.</td>
<td>Diagen Corporation</td>
<td>2002</td>
</tr>
<tr>
<td>6,664,056</td>
<td>Noninvasive prenatal monitoring</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2003</td>
</tr>
<tr>
<td>6,927,028</td>
<td>Noninvasive methods for detecting nonhost DNA in a host using epigenetic differences between the host and nonhost DNA</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2005</td>
</tr>
<tr>
<td>7,645,576</td>
<td>Method for the detection of chromosomal aneuploidies</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2010</td>
</tr>
<tr>
<td>7,709,194</td>
<td>Marker for prenatal diagnosis and monitoring</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2010</td>
</tr>
<tr>
<td>7,718,367</td>
<td>Markers for prenatal diagnosis and monitoring</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2010</td>
</tr>
<tr>
<td>7,727,720</td>
<td>Methods for detection of genetic disorders</td>
<td>Dhallan</td>
<td>Ravgen</td>
<td>2010</td>
</tr>
<tr>
<td>7,754,428</td>
<td>Fetal methylation markers</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2010</td>
</tr>
<tr>
<td>7,785,798</td>
<td>Methods for prenatal diagnosis of chromosomal abnormalities</td>
<td>Cantor et al.</td>
<td>Boston University</td>
<td>2010</td>
</tr>
<tr>
<td>7,799,531</td>
<td>Detecting fetal chromosomal abnormalities using tandem single-nucleotide polymorphisms</td>
<td>Tomita Mitchell et al.</td>
<td>University of Louisville</td>
<td>2010</td>
</tr>
<tr>
<td>7,829,285</td>
<td>Circulating mRNA as diagnostic markers</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2010</td>
</tr>
<tr>
<td>7,838,647</td>
<td>Noninvasive detection of fetal genetic traits</td>
<td>Hahn et al.</td>
<td>Sequenom</td>
<td>2010</td>
</tr>
<tr>
<td>7,901,884</td>
<td>Markers for prenatal diagnosis and monitoring</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2011</td>
</tr>
<tr>
<td>8,008,018</td>
<td>Determination of fetal aneuploidies by massively parallel DNA sequencing</td>
<td>Quake et al.</td>
<td>Stanford University</td>
<td>2011</td>
</tr>
<tr>
<td>8,026,067</td>
<td>Marker for prenatal diagnosis and monitoring</td>
<td>Lo et al.</td>
<td>Chinese University of Hong Kong</td>
<td>2011</td>
</tr>
</tbody>
</table>
consequences of exclusive patenting and licensing policies with respect to clinical and scientific integrity and progress.

SUPPLEMENTARY MATERIALS
http://stm.sciencemag.org/content/4/144/144fs23/suppl/DC1
Table S1. Selected U.S. patent applications pertinent to cell-free fetal DNA testing.

REFERENCES AND NOTES

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