The tragedy of the microarray anticommons is that multimarker assays such as microarrays will have barriers to clinical implementation if they use patented biomarkers that cannot be licensed.

The potential patent problem of multimarker assays is exemplified by a recent multi-institutional study that correlated a gene expression profile of patients’ tumors with the response to chemotherapies (3). This study created a gene expression profile that correlates with mutations or defects in BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, early onset) activity (BRCA1ness profile). The study specifically examined platinum agents, as well as a new category of targeted chemotherapeutics that are inhibitors of poly(ADP-ribose) polymerase (PARP). Platinum agents and PARP inhibitors have previously been shown to have greater effectiveness in patients with BRCA1/2 mutations. The BRCA1ness profile of 60 genes was found to have clinical promise in determining chemotherapy, independent of examining the sequences of the BRCA1 and BRCA2 genes. The potential microarray anticommons was demonstrated by searching the United States Patent and Trademark Office database for any issued US patents that claim the use of the BRCA1ness profile (http://www.uspto.gov; accessed July 1, 2010). Of the 60 genes in the BRCA1ness profile, 7 genes and/or their nucleic acid sequence have previously issued patents (Table 1). Most of the patents for these genes have some description of an assay for use in disease, and several describe use in oncology applications. Of particular interest are 3 of the genes (MGST3, microsomal glutathione S-transferase 3; GBP1, guanylate binding protein 1, interferon-inducible, 67kDa; MTAP, methylthioadenosine phosphorylase), which have patents that specifically claim the use of nucleotide sequences in hybridization assays. Because the final outcome of the Association for Molecular Pathol-

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2 Human genes: BRCA1, breast cancer 1, early onset; BRCA2, breast cancer 2, early onset; MGST3, microsomal glutathione S-transferase 3; GBP1, guanylate binding protein 1, interferon-inducible, 67kDa; MTAP, methylthioadenosine phosphorylase; GGH, gamma-glutamyl hydrolase (conjugase, folylpolygamma-glutamyl hydrolase); MADCAM1, mucosal vascular addressin cell adhesion molecule 1; PSTD1, peristin, osteoblast specific factor; PMS1, PMS1 postmeiotic segregation increased 1 (S. cerevisiae).

3 Nonstandard abbreviations: BRCA1ness profile, gene expression profile that correlates with mutations or defects in BRCA1 and BRCA2 activity; PARP, poly(ADP-ribose) polymerase.
ogy lawsuit is still unknown, the impact of these patented genes on the BRCA
ness profile should be considered. The loss of these 7 genes from the 60-gene panel will likely diminish the utility of the BRCA
ness profile and may render it unusable.

Given that the ultimate goal of developing multimarker tests such as the BRCA
ness profile is clinical use, the potential of assay inoperability due to an inability to license individual biomarkers should be considered from the earliest stages of development. Ideally, a screen for patented biomarkers should occur before a final algorithm is selected. Discovering that key biomarkers are already patented and cannot be licensed during a clinical trial is inopportune. As predicted by the tragedy of the anticommons, multiple owners of patents in the same area of interest may impede commercialization and clinical utilization (1). Multimarker tests such as gene expression microarrays are certainly powerful tools in subclassifying biological samples, but patenting issues should be anticipated to facilitate the transition of these tools into platform technologies that can be used in the clinical laboratory.

An analysis of the BRCA
ness profile indicates several potential solutions to this potential microarray anticommons. First, 88% of the genes were not claimed in any issued US patent. This finding creates hope that multimarker panels may be designed to avoid existing intellectual property; perhaps the BRCA
ness profile could be redesigned to omit the 7 genes identified in this patent analysis. Second, the majority of the patents (4 of 7) were assigned to universities or other nonprofit organizations (Table 1). Although the standard practice in the US is for the exclusive licensing of patents, perhaps these institutions may cross-license with one another. Third, the concept of a gene patent pool should be revisited. A decade ago, the potential for the anticommons was recognized, and gene patent pooling was proposed as a potential solution (4, 5). Patent pools for genes have been envisaged as a service run by nonprofit organizations that would manage the licensing of patents from both nonprofit and commercial entities. For biomedical research institutions seeking to develop new clinical tools, a patent pool of genes could provide a single licensing source for developing new

### Table 1. Previously patented genes that are part of the BRCA
ness profile.

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name</th>
<th>US patent</th>
<th>Claims and descriptions</th>
<th>Assignee</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGST3</td>
<td>Microsomal glutathione S-transferase 3</td>
<td>5,919,627</td>
<td>Nucleotide sequence; claims use in hybridization assays or PCR; description mentions use of nucleotide sequences for diagnosis, prevention, or treatment of cancer</td>
<td>Pharmaceutical company</td>
</tr>
<tr>
<td>GBP1</td>
<td>Guanylate binding protein 1, interferon-inducible, 67kDa</td>
<td>6,894,157</td>
<td>Nucleotide sequence; diagnostic kit is claimed; description mentions use of nucleotide sequences to determine capacity to proliferate or for cellular differentiation</td>
<td>Inventor</td>
</tr>
<tr>
<td>GGH</td>
<td>Gamma-glutamyl hydrolase (conjugase, folylpolygamma-glutamyl hydrolase)</td>
<td>5,801,031</td>
<td>Nucleotide sequence; description mentions use of nucleotide sequences for monitoring the progression of a tumor</td>
<td>University, nonprofit institution</td>
</tr>
<tr>
<td>MTAP</td>
<td>Methylthioadenosine phosphorylase</td>
<td>5,942,393; 6,870,037</td>
<td>Nucleotide sequence; claims use in hybridization assays or PCR to determine malignancy</td>
<td>University, nonprofit institution</td>
</tr>
<tr>
<td>MADCAM1</td>
<td>Mucosal vascular addressin cell adhesion molecule 1</td>
<td>7,750,137</td>
<td>Nucleotide sequence; description mentions use in hybridization assays for disease-association assays</td>
<td>Pharmaceutical company</td>
</tr>
<tr>
<td>POSTN</td>
<td>Periostin, osteoblast specific factor</td>
<td>6,518,063</td>
<td>Nucleotide sequence</td>
<td>University, nonprofit institution</td>
</tr>
<tr>
<td>PMS1</td>
<td>PMS1 postmeiotic segregation increased 1 (S. cerevisiae)</td>
<td>5,922,855; 6,191,268</td>
<td>Nucleotide sequence; description mentions use in hybridization assays</td>
<td>University, nonprofit institution, and hospital, nonprofit institution</td>
</tr>
</tbody>
</table>
multimarker assays. Patent pools have recently been used in the MPEG-2 compression technologies, as well as in DVD formats. Indeed, during World War I, patent pooling was pushed by the US government for technologies in radio and aviation (5). Recently, MPEG LA, the firm better known for managing the MPEG-2 patent pool, announced an initiative to create a gene patent pool as a single source for nonexclusive diagnostic genetic licensing (6). The overall idea is that patenting of genes does not have to deter the clinical development of multimarker assays. There are solutions that can facilitate the commercialization of multimarker assays, regardless of the existence of genetic patents.

Perhaps the recent ruling on BRCA genes will be upheld in the US judicial system. If not, researchers and developers of clinical multimarker assays should be prepared to deal head-on with the issues of biomarker and gene patents. Over the past 2 decades, the utility of multimarker proteomic and gene expression assays as research tools has been well established. There are now several clinical microarray-based assays available in the European and US markets. As technical issues of quality control are solved, these complex assays will inevitably become more clinically useful and commonplace; however, the large number of analytes that power these assays is also the potential Achilles’ heel in terms of commercialization. By embracing issues of intellectual property in the earliest stages of developing a multimarker assay, perhaps a microarray anticommons can be avoided.

**Author Contributions:** All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

**Authors’ Disclosures of Potential Conflicts of Interest:** No authors declared any potential conflicts of interest.

**Role of Sponsor:** The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

**References**