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Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers: Patents and Licensing for Breast, Ovarian and Colon Cancer Testing

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Abstract

Genetic testing for inherited susceptibility to breast and ovarian cancer can be compared to similar testing for colorectal cancer as a “natural experiment.” Inherited susceptibility accounts for a similar fraction of both cancers and genetic testing results guide decisions about options for prophylactic surgery in both sets of conditions. One major difference is that in the United States, Myriad Genetics is the sole provider of genetic testing, because it has sole control of relevant patents for BRCA1 and BRCA2 genes whereas genetic testing for familial colorectal cancer is available from multiple laboratories. Colorectal cancer-associated genes are also patented, but they have been nonexclusively licensed. Prices for BRCA1 and 2 testing do not reflect an obvious price premium attributable to exclusive patent rights compared to colorectal cancer testing, and indeed Myriad’s per unit costs are somewhat lower for BRCA1/2 testing than testing for colorectal cancer susceptibility. Myriad has not enforced patents against basic research, and negotiated a Memorandum of Understanding with the National Cancer Institute in 1999 for institutional BRCA testing in clinical research. The main impact of patenting and licensing in BRCA compared to

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colorectal cancer is the business model of genetic testing, with a sole provider for BRCA and multiple laboratories for colorectal cancer genetic testing. Myriad's sole provider model has not worked in jurisdictions outside the United States, largely because of differences in breadth of patent protection, responses of government health services, and difficulty in patent enforcement.

Keywords

Patents; Intellectual Property; breast cancer; colorectal cancer colon cancer; Lynch syndrome; FAP; familial adenomatous polyposis; BRCA; APC; MSH; Myriad Genetics; genetic testing

INTRODUCTION

One natural case study in the field of cancer genetics can address whether and to what degree intellectual property law affects patients' access to genetic testing. The parallel discovery of inherited mutations for two classes of cancer: breast, ovarian and some other cancers associated with BRCA 1&2 genes, compared to a cluster of genes in which mutations predispose to cancer of the colon and rectum. Specific mutations in genes known as *BRCA1* and *BRCA2* can dramatically increase patients' risks for breast cancer and ovarian cancer (and more rarely, some other cancers). Similarly, specific mutations in other genes can give rise to two inherited conditions highly associated with developing colon cancer, known as Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (sometimes called Hereditary Non-Polyposis Colorectal Cancer, or HNPCC).

Mutations in all six cancer susceptibility genes were discovered in the 1990s, and genetic tests to detect them were patented over a four-year period. Myriad Genetics, Inc., a for-profit company, gained control over the U.S. patents on genetic tests for *BRCA1* and *BRCA2*. The patents for inherited colon cancer family syndromes remain more broadly distributed, with some key patents held by Johns Hopkins University, Oregon Health Sciences University, Dana Farber, and other non-profit entities. The licensing patterns for these tests vary, again providing a natural case-study to compare for-profit patenting and licensing practices versus non-profit patenting and licensing practices. Finally, as of early 2006 there were 62 genetic tests for cancer available for clinical use but only five used for primary prevention, including the tests for BRCA, FAP, and Lynch Syndrome (HNPCC) discussed in this case study.²⁵

BACKGROUND: BREAST CANCER, OVARIAN CANCER AND BRCA1/BRCA2

According to the American Cancer Society (ACS), over 178,000 American women were diagnosed with invasive breast cancer in 2007, and another 62,000 with *in situ*, or non-invasive breast cancer. This made breast cancer the most common cancer diagnosis after skin cancer for women. Finally, over 40,000 women were expected to die from breast cancer in 2007, second only to lung cancer.²⁶

In 2007, the ACS also projected 22,430 women were diagnosed with ovarian cancer, accounting for 3% of all cancers among women. Furthermore, 15,280 women were projected to die from ovarian cancer in 2007, more than any other cancer of the female reproductive tract.²⁶

Both breast and ovarian cancer are associated with age—ovarian cancer incidence peaks around age 70,²⁶ while 95% of new breast cancer cases and 97% of breast cancer deaths occur in women over the age of 40.²⁷ Obesity is also a risk factor for both breast and ovarian cancers, and both cancers correlate with family history.

Approximately 20% of women with breast cancer have either a first-degree or a second-degree relative with breast cancer.²⁸ Scientists have identified several genes associated with elevated risk of breast cancer. Two of these are powerful cancer susceptibility genes, meaning mutations can be traced through families in a classic Mendelian dominant inheritance pattern: *BRCA1* and *BRCA2*. Breast cancers arising from *BRCA1* and *BRCA2* mutations account for between 5 and 10 percent of all breast cancers,²⁷ or between 20,000 and 40,000 cases annually. Overall, the relative lifetime risk of breast cancer is 2.7 to 6.4 times greater for those with *BRCA* mutations compared to other women (Table 6). For ovarian cancer the relative risk for *BRCA* positive women rises 9.3 to 35.3 times (Table 6).

Though the Agency for Healthcare Research and Quality (AHRQ) notes that *BRCA1* and *BRCA2* mutations occur at a frequency of around 1 in 300-500 in the general population, the risk of inheriting one of these mutations is much higher in some ethnic groups. For example, specific mutations have been identified in the Ashkenazi Jewish population, and certain families in the Netherlands, Iceland, and Sweden have a high frequency of *BRCA1* or *BRCA2* mutations.²⁷

Current clinical practice guidelines are available from the National Comprehensive Cancer Network at <http://www.nccn.org>.

BACKGROUND: COLORECTAL CANCER AND FAP/LYNCH SYNDROME (HNPCC)

According to the ACS, colorectal cancer is the third most common cancer among both men and women in the United States. Over 150,000 Americans will be diagnosed with colorectal cancer and over 52,000 Americans will die of colon cancer in 2007, accounting for 10 percent of all cancer deaths.²⁶ Risk factors for developing colorectal cancer include age, diet, obesity, smoking, physical inactivity, and family history.²⁶

Almost one-third of colorectal cancer cases are thought to be related to family history, of which two major conditions have been correlated with specific genetic mutations. Combined, these two conditions are thought to account for between 3 to 5 percent of all US colorectal cancers.

Current clinical practice guidelines are available from the National Comprehensive Cancer Network at <http://www.nccn.org>.

Familial adenomatous polyposis (FAP)

FAP accounts for approximately 1% of all colorectal cancers. The disease is inherited in an autosomal dominant fashion. More than 90% of FAP cases are associated with mutations in the *adenomatous polyposis coli* gene, or *APC* gene. The *APC* gene encodes a tumor-suppressing protein, analogous to the tumor suppressing gene p53 which is found mutated in many kinds of cancer. The percent of individuals with FAP who develop colorectal cancer approaches 100% - or 16.7 times the risk of the general population (Table 6) – with most affected individuals developing cancer around age 40.²⁹ A milder and less common form of FAP is attributed to mutations in the *MYH* gene.

Lynch Syndrome (Hereditary nonpolyposis colorectal cancer, or HNPCC)

Lynch Syndrome accounts for 1-3% of colorectal cancer in the United States, and mutations are inherited in an autosomal dominant pattern. Lynch syndrome is rapidly becoming a disease category defined by DNA characterization, caused by mutations in genes that encode enzymes that repair DNA base-pair mismatches during DNA replication. This molecular

definition replaces the traditional symptomatic and descriptive label hereditary nonpolyposis colorectal cancer, or HNPCC.

The most recent review of evidence about genetic testing in this condition defined Lynch Syndrome as a “predisposition to colorectal cancer and certain other malignancies as a result of a germline mismatch repair gene mutation—including those with an existing cancer and those who have not yet developed cancer” (p. 42).⁸ Mutations in specified genes are thus becoming the basis for disease classification, replacing and refining previous clinical criteria. Lynch Syndrome is becoming the preferred term for those who have these mutations, although we also use HNPCC to refer to the clinical findings in this review.

Individuals must inherit a copy of one mutated gene from either their mother or their father to develop the HNPCC disease. The genes already known to give rise to Lynch Syndrome when mutated include: *MLH1*, *PMS1*, *PMS2*, *MSH6*, *TGFR2*, and *MLH3*.³⁰ Of these, mutations in *MSH2* account for approximately 60% of cases, and *MLH1* another 30%.³⁰ “Mismatch repair proteins are responsible for correcting errors that occur during DNA replication, typically the addition or deletion of one or more nucleotides” (p. 673).²⁹ Patients with Lynch Syndrome have an approximately 80% lifetime risk of developing colorectal cancer—or over 13 times the risk of the general population (Table 6)—though the specific risk varies by mutation.²⁹ There is significantly higher risk of developing endometrial (uterine) cancer and ovarian cancer as well in women with these mutations. In fact, about half of women with Lynch Syndrome who develop cancer present with one of these gynecological cancers as their first malignancy.

PATENTS AND LICENSING

Breast Cancer

Myriad Genetics owns or has licensed the patents for both *BRCA* genes and their mutations. Some *BRCA1* patents are co-assigned to the University of Utah and US Department of Health and Human Services, as the research was supported in part by NIH grants (governed by the Bayh-Dole Act) and intramural research at the National Institute of Environmental Health Sciences (governed by the Stevenson-Wydler Act). While NIH investigators were listed as co-inventors on some patents, NIH assigned administration of those patents to the University of Utah. The *BRCA* patents have been administered by the University of Utah, with exclusive licensing to Myriad, and Myriad in effect controls the patent rights. We therefore refer to them as “Myriad patents.”

Myriad’s first patent, U.S. 5753441, is on *BRCA1* testing and includes both method claims and a testing kit. Its second patent, U.S. 6051379, is on *BRCA2* and includes parts of the *BRCA2* gene in oligonucleotide sequences, method claims, and kits. According to Dr. Shobita Parthasarathy, Myriad purchased this patent along with testing services from OncorMed in 1998 for an “undisclosed sum” (p. 117).¹⁹ Patent rights were included in \$525,000 paid to OncorMed, reported in its Securities and Exchange Commission (SEC) quarterly report from June 30, 1998.³¹ (For more information on patents, see Table 7.) Having sold off its *BRCA* assets, OncorMed entered into a reorganization agreement in which the company Gene Logic, Inc., bought OncorMed for a sum “not to exceed approximately \$38 million” (p. 4).³² OncorMed registered its termination with the SEC on September 30, 1998.³³

Myriad became the sole-provider for both *BRCA1* and *BRCA2* full-sequence tests in the United States, as shown in Table 6. “To perform *BRCA 1/2* mutation analysis, Myriad Genetics and its licensees only use direct sequencing of the whole genomic DNA (DS [double-stranded]) of both genes (BRACAnalysis®)” (p. 289).⁶ In 2003 the *Journal of*

Molecular Diagnostics noted that of the twelve tests that laboratory directors across the United States were called on to stop performing by patent enforcers, Myriad's *BRCA* testing tied for first with nine labs reporting enforcement efforts.²⁰

Lynch Syndrome (HNPCC)

Multiple gene patents cover the major genes involved in Lynch Syndrome (HNPCC). The first patent, U.S. 5922855, covering the *MLH1* gene, was filed by Oregon Health Sciences University and Dana Farber in 1999. The second patent application, U.S. 5591826, was filed by Johns Hopkins in 1997. It covers the *MSH2* protein. Johns Hopkins also later patented a diagnostic method to find mutations in the *MSH2* gene (U.S. 5693470). There are multiple providers, both non-profit and for-profit, for full sequence tests on both genes (see Table 6). Neither patent was noted by laboratory directors as having been enforced.²⁰ Finally, some providers add a third gene to their test – *MSH6* – but the patent situation for *MSH6* is unclear.

FAP

One patent, U.S. 5352775, covers the *APC* gene and was filed by Johns Hopkins in 1994. Again, multiple non-profit entities and one for-profit provider offer full sequence testing for *FAP* as described in Table 6. Finally, Dr. Cho and her colleagues note Johns Hopkins enforced its patent on at least two of the laboratories surveyed in 2001.²⁰

GENETIC TESTS

Breast Cancer

For patients suspected to have one of the *BRCA* mutations—based on strong family history and an early age of onset among cancer-developing family members—two types of genetic testing are available. First, if the patient comes from an ethnic group already known to have specified mutations, or a mutation known from another member of that family, several non-profit university laboratories and one commercial laboratory can perform a targeted genetic test. These tests range in cost from \$325 to \$2,975.²⁸ If the patient is not a member of a known risk-group, or if her physician believes full DNA sequencing analysis is necessary, Myriad Genetic Laboratories is the United States' sole provider of full DNA sequencing for the *BRCA* genes.

The patent story outside the United States is more complicated, and described in a separate case study by E. Richard Gold and Julia Carbone.³⁴ For example, patents have been obtained but the patents are being ignored by provincial health systems in Canada. In Australia and the UK, Myriad's licensee permitted use by health systems, but announced a change of plans in August 2008. (Shobita Parthasarathy provided additional information about Myriad's experience in the United Kingdom.¹⁹) Only a single mutation has been patented in Myriad's lone European-wide patent, although some patents remain under review of an opposition proceeding. In effect, the United States is the only jurisdiction where Myriad's strong patent position has conferred sole-provider status.

AHRQ reports that the analytic sensitivity and specificity for Myriad's tests are greater than 99%.²⁸ Myriad's price for "full sequence analysis," which also includes rearrangement testing, is \$3,120 (Personal communication with Myriad Genetics). Myriad performs redundant testing of each amplicon in both the forward and reverse direction to reduce PCR failure from DNA sequence variants in PCR primers. Myriad resequences any amplicon in which a mutation is detected twice and offers free sequencing of family members to characterize variants of uncertain clinical significance.

Finally, when new information is found about a mutation (i.e., an uncertain variant reclassified as a mere polymorphism or as deleterious mutation), Myriad sends an amended report to the ordering physician of every patient in whom this variant has been found.¹ Myriad performs the same variant characterization services for Lynch Syndrome (HNPCC) and FAP testing.

One report in the *European Journal of Human Genetics* questions the cost-effectiveness of using full-sequence analysis testing as a screening method for at-risk women (defined as women with two first-degree relatives with breast cancer) noting that their “results on genetic testing for breast cancer show that [direct DNA sequencing] is not the most cost-effective method available” and that “the monopolist approach of the firm which owns the patents on the [*BRCA1* and *BRCA2*] genes may, therefore, limit the use of the most cost-effective strategies” (p. 599).³⁵

Lynch Syndrome (HNPCC)

Several laboratories offer full-sequence analysis for Lynch Syndrome, including both non-profit centers and two commercial labs. With the exception of the price listed for Quest Diagnostics, prices are list prices for insurance companies. Prices were collected in 2008. Unless otherwise noted, prices come from personal communications with the relevant laboratories.

- Baylor: \$1,150 per gene or \$3,200 for the *MLH1*, *MSH2* and *MSH6* genes³⁶
- Boston University: \$2,995 for all three genes (*MLH1*, *MSH2* and *MSH6*)
- City of Hope: \$1,771.20 for *MLH1*, \$1,474.56 for *MSH2*, \$1,400.40 for *MSH6*
- Harvard: \$2,700 for all three genes (*MLH1*, *MSH2* and *MSH6*)³⁷
- Huntington Laboratory: \$1,200 for two genes (*MLH1* and *MSH2*) plus \$600 for *MSH6* (\$1,800 for all three genes)
- Mayo Clinic: \$2,000 for two genes (*MLH1* and *MSH2*) and \$ 1,100 for *MSH6* (\$3,100 for all three genes)
- University of Pennsylvania: \$1,360 for *MLH1*, \$740 for *MSH2* and \$740 for *MSH6* (\$2,840 for all three genes)
- Quest Diagnostics: \$2,940.00 for full sequencing of both *MLH1* and *MSH2* and \$1820.00 for *MSH6* (\$4,760 for all three genes)

Among for-profit testing laboratories, Myriad charges \$2,950 for its COLARIS® test which includes full-sequencing of the *MLH1*, *MSH2* and *MSH6* genes as well as testing for major rearrangements. Rearrangement testing complicates the picture further, as each laboratory has its own price:

- Baylor: Rearrangement testing for either *MLH1* or *MSH2* is \$625, rearrangement testing for *MSH6* is not available
- Boston University: Rearrangement testing is included in the cost of \$2,995 for sequencing *MLH1*, *MSH2*, and *MSH6*
- City of Hope: Rearrangement testing and dosage analysis for 7 exons in *MSH2* is \$547.56, rearrangement testing and dosage analysis for all exons in *MSH6* is \$658.80
- Harvard: Rearrangement testing for *MLH1* or *MSH2* is \$600, rearrangement testing for both is \$800³⁷

- Huntington Laboratory: Rearrangement and gene dosage analysis for both *MLH1* and *MSH2* is \$600
- Mayo: Rearrangement testing is included in the above prices
- Quest Diagnostics: Rearrangement testing for both *MLH1* and *MSH2* is \$540.00; Rearrangement testing for *MSH6* is not available

A representative of the University of Pennsylvania Medical Center's lab stated that rearrangement testing for all of the colon cancer genes discussed here is not available as a listed service but can be done on a research basis. Finally, the reported sensitivity of these tests ranges from 50-70%.²⁹

FAP

Four non-profit organizations offer direct DNA sequencing for FAP, as does Myriad Genetics:

- Baylor: \$1,675 for full sequence analysis; rearrangement testing \$625.³⁶
- Harvard: \$1,500 for full-sequence analysis; rearrangement testing \$600.³⁸
- Huntington Laboratory: \$1,200 for full-sequence analysis; gene dosage and rearrangement testing \$600
- University of Pennsylvania: \$1,360 for full-sequence analysis
- Boston University: full-sequencing analysis \$1,675; rearrangement testing \$495
- Mayo Clinic: Full sequencing \$1,300; includes rearrangement testing

Among commercial laboratories, Myriad charges \$1,795 for its COLARIS AP® test, providing a full-sequence analysis for the *APC* gene as well as major rearrangements and two mutations of MYH. The reported sensitivity for these FAP tests ranges from 80-90%.²⁹

MYH

In addition to Myriad, four other providers test the MYH gene for cancer-related mutations.

- Baylor: \$1,150 full-sequence analysis, 2 mutation analysis \$300, no rearrangement testing available
- Huntington Laboratory: \$600 full-sequence analysis, no rearrangement testing available; 2 mutation analysis available for \$250
- University of Pennsylvania: Full sequencing \$500; targeted mutation for 2 mutations \$600
- Mayo: Testing for 2 mutations \$306.60³⁹

Summary of Costs

Table 1 notes the approximate sizes of each of the genes discussed above. Table 2 gives the number of “amplicons” used by Myriad Genetics for its BRCA and hereditary colon cancer tests. The full-sequencing tests are done by choosing PCR primers that flank exons or subsections of exons, amplifying the DNA that spans the relevant exonic sequences, and sequencing those stretches of DNA. The “amplicons” include the protein-coding regions of the genes, plus a small amount of flanking sequence for each unit. Amplicons may span an entire (short) exon, or may break a protein-coding region into segments that can be amplified by PCR (so long exons are represented by several amplicons). At Myriad Genetics, each amplicon is amplified from two sets of PCR primers, so that each amplicon is

sequenced twice. We did not obtain details of laboratory procedure at other testing services, because we did not need to make intra-laboratory comparisons.

We use these figures because Myriad, as sole provider of the BRCA test, is the only laboratory for which we can compare prices for BRCA and colon cancer testing. For other laboratories, we assume that they are using comparable methodology, although they do not use the same PCR primers, likely use a somewhat different number of amplicons, and may not use exactly the same protocols for testing. The comparisons are therefore only rough benchmarks, and the overall price is the main metric. Myriad Genetics is on the high side of pricing for colon cancer testing in overall price (and the only provider for breast cancer testing), but Myriad also includes rearrangement testing and (for FAP and Attenuated FAP) tests common mutations in a gene, MYH, that some other laboratories price as separate tests but do not necessarily analyze with the standard FAP full-sequence test. Table 2 uses these gene sizes to determine the approximate total number of base pairs sequenced per genetic test for both breast and ovarian cancer, as well as colorectal cancers tests, then estimates charge per kilobase (one thousand base-pairs) for each test as well.

As Table 2 shows, Myriad's charge per amplicon varies over the three tests it offers, ranging from \$38.05 for its *BRCA1&2* test, to \$40.80 for its FAP test, to \$49.17 for its Lynch Syndrome (HNPCC) test. Myriad's charge per amplicon is actually lower for its *BRCA1&2* tests, which are done under exclusive provider status associated with Myriad's dominant patent position, compared to the colon cancer tests, despite there being multiple providers and lack of dominant patent position for the various hereditary colon cancer susceptibility tests. This shows no clear *price* premium for the BRCA full-sequence tests.

Myriad's normalized price for colon cancer testing is at the high end for FAP (but that includes two mutations in another gene, MYH, as well as rearrangement testing), and is in the middle of the range for Lynch Syndrome (HNPCC) testing for the three DNA repair genes in that pathway, *MLH1*, *MSH2*, and *MSH6*. All laboratories offering colon cancer testing are presumably paying comparable licensing fees to the patent-holders, although the licensing arrangements are not public information so we do not know details.

The result is somewhat different if normalization is done on cost "per base pair," rather than per PCR amplicon. Calculated per base pair of the full length native gene, BRCA testing price is 15 to 48 percent higher than for colon cancer testing (\$18.87 per kilobase of gene sequence for BRCA1 and 2, compared to \$16.57 for APC, and \$12.71 for the *MLH1*, *MSH2* and *MSH6* test). The "length of gene" basis for normalization is not as relevant for normalization, however, because the test is done by sequencing gene fragments as PCR amplicons, and the unit cost is more related to number of amplicons than total gene size. The price comparisons may be surprising to some, as normalized prices show little if any price premium. This, in turn, suggests the main market impact of the BRCA patents is not on price but rather on volume, by directing BRCA full-sequence testing in the United States to Myriad, the sole provider.

Limitations on price comparison

The comparison of BRCA and FAP/HNPCC testing is confounded by several variables that are not controlled, so it is inexact. Different laboratories use somewhat different methods, and different numbers of amplicons, and different degrees of testing for insertions, deletions, and rearrangements. FAP and HNPCC genes do have patents on them, and prices may include licensing fees, so this is not a "patented versus nonpatented gene" pricing comparison. The rearrangement testing is included in total prices, but the details of those aspects of testing differ between BRCA and colon cancer predisposition mutations. The data cannot rule out a monopoly price effect, but only suggest that any such effect is buried in the

counfounder variables. One other powerful constraint on pricing is reimbursement practices for genetic tests, which tend to start from per-amplicon unit prices and are negotiated for specific tests from that baseline.

CURRENT GENETIC TESTING GUIDELINES

Breast Cancer

Though in 2005 the United States Preventative Services Task Force (USPSTF) recommended against routine genetic testing for the *BRCA1* / *BRCA2* mutations, the USPSTF does recommend testing for women whose family histories suggest *BRCA1* or *BRCA2* risk.⁴⁰ Specifically, the USPSTF recommends that women with family histories suggestive of *BRCA1/BRCA2* mutations be referred for appropriate genetic counseling because “the benefits of referring women with an increased-risk family history to suitably trained health care providers outweigh the harms” (p. 356).⁴⁰

In terms of clinical algorithms, the National Comprehensive Cancer Network (NCCN) publishes and maintains guidelines on its website <http://www.nccn.org/>.

Colorectal Cancer

The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP) published recommendations for genetic testing among newly diagnosed individuals with colorectal cancer.⁷ They examined four genetic testing strategies and found no decisive winner. All four protocols involve genetic testing, but the methods, cost, and selection criteria for which patients get which kind of test differ. The most expensive but also most sensitive method is full-sequence testing, the pathway most comparable to Myriad’s *BRCA* testing. The EGAPP recommendations are based on a January 2009 supplementary evidence review.⁸ That review, in turn, builds on a massive 2007 evidence review by the Tufts-New England Medical Center Evidence-Based Practice Center.⁴¹ The NCCN has published its clinical guidelines on testing for FAP and HNPCC. And a joint committee of the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology (ACS/MSTFCRC/ACR) produced a consensus statement on screening and surveillance for colorectal cancer and polyps in May 2008.⁴²

New EGAPP analysis, in addition to sifting through evidence and assessing four genetic testing strategies, also shifts the framework for genetic testing away from family history, and toward genetic testing of those newly diagnosed with colorectal cancer. This is a significant change, indicating the many individuals who do not know about cancer in relatives or when they are the first individuals in their families identified with the mutations that can now be identified as conferring risk. That is, clinical practice appears to be shifting from genetic testing only when family risk is evident to using genetic testing to identify new individuals and families at risk. This is mainly because many individuals carrying mutations will be missed if family history is a threshold criterion for testing. It is worth noting that if genetic testing becomes less expensive and more widely available, and as more mutations associated with cancer risk are identified, DNA analysis could move higher up the clinical decision tree, not just in Lynch Syndrome but in other cancers as well.

NCCN guidelines specify the following inclusion criteria to consider genetic testing for any of the various inherited colorectal cancers:

- Early-onset colorectal cancer (age < 50), or
- Clustering of same or related cancer in close relative, or

- Multiple colorectal carcinomas or >10 adenomas in the same individual, or
- Known family history of hereditary cancer syndrome with or without mutation.⁴³

From here, the NCCN guidelines split between FAP and HNPCC

FAP

In patients with the FAP phenotype (more than 100 colorectal polyps), genetic testing is recommended to establish the diagnosis. From there, the NCCN recommends:

Genetic testing in individuals with familial polyposis should be considered before or at the age of screening. The age for beginning screening should be based on the patient's symptoms, family phenotype and other individual considerations.⁴³

In the event that a familial mutation is unknown, the NCCN further recommends:

In some families, APC mutations cannot be found with available testing technology, recognizing that the sensitivity to identify APC mutations is currently only about 80%. In other families, affected individuals have died or are not immediately available. Under these circumstances, APC testing should be considered for at-risk family member. If the mutation responsible for FAP within a family is not found, it is important to remember the limitations of interpreting a gene test in a presymptomatic individual. Evaluating presymptomatic individuals at risk in these families presents a difficult problem, since the mutation responsible for FAP within the family is not known. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. But interpreting a test in which "no mutation is found" in a presymptomatic person is not the same as a "negative test." (Document on file with authors)⁴³

The ACS/MSTFCRC/ACR guideline identifies those with a genetic diagnosis of FAP or suspected FAP without genetic testing as "high risk" and recommends considering genetic testing (if not already done). It recommends monitoring starting age 10 to 12, with an annual flexible sigmoidoscopy exam. If genetic testing is positive, "colectomy should be considered" (Table 3, p. 154).⁴²

HNPCC

The NCCN only recommends HNPCC genetic testing only for certain patients:

- Individuals in families meeting either the Amsterdam I or II criteria, and
- Affected individuals meeting Revised Bethesda guidelines.⁴³

The 2008 ACS/MSTFCRC/ACR guideline recommends offering genetic testing for all first-degree relatives of a confirmed case. Monitoring for those with confirmed or at increased risk of HNPCC should begin at age 20 to 25, or a decade before the youngest case in a family (whichever is younger), with colonoscopy every 1-2 years.⁴³

The 2007 Tufts Evidence-Based Practice Center report noted a major gap in knowledge about how best to do the genetic testing and differing views on test algorithms in the literature. The report also noted that sequencing was the "method of choice" for mutation detection, but with many different technologies for doing such sequencing and a need to supplement it with rearrangements/insertion/deletion testing. No clear, consistent "winner" was found among technologies.

Regarding test utility, the report concluded:

Pre-test genetic counseling had good efficacy in improving knowledge about HNPCC and resulted in a high likelihood of proceeding with genetic testing, satisfaction in the decision to undergo genetic testing, and decreasing depression and distress levels among family members of HNPCC probands with cancer and among asymptomatic individuals from HNPCC families.

Identification of HNPCC mutations was associated with an increase in the likelihood that family members of probands with CRC [colorectal cancer] would undergo cancer-screening procedures. HNPCC family members who underwent cancer-screening procedures had a lower risk of developing HNPCC-related cancers and lower mortality rates than those who did not take actions. (p. vi)⁴¹

These conclusions will now be updated by the January 2009 EGAPP recommendations, which do not choose among the four genetic testing strategies, but do recommend genetic testing in newly diagnosed colorectal cancer.⁷ The trend appears to be moving towards genetic testing earlier in the diagnostic process, in order to guide treatment and to identify others in families who might be at risk but do not know it.

If a tumor sample is available, the NCCN recommends testing for both immunohistochemistry and microsatellite stability testing first rather than beginning with DNA sequencing. The results of either of these preliminary tests can direct a clinician to the appropriate gene to sequence for “germline analysis,” thus avoiding the shotgun-like approach of a full-sequence analysis on all three genes.⁷

NON-GENETIC SCREENING OPTIONS

Breast Cancer

The USPSTF currently recommends mammography for all women once every 1-2 years after the age of 40.⁴⁴ AHRQ reports that the Cancer Genetic Studies Consortium recommended annual mammography for women beginning between the ages of 25 and 35, with annual clinical breast exams also beginning between ages 25 and 35 and monthly self breast exams beginning between ages 18 and 21.²⁸ AHRQ also notes that the USPSTF does not currently recommend screening women at any age for ovarian cancer.²⁸ The American Cancer Society issued guidelines in April 2007 calling for MRI screening, in addition to mammography, for women carrying BRCA mutations and first-degree relatives of those with BRCA mutations.⁴⁵

Colorectal Cancer

Beginning at age 50, the American Cancer Society recommends:

- Fecal occult blood testing (FOBT) annually, or
- Flexible sigmoidoscopy every five years, or
- Annual FOBT plus flexible sigmoidoscopy every five years, or
- A double-contrast barium enema every five years, or
- A colonoscopy every 10 years.²⁶

However, according to the USPSTF:

The USPSTF found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer and fair evidence that sigmoidoscopy alone or in combination with FOBT reduces mortality. The USPSTF did not find direct evidence that screening colonoscopy is effective in reducing colorectal cancer mortality; efficacy of colonoscopy is supported by its integral role in trials

of FOBT, extrapolation from sigmoidoscopy studies, limited case-control evidence, and the ability of colonoscopy to inspect the proximal colon. Double-contrast barium enema offers an alternative means of whole-bowel examination, but it is less sensitive than colonoscopy, and there is no direct evidence that it is effective in reducing mortality rates.⁴⁶

INTERPRETING TEST RESULTS/OPTIONS FOR PROPHYLACTIC TREATMENT

Breast and Ovarian Cancer

The clinical utility of *BRCA1* and *BRCA2* screening may be summarized as follows:

- For those testing positive, there are cost-effective approaches to chemoprevention (prophylactic tamoxifen for breast cancer and oral contraceptives for ovarian cancer), screening, and surgery (prophylactic mastectomy, prophylactic salpingo-oophorectomy or tubal ligation), all of which result in gains in both life expectancy and quality-adjusted life years (QALYs) relative to watchful waiting.⁴⁷
- For high-risk patients who test negative, there may be reduced anxiety about the future risks of breast or ovarian cancer. These gains must be balanced against the losses experienced by those who test positive, including elevated anxiety, depression and guilt.⁴⁸
- Finally, though \$50,000 per QALY is the conventional benchmark for cost-effectiveness analysis,⁴⁹ some authors do argue for a standard of \$100,000 - \$150,000 per QALY.^{50, 51}

According to AHRQ, interpretation of the test results for *BRCA1* and *BRCA2* genetic testing can be difficult. For example, if a patient with known positive family history for a specific mutation tests negative, she can be “reassured about her inherited risk.” On the other hand, a negative test is “less useful if her relatives have cancer but no detected deleterious mutations.” Finally, AHRQ noted that up to 13% of tests produce results of “uncertain clinical significance.”²⁸ More recent (2008) data are that variants of uncertain clinical significance are found in fewer than 6% of cases (with the highest rate of “variants of unknown significance” among African Americans, at 11%).⁵² The crucial data are: “Overall, the VUS [Variants of Unknown Significance] rate decreased from 12.8% in 2002 to 5.9% in 2006, a 54% reduction, including decreases of 50.1% (Western European), 58.3% (African), and 48.6% (Asian). From 2006 to 2008 the identification of variants of uncertain significance continued to decline to 5.1% of tests performed. This continued decrease was observed in all ethnic groups, with the largest decline in the African American population where the VUS rate declined from 38.6% in 2002 to 10.9% in 2008.”⁵²

When women do test positive, the USPSTF first noted in 2002 that women at high risk for breast cancer should consider taking chemoprevention (e.g., tamoxifen)⁵³ but then noted in 2005 that there is “insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving health outcomes” (p. 355).⁴⁰ The ACS recommends that women positive for *BRCA1/BRCA2* mutations consider tamoxifen therapy.²⁷ See Table 3 for a break-down of the results found in three different cost-effectiveness studies on chemoprevention in at-risk women.

Surgical options—Both the ACS and the USPSTF note that prophylactic surgery (e.g., bilateral mastectomy and bilateral oophorectomy) significantly decreases the chances of developing cancer in *BRCA* mutation-positive women and should be strongly considered.^{27, 40} Table 4 shows the results from two cost-effectiveness studies on prophylactic surgery. For

a complete cost-effectiveness analysis of all preventative strategies surrounding positive *BRCA* findings, see Anderson K et al.⁵⁴

Colon Cancer

According to the American Gastrological Association (AGA), patients with Lynch Syndrome should receive subtotal colectomy (removal of almost the entire colon, sparing the rectum) with ileorectal anastomosis. This surgical method can preserve some bowel-function by fusing the small intestine to the rectum and creating a “pouch” out of small intestine. Thus, patients should not require a permanent colostomy. The AGA recommends the same surgical approach for patients Lynch Syndrome, both those who already have colon cancer and those who are positive for a mutation but have yet to develop any detectable colon tumors or known symptoms. After surgery, patients should still be followed with regular rectal screening for additional rectal polyps.⁵⁵

We were unable to find cost-effectiveness studies of prophylactic colectomy, but two decision analyses have been published on clinical effectiveness. The first paper was published in *Gastroenterology* in 1996 and demonstrated that compared to a colonoscopic surveillance program, prophylactic colectomy for a 40 year-old male with positive HNPCC mutation yields a life expectancy benefit of 8 months to 1.5 years. For a thirty-year old male with positive HNPCC mutation, this benefit increased to between 1 and 2 years.⁵⁶ However, the authors did not analyze quality of life and did not analyze the subtotal colectomy option.

The second clinical effectiveness paper was published in the *Annals of Internal Medicine* in 1998 and addressed both life-expectancy and quality of life. This paper demonstrated that immediate prophylactic surgery (e.g., either total proctocolectomy or subtotal colectomy) extended overall life-expectancy compared to surveillance alone (defined as “colonoscopy every 3 years if no surgical intervention had been performed and flexible sigmoidoscopy of the remaining rectal segment every 3 years after subtotal colectomy” (p. 788) plus segmental resection if cancer was found) in a hypothetical cohort of twenty-five year-olds with HNPCC mutations.⁵⁷ However, in terms of quality-adjusted life-years (QALYs) both methods of prophylactic surgery actually fared worse than surveillance:

Surveillance leads to the greatest quality-adjusted life expectancy compared with all colectomy strategies. Surveillance led to a gain of 14.0 quality-adjusted life-years (QALYs) compared with no surveillance, 3.1 QALYs compared with immediate proctocolectomy, and 0.3 QALYs compared with immediate subtotal colectomy. Incorporation of quality adjustments resulted in greater quality-adjusted life expectancies for all subtotal colectomy strategies compared with proctocolectomy strategies, with benefit ranging from 0.3 QALYs if colectomy was performed when colorectal cancer was diagnosed to 2.8 QALYs if colectomy was performed at 25 years of age. (pp. 792-793).⁵⁷

For FAP, the American Gastrological Association (AGA) recommends that patients who are positive for FAP receive immediate total proctocolectomy (removal of the colon and rectum) to minimize the potential for malignancy except in certain “life-style” choices. For example, the AGA would accept delaying surgery in teenagers with minimally-concerning polyps (small and non-villous) to accommodate employment and academic commitments.⁵⁸ Appropriate follow-up should include endoscopic monitoring of any remaining colon (e.g., if a subtotal colectomy is performed) every 6 months as well as additional endoscopic monitoring of the upper gastrointestinal tract with biopsies (including the stomach and small intestine) every 6 months to 4 years.⁵⁸ In contrast, the guidelines state that the “use of chemoprevention as primary therapy for colorectal polyposis is not proven and is not recommended” (p. 1004).⁵⁸

LESSONS LEARNED

This comparison was selected because it provides a natural case-study to compare for-profit testing and exclusive licensing practices for BRCA versus a mix of for-profit and non-profit patenting with nonexclusive licensing practices for colon cancer susceptibility genes. Using the conceptual framework developed for a parallel literature synthesis, we now consider what lessons might be learned from this case.

For both breast cancer and colon cancer, the genetic tests discussed above have two major implications. First, genetic tests can distinguish genetic (and thus inheritable) susceptibility from non-genetic cancers in the original patient. Thus, if the original patient tests positive other family members can then test themselves and know with relative certainty whether or not they have inherited the same mutation as their cancer-suffering relative. Second, BRCA and colon cancer genetic tests guide treatment decisions for the original patient as well alerting relatives that they may also be at risk (and can be tested for the same mutation at much lower cost and with greater specificity).

Basic Research

As of August 2008, Myriad has submitted over 18,000 entries (>80% of total entries) for over 2,600 unique mutations to the Breast Cancer Information Core (<http://research.nhgri.nih.gov/bic>) database. As of February 2005, over 4,300 follow-up publications on *BRCA1* and *BRCA2* resulted from more than 100 collaborations between Myriad and independent investigators (Personal communication with William Rusconi, Vice President of Marketing, Myriad Genetics Laboratories).¹ A search of the Breast Cancer Information Core for mutations catalogued as deposited by Myriad Genetics as of September 25, 2008, revealed 8,826 mutations in *BRCA1* and 9,891 mutations in *BRCA2*.² Patent rights are much narrower in Europe. Europe also differs because several countries have explicit research exemptions and diagnostic use exemptions from patent infringement liability that would cover clinical research testing in several European countries. Research, and in some countries also genetic testing, have therefore proceeded in Europe with less concern about patent infringement. (See Text Box 1 for more details.)

Some argue that even in the United States, Myriad's definition of infringing research is too broad. Specifically, in 1998 Myriad asserted that even though Genetic Diagnostics Laboratory (GDL) limited testing to patients in NCI research protocols, GDL was performing a patent-infringing third-party service in which it charged other laboratories and rendered clinical services. As Parthasarathy summarizes Myriad's reasoning, "So long as GDL disclosed results to the patient, [it provided] a commercial service and violat[ed] the patent" (p. 24).³ The 1999 NCI/Myriad Memorandum of Understanding established ground rules permitting use of BRCA testing within a research institution, and discounted testing for research clinical testing contracted to Myriad.⁴

According to a 2005 Lewin Group Report published for AdvaMed:

An unintended effect of patents is that they may slow further innovation by blocking R&D efforts along avenues patented by other companies. This was the case with genetic testing for the *BRCA1* and *BRCA2* genes [mutations], the presence of which are [is] associated with an elevated risk for developing breast or ovarian cancer. The US Patent and Trademark Office (USPTO) issued patent rights for *BRCA1* and *BRCA2* to a privately owned diagnostics firm. These rights included the gene sequences and any resulting applications developed from them, including laboratory tests and targeted drug therapies. The patents allow the firm to control breast cancer susceptibility testing and research. (pp. 62-63)⁵

Though the Lewin Group concluded that Myriad's exclusive patents on the *BRCA* genes stifled further basic research based on this theory, we found few data either to support or to refute this conclusion. The Gold and Carbone case study did identify a decision not to report some *BRCA* mutation analysis by Canadian researchers (p. 40).³⁴ Specifically, at a November 2006 workshop at Edmonton, researchers from a Canadian university reported that they had refrained from reporting *BRCA* testing results to the public database because they had been advised by their university's general counsel that it could alert Myriad to infringing activity. The researchers were cautioned not to leave a public trace that they had done *BRCA* testing without a license, and this meant they did not contribute their research results to the appropriate public database despite their results being of general interest.

Myriad maintains it has never enforced its patents against researchers, and does not enforce its patents against laboratories providing *BRCA* testing services in a form it does not do itself (such as pre-implantation genetic diagnosis and real-time PCR of DNA amplified from paraffin-embedded tissues). Myriad notes it permitted rearrangement testing, and even referred patients to Mary-Claire King and others until it began to offer such testing itself. Myriad says it has never even threatened to take action against basic researchers or those doing pre-implantation diagnostic testing.

A chilling effect, however, does not take hold only when each and every instance of potential infringement is the subject of patent enforcement. Moreover, Myriad never publicly stated its *de facto* research use exemption policy. Myriad either passed on an opportunity to demonstrate its intentions publicly in written form, or avoided comment to keep legal options open. And keeping options open equates to a chilling effect in zones of uncertainty. Myriad therefore cannot fully elude responsibility for any chilling effect on research, because the company could fully anticipate that others would refrain from research for fear of being sued for infringement. Requesting "simple notification" to Myriad is not a full remedy, as it requires notifying the very party that might, at its option, take legal action once alerted. That is, for Myriad to make credible claims of being fully supportive of unfettered research, it would need to express that policy in a form that could be the basis for others' actions, and not passively rely on others to ask them for permission. Other laboratories would need to know what activities Myriad would and would not pursue as infringement, specified in a way that courts could interpret. Ambiguity may itself stifle basic or clinical research as researchers either avoid the work altogether or are wary of publicly reporting results.

We have not found similar evidence of a chilling effect in the basic science arena for either FAP or HNPCC. This may be due to three related features: (1) lack of enforcement actions, (2) patent holders are academic institutions, and (3) licenses are nonexclusive.

Development

The Lewin report concluded that Myriad's patents "also were found to affect development and provision of potentially more cost-effective testing strategies" (pp. 62-63).⁵ More specifically, a French study found that:

...there exist alternative strategies for performing *BRCA1* diagnosis: prescreening techniques such as FAMA [fluorescent assisted mismatch analysis] and, potentially, DHPLC [denaturing high performance liquid chromatography] or DGGE [denaturing gradient gel electrophoresis], based on the current estimates of their sensitivity, would minimize the cost of diagnosis while also ensuring a comparable level of effectiveness to that of applying DS [direct sequencing of the whole genomic DNA] to the entire gene. (p. 296)⁶

When compared to the most cost-effective mutation detection strategy analyzed (in common use in French testing labs), the average cost per mutation detected using the Myriad approach was 5 times as high.⁶ That is, leaving aside the issue of pricing, the costs entailed—including consumable supplies, equipment and personnel—to carry out the Myriad approach was much higher than alternative approaches that had been developed and were in use in Europe. This criticism suggests that Myriad has eschewed cheaper testing methods because as a monopoly provider it has little incentive to support them. It is difficult to judge this assertion. The comparison to colon cancer genetic testing suggests, however, that (1) Myriad is well within range in its pricing of colon cancer tests compared to other providers, and (2) its cost per unit for BRCA testing is in the same range as colon cancer testing and, if anything, a bit less expensive. Moreover, the analysis of genetic testing strategies has low-cost and high-cost options analogous to BRCA testing, and it is not clear which strategy is optimal.^{7, 8}

The technologies for testing are not qualitatively different among these different genes, so if Myriad has failed to shift to cheaper testing technology, then so have other providers for comparable colon cancer tests. Both BRCA and colon cancer susceptibility genes are large and complex, and there are hundreds of documented mutations in them that cannot be predicted in advance except in subpopulations (such as Ashkenazim).

The pricing data do not address whether early resort to full-sequence testing in high-risk families is optimal for a health system. Myriad believes it is, and in the United States with Myriad as sole provider, that becomes policy *de facto*. In other countries, Myriad can still supply full-sequence testing, but health systems may adopt testing algorithms that resort to full-sequence testing later in the process, and use other tests as screens. Myriad's patent position in effect allowed it to establish the standard of care in the United States, but in other countries it did not.

Those in human genetics and cancer also tell of a patent race between Johns Hopkins University and Oregon Health Sciences University-Dana Farber Cancer Institute for the HNPCC gene *MLH1*. Both Oregon Health Sciences and Johns Hopkins hold patents claiming *MLH1*. The Oregon patent is shared with Dana Farber. It was filed December 9, 1994, and was issued as U.S. 6191268 on February 20, 2001 (Oregon Health Sciences and Johns Hopkins later filed two method patents as well). The Johns Hopkins patent, on the other hand, is shared with the for-profit firm Human Genome Sciences. The Hopkins/Human Genome Sciences patent application was filed on June 6, 1995 and issued as U.S. 6610477 on August 26, 2003. Though the details of this race do not appear in the literature, clearly patenting and ultimately test development played a role in the search for *MLH1* as Johns Hopkins ultimately partnered with a for-profit corporation to complete its work.

Dr. Merz notes the additional concern that Myriad's patents could allow it to collect license royalties as new mutations are sequentially patented, in effect extending the patent term. Dr. Merz writes:

Think of it this way: new mutations are continually being found in the *BRCA1* and *BRCA2* genes. Assuming that patent applications are continually being filed on them, then the patent holders may have an effective monopoly on testing for the period extending from the grant of the first patent for the first discovered mutation until the end of the patent term on the last discovered mutation. If the patentee were to license the patents, royalties could only be collected for the term of each individual patent (the courts would invalidate attempts to extend the patent term by contract or to tie licenses of the patented and off-patent tests). Thus, by monopolizing the testing service, the patentee undermines the time limitation on the grant of monopoly. (p. 327)⁵⁹

Another critique of patenting centers on reduced incentives of a monopoly provider to introduce newer, cheaper, or otherwise better alternative tests. For example, there is an alternative diagnostic technique to *BRCA* called multiplex ligation-dependent probe amplification, or MLPA, a molecular way to detect genetic variations, including *BRCA1* and *BRCA2* mutations, under development at University of Washington.⁶⁰ Using MLPA, a 2006 study published in the *Journal of the American Medical Association* found that Myriad's testing strategy missed up to 12% of large genomic deletions or duplications.⁹ The authors noted that the missed mutations were not due to a technical error in Myriad's testing, but a flaw in the testing strategy. That is, the rearrangements were missed not because of sequencing errors in the amplicons, but because sequencing fragments of *BRCA* as amplicons did not detect large-scale chromosome rearrangements and deletions. The paper noted "many mutations are inherently not detectable by short-range polymerase chain reaction (PCR) followed by genomic sequencing" (p. 1380).⁹ Drs. Grodman and Chung state in their testimony before the House Subcommittee on Intellectual Property that this testing deficit was only corrected after "considerable pressure from the scientific community,¹⁰ 11 but Myriad notes it began testing for the 5 most common rearrangements (accounting for about a third of all rearrangements) in 2002 and would have detected one-third of those the JAMA paper reported as "missing"—and simultaneously began developing a test for large rearrangements (BART®) that it launched in August 2006 for the higher risk patients (similar to the JAMA article's criteria) as part of BRACAnalysis®. Myriad's claim that it was already working on BART® before the JAMA paper appeared is corroborated by poster presentations on large-scale rearrangement testing in 2004, a chronology that does not fit with the characterization of Myriad responding "under considerable pressure" only after the JAMA paper. The JAMA publication no doubt accelerated Myriad's efforts to introduce the new BART® test, however, as indicated by Myriad's Clinical Update of September 2006.¹² 14: 61

In her written statement to the House Judiciary Committee, Dr. Chung noted that she believed, "In a competitive marketplace, this delay would have never occurred" (p. 3).¹¹ Myriad does not agree, and asks: "Could a cost-effective, high throughput, scientifically valid assay be designed and used clinically? It must be noted that the MLPA kits are not FDA approved and are labeled for research use only."⁶²

Rearrangements are also common in colon cancer susceptibility genes, and are included as part of such testing at Myriad and many other laboratories. However, we found no literature about a major controversy among test providers for colon cancer comparable to the very public brouhaha over breast/ovarian genetic testing.

Dr. Chung's written statement for the October 30 House Judiciary hearing states that Myriad's decision not to test paraffin-embedded tissue has hampered availability of that type of testing in instances where it might be clinically useful.¹¹ According to Myriad's technical specifications sheet available online, Myriad isolates only the white blood cells from each sample to extract and purify DNA for testing.⁶³ Without market pressure to innovate, Dr. Chung notes that Myriad has little incentive to develop techniques to analyze samples other than blood samples, thereby "leaving families at risk with no remedy" (p. 4).¹¹ Myriad responds that it refers such cases to known testing services with relevant technical capacity when it learns of instances where such testing is needed. And it notes that in most cases where paraffin-embedded testing is relevant, the living person (or persons) at risk could be directly tested using full-sequence analysis, followed by mutation-specific testing for others in the family. Myriad states it has never enforced its patents against a provider offering testing in a form Myriad does not offer itself, such as pre-implantation diagnosis, prenatal diagnosis, or real-time PCR of paraffin-embedded tissue samples.¹ The implication is that Myriad would not enforce its patents in such circumstances, although again, as in research,

there is no public written statement of that policy. Myriad has licensed three laboratories to perform preimplantation diagnosis, for example.¹⁶ While this may be a policy, we did not find a public statement to this effect on Myriad's website (indeed it took some digging to find this information). Thus, individuals likely would not know about this policy unless they contacted Myriad, thereby alerting them of their intention to test, and alerting Myriad of the option of taking legal action to prevent patent infringement.

Finally, the U.S. Food and Drug Administration has also approved an investigational device exemption study for a breast cancer risk test developed by InterGenetics called OncoVue®. Billed as "the next-generation genetic breast cancer risk test," OncoVue® reports that it is "the nation's first genetic-based breast cancer risk test to undergo the FDA approval process" (p. 1).⁶⁴ Opaldia plans to release OncoVue® in the U.K. and Ireland under an exclusive agreement.⁶⁵

These are not isolated counter-examples: AHRQ estimated that for all three areas of cancer included in this case study there are more genetic tests for cancer in the pipeline than are currently available. While we cannot be certain of what this picture would have looked like absent patents, it appears that gene patents notwithstanding, the genetic testing for inherited risk of cancer is moving in the direction of an even more bountiful range of clinical genetic tests. (See Table 5, Summary of Clinical Genetic Tests.)

The foregoing also is a reminder that patent protection never guarantees permanent protection from competition. It remains to be seen whether these developments culminate in Myriad's having to reduce its price or relax its licensing well before its patent expires, and to offer new testing modalities. And the same competitive effects may enter colon cancer genetic testing, for which there is no single provider with a dominant patent position.

BRCA and colon cancer genes also differ in measures of patent enforcement activity. Dr. Cho's 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad Genetics on its *BRCA* patents; by comparison, Johns Hopkins enforced its *APC* patent for FAP genetic testing twice, and no laboratory directors reported enforcement of the *HNPCC* patents.²⁰

In a paper reviewing litigation over U.S. gene patents, Christopher Holman found 31 total cases of litigation (covering an estimated 1 percent of gene patents). Two of those cases centered on *BRCA* patents, compared to none for patents associated with colon cancer genes (pp. 347-348).²¹ One case entailed a suit and counter-suit between OncorMed and Myriad, which was settled out-of-court. The other *BRCA* case was between Myriad and University of Pennsylvania, which was also settled out-of-court.

Commercialization

Myriad's centralized testing service does provide some benefits to patients, including Myriad's ability to provide free testing to first-degree relatives to elucidate variants of uncertain clinical significance.

This case study demonstrates several major implications of patents on access:

First, the main effect of the patent appears to be on volume rather than price.

1. Any price effect attributable to patents is buried in noise and confounding variables.

2. Myriad's patent position has made it in effect a sole provider of clinical BRCA testing in the United States, and indeed BRCA testing in clinical research except when such testing is conducted at the same research institution as the research.

Based on per-amplicon charges, price data—comparing mutation testing for colon and breast cancer at Myriad and comparing BRCA testing to colon cancer predisposition testing—suggest a small price effect, if any, and suggest the main impact of patenting is to drive volume to Myriad for BRCA testing. The price data constitute an imperfect comparison for many reasons. Colon and BRCA cancer testing does not compare patented to unpatented sequences, but rather a group of patents aggregated by Myriad genetics compared to colon cancer gene tests nonexclusively licensed by several academic institutions that are presumably collecting royalties. Moreover, one major constraint on pricing is the reimbursement system, which codes genetic tests and limits price flexibility. The price comparison does, however, at least provide a benchmark and shows any price effects of patents in these two kinds of genetic testing are not of the magnitude associated with therapeutic pharmaceuticals and some other technologies, for which patents command dramatic price premiums for a patented versus generic product.

The downstream costs of a positive test can be far greater than the test itself, including counseling and potential surgical action.⁶⁶ Thus, for any patient contemplating the combined costs of the test and surgery in the event of a positive test, the cost of genetic testing would be a relatively small share of the total.

Second, the coverage and reimbursement practices of insurers and other payers are crucial. Anecdotal reports from interviews with laboratory employees note that many non-profit centers charge patients up front for genetic testing. These anecdotal reports note that insurance companies are slow to respond to claims for genetic tests, and that such tardy reimbursements induced non-profit centers to either charge differential rates for cash-paying and third-party tests or to drop the third-party payer option altogether (so that payment is paid out-of-pocket up front, and patients seek reimbursement for themselves from their insurer or health plan). For its part, Myriad provides a wide variety of payment options as noted on its “Reimbursement Assistance Program” website, both insurance-based and cash-based.⁶⁷ Myriad reports that initial inconsistency of coverage and reimbursement is less of an issue now. A much larger number of agreements and more consistent coverage and reimbursement have reduced the number of self-pay patients to single-digit percentages of its clientele. Myriad has established contracts or payment agreements with over 300 carriers and has received reimbursement from over 2500 health plans (Personal communication with William Rusconi).

Finally, as the monopoly provider for *BRCA* testing Myriad will benefit from receiving the entire volume of *BRCA* tests through its laboratories no matter what it charges, though that volume will certainly vary with the price-point. The price comparison we made is compatible with a scenario in which Myriad, as a monopolist, maximizes its profit through price discrimination in which it charges the highest price to those women who most value the test. According to standard economic analysis of monopolist behavior, such discrimination in pricing for different customers would be expected, and paradoxically can enable the monopolist to lower prices for those with lower willingness or ability to pay (in Myriad's case, through its patient access programs). This flexibility is, however, entirely at the discretion of the company. Thus, the patent premium depends on both the price-elasticity of demand for *BRCA* testing and on how Myriad has chosen to set its price point for different purchasers, including consumers with lower ability to pay.

Other firms may enter the breast cancer susceptibility testing market. Myriad is not alone in building a dedicated testing facility around its gene patents. InterGenetics, Inc., is

developing OncoVue®, the “next-generation” genetic breast cancer risk test that will be available through a network of breast care centers.⁶⁸ How this facility will affect the *BRCA* market is yet to be seen. OncoVue-BRE® tests genes that, when combined, confer a moderately increased risk. The target population is the general population rather than those with family history. Effectively, this test seeks to determine risk for those not in the *BRCA* risk category. So, the tests are more complementary than competitive. In September 2008, Perlegen announced that it will release a breast cancer diagnostic panel intended to guide treatment choices as well as provide risk stratification, in which case it would compete with Myriad’s testing.⁶⁹ Many of the “personal genomics” firms offering genome-wide scans, such as 23andMe, Navigenics, SeqWright, Knome, and deCODEme also include some analysis of cancer risk, including breast and colon cancers. None of these genome-wide cancer risk-assessment tests, however, offers comprehensive analysis of *BRCA*, *FAP*, or *HNPCC* genes, and so genome-wide scans are not comparable to those genetic testing services for high-risk families. The exception is the full-sequence Knome service. If a cancer susceptibility mutation were identified in the Knome full genomic sequence, it would require re-testing for the identified mutation in a CLIA-certified laboratory to ensure reliability of the result, which the patient could obtain by referral, or which Knome might bundle with its initial price as a subcontracted service. (The price on Knome’s website was originally \$350,000 for full-genome, full-sequence analysis. The website now asks prospective customers to call for individualized pricing, but Steven Pinker reported it to be \$99,000 in his January 2009 article in the *New York Times Magazine*.⁷⁰ The idea of subcontracting to CLIA-approved laboratories was discussed by Duke research assistant professor Misha Angrist and Knome CEO and founder Jorge Conde in November 2008.)

What’s Going on in Australia?

As this case study was being prepared, a controversy over *BRCA* testing erupted in Australia. This was precipitated when Genetic Technologies Ltd. (GTG), Myriad’s licensee in Australia and New Zealand, sent “cease and desist” letters to laboratories testing for *BRCA* in its licensing territory.⁷¹⁻⁷⁴ GTG had announced in 2003, when it secured the license, that it would allow unlicensed testing as a “gift” to the people of Australia. It changed this policy and decided to enforce its patent rights, and the policy change became public in July 2008 when it was widely covered in the Australian public media.⁷⁵ 76 On October 31, as the November 6 deadline it had set in the cease and desist letters loomed, GTG announced it would refrain from enforcing its patent rights pending discussions with “all the relevant stakeholders.”¹⁸ It is now the subject of an Australian Senate inquiry.^{77, 78} The decisions about enforcement of licensing for *BRCA* testing may have stemmed from financial pressures on GTG, especially in light of its dwindling stock price, a need to generate revenues, and some disarray in the company’s governance. According to NASDAQ pricing data, GTG’s stock price drifted downward during the year from a high of \$5.00 per share on 29 November 2007 to \$0.66 on 4 November 2008. In addition to the July 2008 change of policy about *BRCA* testing, the company also announced its intention to remove five of seven directors at its 19 November 2008 Board meeting, leaving only two directors, which would cause it to fall out of compliance with its corporate bylaws. The proposed new Board member declined to serve, leading to a proposal for an interim board appointment.⁷⁹ While not directly relevant to US policy, the developments in Australia did spill over to coverage in the United States; GTG actions in Australia also indicate that companies under financial stress may turn to patent assets as revenue sources when their company’s survival is being threatened. (See Text Box 1 for an update.)

Communication/Marketing

Myriad’s position as sole US provider of *BRCA* testing increases its incentives for communication and marketing up to the point of market saturation. The incentive to

advertise the service and broaden the market is stronger for a monopoly provider than in a shared market because a monopolist will gain the full benefit of market expansion. In a competitive market, advertising may increase market *share* of a given provider, or it can expand the size of the market, but the expansion effect spills over to benefit competitors as well, and so the incentive to advertise is weaker. Once a market is saturated, a monopolist no longer gains from advertising to expand market (but may advertise for other reasons).

For the same reason, communication and marketing incentives are also strong to educate health professionals who order the tests, because any increase in orders results in higher volume of testing for Myriad. Again, this increase is not shared with other providers; Myriad gets the full benefit of any market expansion. The downside of this incentive is that Myriad's financial incentive is to expand testing, not just appropriate testing. Myriad makes money off of any test, regardless of whether the person is actually at risk. The incentive is not just for appropriate testing; the risk is overutilization.

There are some checks on overutilization. Medical societies establish guidelines for their membership which, in turn, form the basis for payer coverage criteria. Insurers and other payers work not to reimburse for tests when patients do not meet clinical appropriateness criteria. One further check is the bottleneck of determining eligibility for testing. The limited pre-test counseling resource is used to fulfill specific payer criteria for high-risk patients eligible for coverage and reimbursement. Low-risk candidates can clog the pre-test filters of counseling and coverage determination, occupying them with cases that would not ultimately lead to testing, or if tested, would not be reimbursed by third parties.

In the context of breast cancer testing, Myriad has a strong incentive to “get the word out” about genetic testing for inherited risk of breast cancer. That incentive is stronger for BRCA testing, for which Myriad is sole US provider, than for colon cancer testing, where there are alternative providers. This may be one reason Myriad's past direct-to-consumer advertising—both the 2002 pilot in Denver and Atlanta and the 2007-8 campaign in the northeastern states—focused on breast-ovarian cancer testing rather than Myriad's colon cancer testing services. The social benefit from this incentive is more public knowledge of test availability. The potential harms are overutilization of BRCA genetic testing, and public fear of genetic risk of breast cancer amplified by advertising.

Caulfield and Gold note in their 2000 article from *Clinical Genetics* that:

Myriad Genetics, a commercial testing company that holds patent rights underlying the [*BRCA1* and *BRCA2*] test, does not exclude women without any family history of breast or ovarian cancer from taking its test. This contrasts sharply with the Working Group with Stanford's Program in Genomics, Ethics and Society, which recommends that ‘for most people, testing for *BRCA1* and *BRCA2* mutations is not appropriate.’ While all genetic testing policies are undoubtedly motivated by a degree of self-interest, it is hard to deny the strong, and possibly adverse, impact of the profit motive in this context. (p. 371)⁸⁰

Myriad states it does not want to expand inappropriate testing, but rather to saturate testing among high-risk families. Myriad's “television, radio, and print advertising campaign” in September 2002, included ER, *Oprah* and *Better Homes and Gardens*.¹⁹ A follow-up survey on 300 women who had seen the ads noted that “85 percent would contact their physician regarding *BRCA* testing and 62 percent would go so far as to switch health care professionals in order to find one who would help them gain access to the test” (p. 129).¹⁹ This interest can include spurious demand for the tests, and consumes the time of health professionals in filtering out such spurious demand and explaining the complicated genetics of cancer susceptibility to many not actually at elevated risk.

A CDC survey done during the 2003 direct-to-consumer pilots in Denver and Atlanta compared experience in those DTC campaign cities to Raleigh-Durham and Seattle, which did not experience regionally targeted advertising. CDC found an increase in test requests and questions about testing among women, an increase in test-ordering among physicians and providers, and no difference in levels of reported anxiety.⁸¹ The CDC concluded that:

Advertisements might have motivated women interested in learning more about BRCA1/2 testing to talk to their physicians and request testing. Findings from the consumer survey suggest that women in the pilot cities were more aware of BRCA1/2 testing than those in the comparison cities. No evidence suggested an increased interest in the test among women most suited for BRCA1/2 testing (i.e., those having a first-degree relative). (p. 606)⁸¹

Judy Mouchawar and colleagues did the most systematic studies of consumer, provider, and health plan responses to the Denver DTC advertising campaign. They surveyed health professionals and consumers and assessed impact on health systems in the advertising market (Denver Kaiser Permanente) and in a comparison city (Detroit) and health system (Henry Ford) not exposed to the advertisements. The number of women at high risk who got referred went up by 2.38 times, from 100 to 238, suggesting that over 100 women at high risk got tested who otherwise might not have known about the test. The number of women contacting the systems about testing rose 3.46 times (from 144 to 499) with advertising, including a higher fraction of women not at high risk and therefore not warranting testing (the fraction at high risk dropped from 69 to 48 percent).⁸² Thus the number of women at risk who might benefit from testing went up, but there was also a dilution of such high-risk women among an even greater increase of contacts about testing. There was no increase in actual testing among women with low risk *in the population studied*. This caveat is important, because Kaiser Permanente has practice guidelines for BRCA testing, and it cooperated with Myriad to prepare for a surge in demand during the DTC advertising period. Physician surveys showed a modest effect on physicians, with 3 percent reporting significant patient anxiety, 19 percent reporting significant increase in time spent explaining and another 23 percent a little extra time, and 7 percent reporting significant and 8 percent a little strain on the doctor-patient relationship.⁸³ Eighty-two percent reported the DTC campaign had no effect on their relationship with patients.

Consumers reporting “any anxiety” varied from 28 percent (low family risk) to 55 percent (high risk). Anxiety was most pronounced among Latina/Hispanic women (65 percent), and much more common in low-income (62 percent among those making less than \$30,000) than high-income women (30 percent among those making over \$80,000)(Table 2).⁸³ Among those exposed to the ad, 63 percent reported no anxiety at all, but 65 percent reported feeling somewhat or very concerned. It is hard to fully interpret the answers to various questions. Physicians were asked to assess the effect overall on their practice, and 6 percent were positive or very positive, 14 percent were negative or very negative, and 79 percent reported no effect (Table 4).⁸³

The overall impact of the DTC ad campaign on the Kaiser Permanente health system in Denver was a more than two-fold increase in number of women in the high risk category getting tested, a more than three-fold surge in contacts about testing, a moderate increase in anxiety among consumers and a mixed reaction among physicians, but with the vast majority reporting no effect. A comparison between the experience of physicians and women in Kaiser Permanente to other parts of the health system in Denver at the same time would have been immensely useful, as the Kaiser Permanente system is much more organized for genetic services than general medical care. The Mouchawar studies are illuminating as a “best case” of a health system prepared for a surge and with practice guidelines in place; it is very unlikely to represent the effects of the ad campaign elsewhere

in Denver (or anywhere else) with a less organized and prepared genetic services program and with physicians less educated about how to triage testing.

Myriad Genetics' marketing campaign both to providers and patients is concisely summarized in Dr. Parthasarathy's book (pages 120-129).¹⁹ Myriad aggressively marketed its *BRCA* genetic tests to providers through a "Professional Education Program," through continuing education accredited by the American Medical Association and at various professional meetings. Highlighting the importance of reaching providers with such educational campaigns, one study showed that high-risk women—those eligible for *BRCA* testing based on family history—were three times as likely to get tested following a physician recommendation as those who did not get such a recommendation.⁸⁴

On September 10, 2007 Myriad announced it would begin a new "public awareness campaign" throughout the northeastern United States to spread the word about *BRCA* testing.⁸⁵ This campaign concluded in March 2008. Myriad's quarterly report through March 2008 reported a jump in molecular diagnostic revenue from \$38 million to \$59 million, and attributed the 55 percent jump to its northeast advertising campaign.⁸⁶ Given these financial results, it is not surprising Myriad is said to be contemplating similar DTC advertising initiatives in Texas and Florida or elsewhere. (Suggestions of future DTC advertising plans were reported to the authors, but were neither confirmed nor denied by Myriad staff.) This clearly illustrates the link between status as a single provider and incentives for direct-to-consumer advertising, with single provider status in this case associated with exclusive patent rights for *BRCA* testing.

We have not found similar marketing campaigns launched by Myriad or other groups on behalf of other tests. However, a future research project could compare *BRCA* testing uptake in the Denver and Atlanta markets in 2002 or in the northeast 2007-8, where Myriad's advertising was concentrated, to utilization in other regions. This could be done through a large health-insurer's database or using billing records of Medicare/Medicaid for relevant CPT codes matched to clinical indications. The link between DTC advertising and patenting is mediated by the monopoly incentive for advertising noted above. Dynamics in genetic testing markets have changed considerably since 2002. The growing number of physicians ordering genetic tests, the greater availability of third party coverage, the accumulating experience in using genetic tests to manage hereditary cancer risk, and the greater consumer awareness about genetic testing all suggest the 2003 surveys may not predict current or future behavior. Moreover, the increasing conspicuousness and commercial interest in personal genomics may also change perceptions and behaviors. DTC advertising is not directly related to access *per se* although it is highly relevant to projections of demand and perceptions of access.

Adoption by Third-Party Payers

Myriad has a strong incentive to develop the infrastructure to handle billing and payment for *BRCA* testing because it captures all the revenues from market expansion. This benefits the company, but it also benefits patients to the degree it relieves them of the hassle and paperwork of dealing with health plans and insurers, and it benefits providers by relieving them of those duties as well as legal liability for test inaccuracies. The countervailing force here is that Myriad as a sole-source provider requires providers to send samples, track paperwork, and bill for services providers might otherwise handle at their own institution through internal billing and administrative procedures. The comparison to colon cancer testing is suggestive here. Most colon cancer genetic testing is done by the handful of laboratories set up to offer this complex set of tests, and the test algorithms for *BRCA* and colon cancer susceptibility genes appear to have comparable costs and decision pathways. It thus appears there is some advantage to consolidating testing at a few laboratories that can

attain sufficient volume to justify sunk costs in developing the test and resources to ensure quality and reduce legal liability for errors. In the case of colon cancer testing, this has resulted in an oligopoly; BRCA patents have made testing a Myriad monopoly in the United States.

The US monopoly on BRCA testing may not be absolute; there is no legal barrier to sending samples abroad, and US courts would be unlikely to interpret merely sending results from tests performed abroad (information) back to the United States as infringement. Myriad would have grounds for infringement liability only if the invention (making and using the patented sequences and methods) were performed abroad in a jurisdiction where those activities are claimed in patents, and Myriad would have to sue in those jurisdictions. Laboratories in countries with diagnostic use exemptions would not face infringement liability.

Regarding third-party payers, at least one study noted in the Lewin Group report showed that as of late 1995, “only 4% of insurance providers... had granted coverage of *BRCA* testing[, and] 55% of respondents cited concerns about the high cost of *BRCA* testing, averaging \$2,400 per patient” (p. 153).⁵ As noted above, these data no longer represent practices for BRCA testing, which Myriad reports now generally is covered for roughly 95% of those requesting tests, and reimbursed to cover 90% of their charges. The same study cited by the Lewin Group had two other findings of relevance to patented gene tests. First only 6 percent of the decision-makers for private health insurance plans would cover *BRCA* testing if were extended to all women in the general population, whereas 48% would offer it if it were restricted only to women with a positive family history who were enrolled in an approved research trial. Second, the proclivity to offer coverage was sharply dependent on cost: 25% were willing to cover it if the testing cost were \$250, but only 14% would cover if the cost rose to \$1,000 (it was \$2400 at the time). Taken at face value, the figures imply that even if gene patents confer a premium of \$750 this would only reduce the likelihood of third party coverage by 11 percentage points. However, the low response rate (22%) and early timing of this study limit the current usefulness of this study.²²

In 1998, Myriad reported that over 300 different insurers covered *BRCA1* and *BRCA2* testing; they further stated that 94.3% of processed claims for *BRCA1* and *BRCA2* testing had resulted in at least partial payment from insurance companies (suggesting the test was covered to some extent).⁸⁷ As of 2002, 38% of testers said they had no problems in getting coverage for genetic services from their insurance plan. But a more telling statistic was that only 59% of women undergoing full sequence *BRCA* analysis in one study (in which 99% of women had health insurance) filed health insurance claims.²³ Furthermore, 15% of women in a second study undergoing *BRCA* analysis chose to self-pay, and each of those women did so in fear of insurance or employment discrimination.²⁴ As noted above, Myriad states that only approximately 5 percent of patients now self pay, and more than 2500 payers and health plans have reimbursed testing with Myriad. Finally, the enactment of the Genetic Information Nondiscrimination Act of 2008, and its implementation in 2009 and 2010, may reduce fears of discrimination in employment and health insurance.

In the most recent study to address reimbursement for genetic testing, 56% of non-testers from a sample who had received genetic counseling services and declined testing said they could not afford all costs of the test or their share not covered by insurance, yet more than half also reported income of over \$70,000 annually.⁸⁸ Of only 77 individuals for whom insurance status was reported, 42% had insurance that provided no coverage for testing, 25% had partial coverage and the remainder had full coverage. But this was not a random sample of the population, since no one was reported as uninsured. Nationally, 18.8% of women age 19-64 are uninsured,⁸⁹ so if we assume the same is true of women with *BRCA* mutations and

that 42% of the remainder are insured but have no coverage for *BRCA* testing, this would imply that roughly half of the at-risk group had no insurance coverage for this test at that time.

One conclusion from multiple studies is that when payment is out-of-pocket, price has a strong and direct impact on testing utilization, and thus affects patient access. People do forego potentially beneficial genetic tests when they are expensive and not covered by health plans or insurance. Access is thus linked tightly to coverage and reimbursement policies, which are far more important than any direct patent effects. Patent status matters to the degree it affects price, where high prices require payers to assess a specific new test. Patent status may also affect likelihood to create a bargaining impasse with payers, if patent-holders and payers simply cannot agree on reimbursement. The *BRCA* experience suggests that over ten years, the vast majority of payers have decided to cover most of the cost of a test when its use is restricted to those at high risk. For those who are not covered by such payers, access is still a problem, in part because of price.

Problems in access may still occur with: 1) Medicaid programs, 2) insurance policies that exclude all genetic testing, and 3) practices and health plans (e.g., in southern California) where there is a strong financial incentive to minimize utilization. These access constraints, however, do not appear to be keyed to patent status, but rather blanket policies focused on cost containment and contractual transaction costs.

Coverage for Risk-Reducing Surgery

A national study on coverage for prospective mastectomy or oophorectomy showed that 10-11% of private insurers and 48 to 50% of public health plans had policies that specifically denied coverage for risk-reducing surgery for women with *BRCA* mutations; 52 to 64% of private insurers and 40% of public carriers had no identifiable policy regarding coverage of either form of surgery for such women.⁹⁰

A retrospective analysis of 219 Memorial Sloan-Kettering Cancer Center patients with known *BRCA1/2* mutations found that of 35 women undergoing 39 risk-reducing mastectomies or oophorectomies, 97% were covered in full (minus applicable deductibles and coinsurance). The single instance in which an indemnity plan refused to provide coverage occurred in 1997 when there were few data about the efficacy of prophylactic oophorectomy.⁹¹ This study is now eight years old, however, and clinicians with whom we have spoken believe that prophylactic surgery in mutation-positive women is broadly covered, although we have no empirical data to corroborate that impression.

Adoption by third-party payers as well as providers and testing laboratories is only a rough proxy for patient access. If possible, future research should focus on getting at direct patient access data, or at least at utilization rather than highly indirect measures such as number of providers or price.

Consumer Utilization

In studies done several years ago, 19-74% of at-risk individuals who could benefit from *BRCA* testing were not being tested.⁸⁸ Cost was not the only consideration: nearly 70% of patients eligible for free *BRCA* testing elected to get tested; however, cost certainly mattered since only 22% of self-pay patients in the same sample chose to be tested.⁸⁸ The financial barriers to individual patients appear to have been reduced considerably for those who have health plans so the financial access questions reduce to how many have such coverage, which as shown above, is still a grey area in terms of hard numbers. In the RAND Health Insurance Experiment, the price elasticity of demand for outpatient health services for those with high cost-sharing was -0.31.⁹² If the patent premium on *BRCA* were 50

percent, for example, this would predict 15.5% fewer high-risk patients without coverage would purchase the test. Any reduction in access due to cost, however, is difficult to attribute to BRCA patents because of the absence of a clear price effect of the patents. Our data do not allow us to tease out any price-utilization effects attributable to patents *per se*.

Finally, Table 6 notes the difference in number of providers for the three genetic tests, with Myriad as the sole *BRCA* full-sequence provider, nine providers for the Lynch Syndrome tests, and five for the FAP test. This sole-provider status of Myriad for BRCA testing in the United States is clearly attributable to patent status, although differences in patent status and patent enforcement outside the United States have resulted in Myriad not being sole provider in other jurisdictions.

UPDATE ON BRCA AND COLORECTAL CANCER TESTING, PATENTS AND LICENSING (FEBRUARY 2010)

Several events have taken place since the case studies were submitted to SACGHS in February 2009, to be posted with the “public comment draft” of the SACGHS report in March 2009. Some of the most salient events are described below.

Events in the United States

On May 12, 2009, a group of plaintiffs—professional medical organizations, genetic researchers, clinical geneticists, genetic counselors, breast cancer advocacy groups, and breast cancer patients—sued Myriad Genetics, the Directors of the University of Utah Research Foundation, and the United States Patent and Trademark Office (USPTO) in the Southern New York Federal District Court.¹⁰⁵ In the plaintiffs’ eyes, claims in patents assigned to Myriad Genetics and the University of Utah cover “products of nature, laws of nature and/or natural phenomena, and abstract ideas or basic human knowledge or thought” (p. 29).¹⁰⁵ The plaintiffs assert that the patent claims violate Article I, section 8, clause 8 of the Constitution, which does not allow exclusive rights to scientific laws or products of nature, and the First Amendment, which does not allow preventing patients from accessing their genetic information. They also assert the claims are not within the realm of patentable subject material enumerated in 35 USC 101. The plaintiffs have asked the Court to find the disputed patent claims “invalid and/or unenforceable” and to prevent the defendants from enforcing their patent claims (p. 30).¹⁰⁵

As of November, 2009, the parties are involved in initial procedural matters. The defendants argue that the plaintiffs lack a constitutional or statutory basis to challenge the patents, that Myriad has not enforced its patents against the defendants recently enough to create a case or indicated an intent to do so, and that the Directors have no business in New York relevant to the case that would put it within the Southern District Court of New York’s jurisdiction.^{106, 107} On the other side, the plaintiffs made a motion for jurisdictional discovery to allow them to gather evidence to prove that they have a controversy suitable for judicial resolution and that the court currently hearing the case has the legal authority to do so.¹⁰⁸ The plaintiffs also filed a motion for summary judgment, which asked the court to rule on the legal questions based on the facts already provided to the court.¹⁰⁹ Several professional organizations and advocacy groups ranging from the American Medical Association to the Pro-Choice Alliance for Responsible Research to the Indigenous Peoples Council on Biocolonialism have filed amicus briefs in favor of the plaintiffs’ motions for summary judgment. Briefs in favor of the plaintiffs are available under “Case Documents” at <http://www.aclu.org/freespeech/gen/brca.html>. Presiding Judge Robert W. Sweet heard the plaintiffs’ motions for summary judgment and jurisdictional discovery on September 30, 2009. Judge Sweet denied the defendants’ motion to dismiss on November 1.¹¹⁰

His ruling indicates that he understands the case's importance for medical research and innovation. "The challenges to the patents-in-suit raise questions of difficult legal dimensions concerning constitutional protections over the information that serves as our genetic identities and the need to adopt policies that promote scientific innovation in biomedical research. The widespread use of gene sequence information as the foundation for biomedical research means that resolution of these issues will have far-reaching implications, not only for gene-based health care and the health of millions of women facing the specter of breast cancer, but also for the future course of biomedical research" (pp. 2-3).
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Events in Europe

Myriad's legal position in Europe has changed as the result of an opposition procedure launched in 2001 and concluded in November 2008. The partial restoration of claims in patents covering the BRCA1 gene in Europe were announced, but not publicly available at the time the case studies were submitted to SACGHS. The claims and the record of the opposition proceedings have since been made public. The European opposition procedure is a way for third parties to challenge patents through administrative proceedings, short of litigation. The Institut Curie began in opposition procedure in 2001, when it feared that Myriad would prevent the institution from using its in-house test.³⁴ The Institut challenged the validity of Myriad's key patent for BRCA1 testing. Later, the administrative center for Parisian hospitals, another French laboratory, other European research institutions and medical associations, and Greenpeace joined the opposition proceeding.¹¹¹ In November 2008, the European Patent Office stated that it would allow a set of patent claims it had revoked pending the opposition proceeding. Myriad retained claims to "determining whether there is germline alteration 185delAG-->ter39 in the BRCA1 gene in a tissue sample of said subject" and then determining a patient's predisposition to breast or ovarian cancer. Myriad also retained claims to associated diagnostic methods and biological materials (pp. 117-188).¹¹² The 185delAG mutation, one of the first discovered and most common among Hispanic and Ashkenazim Jewish populations is claimed.¹¹³ 114

Regardless of its patent claims, Myriad must contend with diagnostic use exemptions and compulsory licensing provisions in several national jurisdictions, including France and Belgium,¹¹⁵ 116 in effect meaning these claims cannot be asserted against such uses. Authorities in those countries could be petitioned to exercise statutory authority to compel licensing of patents being used in a way that adversely affects public health. Diagnostic use of gene patents was explicitly discussed as such a possible use of these statutory licensing authorities when the laws were being passed.¹¹⁵ 116 The situation in Europe thus remains uncertain, with Myriad now having stronger patent rights, but also facing untested and hitherto unused exemptions and compulsory licensing provisions in some of the largest markets based on laws passed with BRCA testing specifically in mind. A draft European Council regulation on a European Union-wide patent system discussed in early October at the Working Party on Intellectual Property, an organ of the Council of the European Union, included clauses for compulsory licensing.¹¹⁷ Those clauses may add to Myriad's legal and political difficulties in competing in Europe. The public attitudes in Europe may also mirror those in Australia that led Myriad's Australian licensee to back away from enforcement actions (see below). Efforts to enforce patent rights in Europe might provoke similarly intense public controversy.

Events in Australia

In Australia, the 2008 controversy over a decision by Genetic Technologies Limited (GTG, Australian Stock Exchange) to re-assert its intellectual property rights of BRCA1 and 2

testing was resolved for all practical purposes in December 2008, although a Senate investigation continues. GTG has thus backed away from re-asserting its threats to reassert patent rights licensed from Myriad genetics. According to a public announcement from GTG, “On November 24th, 2008, Genetic Technologies Limited...informed the Market that its new Board of Directors, which largely replaced the previous Board, was undertaking a formal review of the Company’s recent decision to enforce its BRCA testing rights. GTG is now pleased to announce that the new Board has duly completed this review and resolved to immediately revert to its original decision to allow other laboratories in Australia to freely perform BRCA testing.”¹¹⁸ The company’s stock on the Australian Stock Exchange was worth less than ten cents a share as of October 20, 2009.¹¹⁹

GTG’s decision to back down may have been influenced by two national investigations. The Australian Competition and Consumer Commission launched one investigation in October 2008.⁷⁶ The Australian Senate also launched an investigation and held a series of hearings. The Australian Senate asked the Committee on Community Affairs for a report on “[t]he impact of the granting of patents in Australia over human and microbial genes and non-coding sequences, proteins, and their derivatives, including those materials in an isolated form.”¹²⁰ The Committee’s mandate included a request for inquiry into statutory changes and gene patents’ impact on medical services, education, and research as well as “the health and wellbeing of the Australian people.”¹²⁰

The Senate Committee held hearings in March, August, and September, 2009, when doctors, industry representatives, representatives of the Australian government agency that grants patents, intellectual property experts, and patient advocacy groups gave testimony.¹²¹ Rhetoric was, at times, fiery. Senator Heffernan asked one speaker, for example, whether, “given the overwhelming evidence from the clinically driven, vocationally guided and humanely inspired side of this debate, which is lining up against, from what I can see, a bunch of lawyers, bankers and people who are financially driven, is it time for the [Australian] Commonwealth to step up to the plate and fund a test case and we can just sort this out in the courts?” (p. CA-13).¹²² Not all Senators were as forceful in their comments, but discussion was spirited and referred back to Myriad Genetics. The committee was scheduled to report to the Senate on November 26, 2009, but its report has been delayed until at least March, 2010.¹²³

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TABLE 1

APPROXIMATE SIZE OF GENES

Gene	Amplicons ^a	Size (Base-pairs)
<i>BRCA1</i> ⁹³	35	81,155
<i>BRCA2</i> ⁹⁴	47	84,193
<i>APC</i> ⁹⁵	42	108,353
<i>MLH1</i> ⁹⁶	19	57,359
<i>MSH2</i> ⁹⁶	16	80,098
<i>MSH6</i> ⁹⁷	25	23,807

^a Amplicons used by Myriad for its “full sequence” analysis

The number of amplicons is based on Myriad Genetics’ method of “full sequence” analysis, based on publicly available data from Myriad’s technical specification sheets for its tests, and confirmed by phone conversations with Myriad staff. This allows rough comparison of BRCA versus colon cancer gene tests at Myriad. The amplicons and testing protocols are different from other laboratories, but for those laboratories the overall cost is the relevant metric. The objective of the table for hereditary colon cancer susceptibility testing is to compare *inter*-laboratory prices for hereditary colon cancer susceptibility, so overall price is the relevant measure, and per-amplicon cost is merely a rough indicator of marginal price per unit among laboratories. Gene sizes are taken from the National Center for Biotechnology Information database, and cross-checked with the Genome Browser, University of California Santa Cruz. Full-length gene sizes do not reflect the number of bases sequenced in the actual gene tests, because actual genetic tests sequence neither the entire genomic sequence nor the cDNA sequence (with introns edited out) of the genes, but rather “amplicon” fragments of the gene that can be amplified by PCR.

TABLE 2
COMPARISON OF COST-PER-BASE-PAIR AMONG GENETIC TESTS

Disease	Genetic Test	Total Amplicons	Test Provider	Provider's Charge	Charge per Amplicon
Breast / Ovarian Cancer	<i>BRCA1</i> and <i>BRCA2</i> full sequencing	35 + 47 = 82	Myriad ^a	\$3,120	\$38.05
			Baylor	\$ 1,675	\$ 39.88
			Boston	\$1,675	\$39.88
FAP	<i>APC</i> full sequencing	42	Harvard	\$1,500	\$35.71
			Huntington	\$1,200	\$28.57
			Univ. of PA	\$ 1,360	\$ 32.38
			Mayo Clinic	\$1,300	\$30.95
			Myriad ^b (44 amplicons)	\$1,795	\$40.80
Lynch Syndrome (HNPCC)	<i>MLH1</i> , <i>MSH2</i> , and <i>MSH6</i> full sequencing	19 + 16 + 25 = 60	Baylor	\$ 3,200	\$ 53.33
			Boston Univ.	\$2,995	\$49.92
			City of Hope	\$ 4646.16	\$ 77.44
			Harvard	\$2,700	\$45.00
			Huntington	\$1,800	\$30.00
			Mayo Clinic ^c	\$ 3,100	\$ 51.67
			Myriad ^c	\$2,950	\$49.17
U. Pennsylvania	\$ 2,840	\$ 47.33			
Quest Diagnostics	\$4,760	\$79.33			

Notes: Cost per base-pair represents authors' calculations based on costs reported by the testing facilities and the size of each gene as reported by NCBI.

^aIncludes major rearrangement testing (5 common insertions/deletions and analysis for any other rearrangements in high-risk individuals)

^bIncludes Southern Blot analysis for rearrangements and 2 MYH mutations (an additional 2 PCR amplicons) with full sequence of MYH if one of the 2 common mutations is detected.

^cIncludes rearrangement analysis

TABLE 3**COST EFFECTIVENESS STUDIES COMPARING CHEMOPREVENTION TO SURVEILLANCE ALONG**

Study	Context	Results (Cost per QALY)
Grann (2000) ⁹⁸	Positive <i>BRCA</i> test	30 year old women = \$990
		40 year old women = \$1,800
		50 year old women = \$3,600
Hershman (2002) ⁹⁹	Two-or-more first-degree relatives diagnosed with breast cancer	30 year-old women = \$45,000
		50 year-old women = \$89,000
		60 year-old women = \$140,000
Eckermann (2003) ¹⁰⁰	Hypothetical cohort of healthy women at high risk of breast cancer	5 yrs of tamoxifen / 5 yrs of benefit = \$32,000
		5 yrs of tamoxifen / 10 yrs of benefit = \$16,000
		5 yrs of tamoxifen / no reduced incidence at 10 yrs = \$170,000

Notes: QALY = "Quality Adjusted Life Year"

TABLE 4

COST EFFECTIVENESS STUDIES COMPARING PROPHYLACTIC SURGERY TO SURVEILLANCE ALONE

Study	Context	Results (Cost per QALY)
Grann (1998) ¹⁰¹	Positive <i>BRCA</i> test in 30-year-old women at high-risk	Prophylactic Oophorectomy and Mastectomy = Dominated Prophylactic Oophorectomy = \$5,600 <i>BRCA</i> testing then oophorectomy if positive by mutation probability: <i>High Risk</i> <i>BRCA1</i> (p=0.5) and <i>BRCA2</i> (p=0.0) = \$3,900 <i>BRCA1</i> (p=0.25) and <i>BRCA2</i> (p=25) = \$4,700 <i>BRCA1</i> (p=0.0) and <i>BRCA2</i> (p=0.5) = \$5,400
Tengs (2000) ¹⁰²	High-risk 30-year-old women assuming varying risks of mutation	<i>Moderate Risk</i> <i>BRCA1</i> (p=0.1) and <i>BRCA2</i> (p=0.1) = \$17,000 <i>Slight Risk</i> <i>BRCA1</i> (p=0.05) and <i>BRCA2</i> (p=0.05) = \$42,000 <i>Average Risk</i> <i>BRCA1</i> (p=0.0006) and <i>BRCA2</i> (p=0.0002) = \$1,600,000

Notes: "QALY" = Quality Adjusted Life Year. "Dominated" means that prophylactic mastectomy and oophorectomy in the Grann article actually saved money compared to surveillance alone.

TABLE 5**SUMMARY OF CLINICAL GENETIC TESTS**

	Breast	Colorectal	Ovarian
Currently Available	15	15	7
Under Development	22	19	14
Primary Prevention	1	1	0
Detection	0	8	7
Prognosis	2	0	0
Diagnosis	12	8	4
Management	7	2	3

Compiled by author based on raw data presented by the AHRQ²⁵

TABLE 6

SUMMARY TABLE^{19, 20, 28, 29, 103, 104}

Measures	Breast / Ovarian Cancer <i>BRCA1</i> / <i>BRCA2</i>		Colorectal Cancer HNPCC / FAP	
Total annual number of new diagnoses (deaths)	<i>Breast</i>	178,480 (40,910)	<i>Colorectal</i>	153,760 (52,180)
	<i>Ovarian</i>	22,430 (15,280)		
Percent of cancers caused by mutation	<i>Breast and Ovarian</i>	5-10%	<i>Colorectal</i>	~5%
Lifetime percent risk if positive for mutation	<i>Breast</i>	35 – 85%	<i>HNPCC</i>	80%
	<i>Ovarian</i>	16 – 60%	<i>FAP</i>	~100%
Lifetime relative risk if positive for mutation	<i>Breast</i>	2.7 – 6.4	<i>HNPCC</i>	13.3
	<i>Ovarian</i>	9.4 – 35.3	<i>FAP</i>	16.7
Patent holder	Myriad Genetics, 1998 U.S. 5753441 (<i>BRCA1</i>) U.S. 6051379 (<i>BRCA2</i>) ^a		<i>HNPCC</i>	<i>MLH1</i> gene: Oregon Health Sciences Univ. and Dana-Farber, 1999 – U.S. 5922855
			<i>FAP</i>	<i>MSH2</i> protein: Johns Hopkins, 1997 – U.S. 5591826 <i>APC</i> gene: Johns Hopkins, 1994 U.S. 5352775
U.S. licensees	Myriad Genetics		<i>HNPCC</i>	<i>Non-profit</i> Baylor College of Medicine, Boston University School of Medicine, City of Hope National Medical Center, Harvard-Partner's Center for Genetics and Genomics, Huntington Medical Research Institutes, Mayo Clinic, University of Pennsylvania School of Medicine
			<i>FAP</i>	<i>For profit</i> Myriad Genetics, Quest Diagnostics
Cost of genetic test	\$3,120 for two genes		<i>HNPCC</i>	<i>Non-profit</i> Baylor College of Medicine, Harvard-Partner's Center for Genetics and Genomics, Huntington Medical Research Institutes, University of Pennsylvania School of Medicine
			<i>FAP</i>	<i>For profit</i> Myriad Genetics \$600 - \$1,800 for one gene \$1,200 to \$2,000 for two genes \$2,050 to \$2,995 for three genes \$1,200 - \$1,800 for one gene

^aPurchased from OncorMed in 1998. (See Table 7 for more patent information.)

Patent data obtained from Delphion Patent Database

Provider list according to GeneTests.org – limited search to “Analysis of the entire coding region: Sequence analysis”

TABLE 7

BRCA 1 AND BRCA2 PATENTS

US Patent	Nature of Claims	Assignee	US Licensee
5654155	Consensus cDNA sequence for BRCA1, method for detecting <i>BRCA1</i> mutations	OncorMed	Rights acquired by Myriad
5622829	Mutant allele probes and methods for BRCA1	University of California	OncorMed (acquired by Myriad)
5693473	<i>BRCA1</i> mutations	Myriad Genetics; Centre du Recherche du Chul; Tokyo Cancer Institute	Myriad Genetics
5709999	Method for detecting <i>BRCA1</i> mutations	Myriad Genetics; Centre du Recherche du Chul; Tokyo Cancer Institute	Myriad Genetics
5710001	Method for detecting BRCA1 mutations in tumors	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5747282	cDNA sequence for <i>BRCA1</i> , cloning vectors containing <i>BRCA1</i> cDNA, kit for detecting mutations in <i>BRCA1</i> , and method for screening for therapeutics for cells with <i>BRCA1</i> mutations	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5750400	cDNA sequence for <i>BRCA1</i> and methods for detecting <i>BRCA1</i> mutations	OncorMed	Rights acquired by Myriad
5753441	Method and kit for detecting <i>BRCA1</i> germline mutations	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5837492	<i>BRCA2</i> sequence and methods	Myriad Genetics, Endo Recherche, HSC (Hospital for Sick Children) Research & Development Limited Partnership, and Trustees of the University of Pennsylvania	Myriad Genetics
6045997	<i>BRCA2</i> sequences and methods	Duke University and Cancer Research Campaign (UK)	Expired
6051379	Probes, methods, and kits for detecting <i>BRCA2</i> mutations and rearrangements	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
6130322	cDNA sequence for segments of <i>BRCA1</i>	Gene Logic	N/A
6162897	Amino acid sequence translated from <i>BRCA1</i>	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
6686163	<i>BRCA1</i> mutations and cloning vectors containing mutations	Gene Logic	N/A
6720158	<i>BRCA1</i> sequence for splicing variations	Philadelphia Health & Education Corp. (now assigned to Drexel University, Personal communication with Drexel University Office of Technology Commercialization)	Unlicensed
6838256	<i>BRCA1</i> consensus coding sequences, mutations, vector comprising sequence, methods for detecting mutations	Gene Logic	N/A
6951721	Method for determining functional sequence variations in <i>BRCA1</i>	Gene Logic	N/A

Duke University researchers requested licensing information from Gene Logic but to date have not received licensing information.

Information compiled by authors.