

Genetic testing for risk of inherited
breast and ovarian cancers:
Payment issues following the 2013 Myriad Supreme Court Case

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Introduction

Today, genetics plays an important role in medicine. While most of the world's deadliest diseases do not have a purely genetic basis, researchers have discovered the genetic link behind diseases such as cystic fibrosis, Tay-Sachs, Huntington's, hemophilia, Down syndrome, and sickle cell disease. Aside from these disorders (which have a clear genetic origin), researchers have made enormous progress in understanding the clinical significance of mutations that lead to other diseases, including many cancers.

The most widely studied cancer, especially with regard to its genetic basis, is breast cancer.¹ Among women, breast cancer is the second leading cause of cancer death (behind lung cancer) and the second most commonly diagnosed cancer (after nonmelanoma skin cancer).² Though about 12% of women are already expected to develop breast cancer at some point in their lives, certain genetic mutations in two genes called *BRCA1* and *BRCA2* significantly increase one's risk.³ These mutations are rare (inherited by only 0.25% of the population), but can result in a 65% chance of developing the disease.⁴

After a genetic link between breast cancer risk and chromosome 17 was discovered in the 1990s, researchers and companies raced to develop a test to check for a mutation in *BRCA1* and

¹ **Note:** For each of the past three years, the National Cancer Institute (NCI) has spent about twice as much money funding breast cancer research than lung and prostate cancer research, even though breast cancer has a lower incidence rate. **Source:** "Cancer Research Funding," National Cancer Institute, National Institutes of Health. <http://www.cancer.gov/cancertopics/factsheet/NCI/research-funding>. Accessed March 28, 2014.

² "Genetics of Breast and Ovarian Cancer (PDQ®)," National Cancer Institute (NCI), National Institutes of Health (NIH). <http://www.cancer.gov/cancertopics/pdq/genetics/breast-and-ovarian/HealthProfessional/>. December 16, 2013. Accessed February 2, 2014.

³ "Breast Cancer Risk in American Women," National Cancer Institute, National Institutes of Health. <http://www.cancer.gov/cancertopics/factsheet/detection/probability-breast-cancer>. October 24, 2012. Accessed February 1, 2014.

⁴ "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," National Cancer Institute, National Institutes of Health. <http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA>. August 5, 2013. Accessed February 2, 2014.

BRCA2.⁵ Such a test would be used to shed light onto one's predisposition for the disease and to help guide prevention and screening options. In 1994, a research team from a company called Myriad Genetics won the race to isolate *BRCA1*, patented the genes, and commercialized the first *BRCA1/2* genetic test.⁶ In the following years, controversy surrounding Myriad's business practices emerged, resulting in a lawsuit challenging the validity of gene patents.

On June 13, 2013, the Supreme Court unanimously ruled that genes cannot be patented. This decision, widely supported by physicians, academic researchers, and patient advocacy groups, broke Myriad's monopoly in the *BRCA1/2* testing market. Immediately following the ruling, new companies announced plans to commercialize similar tests, but at much lower costs. Now, less than a year later, over ten companies and academic centers have developed *BRCA1/2* tests.

Though these new testing companies offer *BRCA1/2* testing at a lower cost, many payment and access issues still exist. This research paper aims to survey these access issues and to investigate why payer policies are so varied. Given little literature exists that discusses how payers are addressing *BRCA1/2* testing, this paper also acts as a first step in the creation of a comprehensive report on new *BRCA1/2* testing options (post-Supreme Court case) and insurance policies for the reimbursement of this test.

Results have shown that insurance policies for genetic tests, especially for *BRCA1/2*, vary widely. Some of the nation's largest private payers do not even have published policies. Other large payers have local coverage policies, but no national determinations. Additional companies

⁵ **Note:** From here on out, unless individually distinguished, *BRCA1* and *BRCA2* will be collectively referred to as *BRCA1/2*.

⁶ **Note:** There are two separate 'discovery' stories for *BRCA1* and *BRCA2*, the details of which are not discussed in this paper. *BRCA1* was patented in 1994 and *BRCA2* was patented in 1996. For more information regarding the discovery stories of each of these two genes, consider the following article: Matthijs, G., Huys, I., Van Overwalle, G., & Stoppa-Lyonnet, D. (2013). The European BRCA patent oppositions and appeals: coloring inside the lines. *Nature biotechnology* 31, no. 8: 704-710.

only seem to be contracted with Myriad, meaning that (though cheaper test options exist with other companies), care providers are forced to order through Myriad for some patients.

Coverage for genetic counseling and large rearrangement testing also varies.

Though there are inconsistencies among private payers, public payer policies are even more vague. Medicare will not cover testing unless an individual has had breast or ovarian cancer. Given the main purpose of the test is to guide prevention and screening options, this policy makes little sense. Similar to Medicare, Medicaid does not have a national coverage policy for *BRCA1/2* (or for most genetic tests), and many state Medicaid policies do not cover testing.

Aside from these reimbursement issues, there are also inconsistencies in the guidelines for whom should even get tested for a *BRCA1/2* mutation. There are two main recommendations for *BRCA1/2* testing, those by the National Comprehensive Cancer Network (NCCN) and the United States Preventative Services Task Force (USPSTF). These recommendations differ slightly and could benefit from many clarifications.

Given the complex nature of the United States' healthcare system, it is not surprising that so many discrepancies exist in coverage for *BRCA1/2* testing. After all, this is a relatively new technology, and because the market was recently opened for new companies to enter, one could view it as a new industry as well. Nevertheless, despite the inherent complexities that arise with an emerging healthcare technology and its implementation and dissemination, it is important for policy makers and payers to develop clear, concise, and thoughtful payment and coverage guidelines.

The importance of properly addressing *BRCA1/2* testing and reimbursement is even more apparent given its potential to act as a model for the commercialization of future genetic tests. In

many ways, *BRCA1/2* could be thought of as a ‘poster child’ for genetic testing. After all, *BRCA1* and *BRCA2* are two of the most widely studied genes in human history and research on these two genes has been extremely well funded.^{7,8} Additionally, the genes’ important role in breast cancer susceptibility is extensively documented in the scientific and medical literature. The controversy surrounding Myriad Genetics and the publicity generated by Angelina Jolie’s double mastectomy have also increased awareness of the two genes.⁹ Lastly, breast cancer has very vocal advocates and is characterized by high political mobilization. All of these factors have placed *BRCA1/2* in a unique position to act as a model for how genetic testing should be addressed going forward. Though challenging to create uniform testing guidelines and consistent reimbursement standards, researchers and policy makers should view the recent openness of the *BRCA1/2* testing market as an opportunity to set an important precedent for situations that are sure to be even more complex.

⁷ **Note:** Myriad Genetics alone claims it has spent over \$500 million on *BRCA1/2* research. **Source:** Ray, T., "Not Backing Down in BRCA Test Infringement Case, Ambry Slaps Myriad with Antitrust Countersuit," GenomeWeb. August 7, 2013. <http://www.genomeweb.com/clinical-genomics/not-backing-down-brca-test-infringement-case-ambry-slaps-myriad-antitrust-counte>. Accessed April 24, 2014.

⁸ **Note:** A search for "BRCA1" on PubMed retrieved over 10,000 scientific and medical abstracts/citations. A similar search with the keyword "BRCA2" brought up over 6,000 results. **Source:** "NCBI Global Cross-database Search," NCBI. <http://www.ncbi.nlm.nih.gov/gquery/?term=BRCA1>. Accessed March 30, 2014.

⁹ **Note:** On May 14, 2013, Angelina Jolie (famous Hollywood actress and director) wrote an opinion piece in *The New York Times* detailing her decision to get a double mastectomy. With a mutation in *BRCA1* and a strong family history, Jolie’s doctors estimated that she had an 87% chance of developing breast cancer. By getting a double mastectomy, Jolie reduced her risk to under 5%. In her article, Jolie wrote how she was motivated to undergo the surgery because she lost her mother to breast cancer and hopes to remain in her children’s lives for a long time. This opinion piece received a significant amount of media attention and increased awareness of the *BRCA1/2* genes. **Source:** Jolie, A., "My Medical Choice," *The New York Times*. Opinion Pages. <http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html>. Accessed April 8, 2014.

Historical & Scientific Background

Overview

- A. Genetic Testing
- B. Breast Cancer
- C. *BRCA1/2*
- D. Testing for *BRCA1/2*
- E. Myriad Genetics
- F. Myriad's Business Practices
- G. Gene Patents
- H. AMP v. Myriad Genetics (June 2013)
- I. Summary

Genetic Testing

Genetic testing is now considered a routine and important component of medicine. Well known since the 1970s for its use during pregnancy (to check for inherited conditions), DNA testing has various other applications as well.¹⁰ For instance, genetic information is used to personalize drug regimens and to lend insights into one's predisposition for diseases, such as cancer. Unfortunately, one of the difficulties associated with cancer research is that there are many different factors that come into play and genetics is only one piece of the puzzle.

Improvements in DNA sequencing over the past two decades have made it economically feasible to incorporate various genetic tests into standard medical practice. Current market leaders, such as Illumina and Life Technologies can sequence a human genome, with high accuracy, for a few thousand dollars (see Figure 1).¹¹ To compare, it took an international

¹⁰ Press, N., "Genetic Testing and Screening," from *Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*, ed. Mary Crowley. 2008. Garrison, NY: The Hastings Center: 73-78.

¹¹ Wetterstrand, K., "DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program," National Human Genome Research Institute. www.genome.gov/sequencingcosts. October 29, 2013. Accessed February 1, 2014.

collaboration of researchers approximately 13 years and \$3.8 billion to sequence the first human genome, completed in 2003.^{12,13,14}

Though we now have the ability to sequence full genomes, other genetic tests have also been developed that look for mutations in just one, or a handful, of genes. In addition to being much cheaper, these tests are much more practical because they target specific areas of the genome where doctors suspect a mutation(s). Tests that analyze a genome for mutations in a specific gene are usually referred to as *single-gene tests*, whereas *multi-gene panels* look for a greater number of mutations that influence one's predisposition to a disease.¹⁵

¹² **Note:** In 2003 a “high quality” “rough draft” of the human genome was completed. It was not until 2006 that the final Human Genome Project (HGP) papers were published. These final papers helped “to close gaps, reduce ambiguities, and allow for only a single error every 10,000 bases, the agreed-upon standard for the HGP.” **Source:** “Human Genome Project Information,” Genomics.energy.gov.

http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml. July 25, 2011. Accessed February 2, 2014.

¹³ **Note:** The exact ‘cost’ of the Human Genome Project has been disputed, as the project was multi-faceted. According to the Battelle Institute report in 2011, the Federal Government “had direct expenditures totaling almost \$3.8 billion” for the sequencing programs. Another commonly referenced figure for the total cost of the project is \$13 billion. However, this larger figure refers to “a wide range of scientific activities related to genomics;” the “human genome sequencing represents only a small fraction of the overall 13-year budget.”

¹⁴ “Economic Impact of the Human Genome Project,” Battelle Technology Partnership Practice. [http://battelle.org/media/press-releases/\\$3.8b-investment-in-human-genome-project-drove-\\$796b-in-economic-impact-creating-310-000-jobs-and-launching-the-genomic-revolution](http://battelle.org/media/press-releases/$3.8b-investment-in-human-genome-project-drove-$796b-in-economic-impact-creating-310-000-jobs-and-launching-the-genomic-revolution). May 2011. Accessed February 2, 2014.

¹⁵ **Note:** It should be noted that even within one gene, there can be a wide range of possible mutations. Thus, some genetic tests can test for a specific mutation in a gene (a ‘point mutation’), multiple mutations within one gene, or multiple mutations that span several genes.

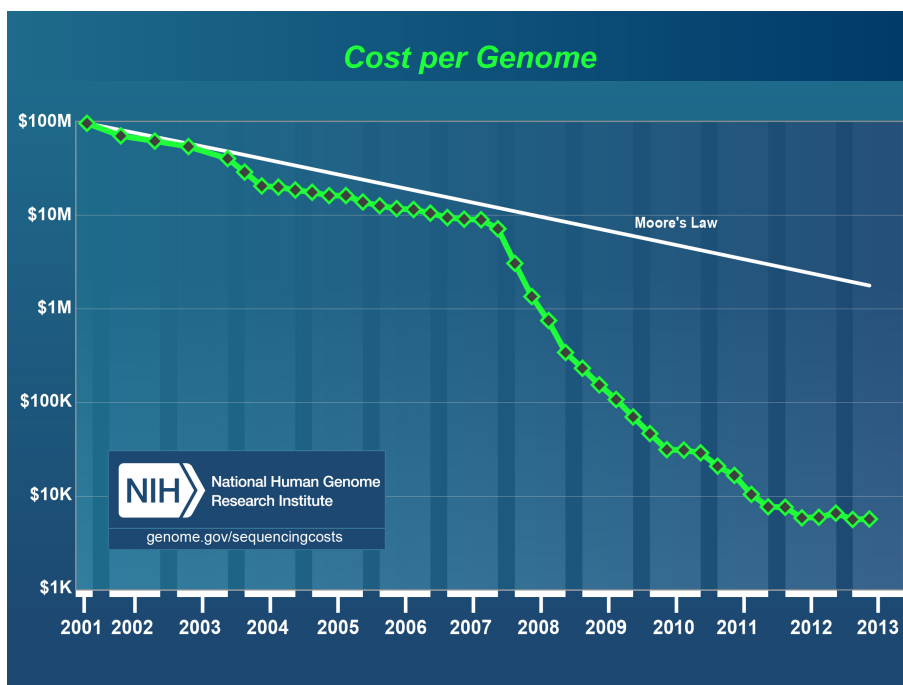


Figure 1 | Cost per Genome. This figure displays the rapid decrease in cost for sequencing an entire human genome. Source: Wetterstrand, K., “DNA Sequencing Costs: Data from the NHGRI Large-Scale Genome Sequencing Program,” National Human Genome Research Institute. www.genome.gov/sequencingcosts. October 29, 2013. Accessed February 1, 2014.

Breast Cancer

Breast cancer is one of the most widely studied diseases. According to the National Cancer Institute (NCI), the most common type of breast cancer is ductal carcinoma, which “begins in the lining of the milk ducts;” however, breast cancer refers quite broadly to any cancer that forms in the breast tissue. The cancer is far more common in women than in men. In 2013, there were an estimated 232,430 new female cases and 2,240 new male cases. In the same year, about 39,620 females died due to the disease, compared to 410 males.¹⁶

The Surveillance, Epidemiology, and End Results (SEER) Program of the NCI estimates that 12.4% of women born in the United States today will develop breast cancer at some point in

¹⁶ “Breast Cancer,” NCI, NIH. <http://www.cancer.gov/cancertopics/types/breast>. Accessed February 1, 2014.

their lives (“about a 1 in 8 chance of being diagnosed).”¹⁷ Though incidence rates are expected to fluctuate year-to-year, there has been a slight overall increase since the 1970s, when women had about a 10% chance of being diagnosed.¹⁸ These rates are averages, and more specific incidence rates (by race, age group, etc.) can be found from the SEER report. For instance, the probability of developing breast cancer increases with age; most breast cancers are diagnosed after age 50 (Table I).^{19,20}

Table I | Age and Breast Cancer Risk.

Current Age (yrs)	Risk of Developing Breast Cancer in the Next 10 Years (%)
20	0.06
30	0.44
40	1.47
50	2.38
60	3.56
70	3.82
80	3.04

As Table I demonstrates, age is a very strong risk factor for developing breast cancer. Other risk factors include breast density, family history and personal history of breast cancer, high amounts of radiation therapy, high alcohol consumption, long-term use of hormone therapies, high body mass index, reduced physical activity, and race.²¹ Furthermore, though only

¹⁷ "Breast Cancer Risk in American Women," National Cancer Institute, National Institutes of Health. <http://www.cancer.gov/cancertopics/factsheet/detection/probability-breast-cancer>. October 24, 2012. Accessed February 1, 2014.

¹⁸ **Note:** More information on breast cancer incidence can be found from the SEER (Surveillance, Epidemiology, and End Results Program) Cancer Statistics Review Report, last updated in August of 2012. Visit: Howlader, N., *et al.* (eds), SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.

¹⁹ Data Selected from Table 4.18: Cancer of the Female Breast (Invasive)" of the SEER Cancer Statistics Review 1975-2009. http://seer.cancer.gov/csr/1975_2009_pops09/results_single/sect_04_table.18.pdf.

²⁰ "Genetics of Breast and Ovarian Cancer (PDQ®)," NCI, NIH.

²¹ **Note:** According to the American Cancer Society, "white women are slightly more likely to develop breast cancer than are African-American women, but African-American women are more likely to die of this cancer. However, in

a small proportion of breast cancer cases (5-10%) have a known genetic link, individuals with these known genetic mutations have a significantly higher risk of developing heritable breast cancer.²²

BRCA1/2

The two genes that are most strongly associated with a significantly increased risk of developing heritable breast cancer are *BRCA1* and *BRCA2*. Genes are sections of DNA that code for certain proteins.²³ A gene's DNA sequence dictates the primary structure of a protein, so when a mutation occurs in DNA, proteins often become misfolded and damaged. This change in structure then affects a protein's function. Random mutations in our DNA actually occur quite frequently; however, it is the presence of key machinery, such as repair proteins, that help to modulate these damages. Both *BRCA1* and *BRCA2* are tumor suppressor genes. Tumor suppressor genes code for proteins that are essential for DNA repair pathways.²⁴ Thus, when a mutation in *BRCA1/2* occurs, the proteins created by these genes (tumor suppressor proteins) become damaged and are unable to repair damaged DNA.

Specific mutations in *BRCA1/2* greatly increase the risk of developing breast (and ovarian) cancer. These mutations are inherited in an autosomal dominant pattern, which means that mutations can be passed down from one's mother *or* father and that the harmful effects will be present even if only one parent passes on a mutated copy of the gene. If one parent has a

women under 45 years of age, breast cancer is more common in African- American women. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer." Source: "What are the risk factors for breast cancer?," American Cancer Society. January 31, 2014.

<http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors>. Accessed April 24, 2014.

²² "Genetics of Breast and Ovarian Cancer (PDQ®)," NCI, NIH.

²³ **Note:** Following the Central Dogma of Molecular Biology, DNA is converted to RNA through a process called transcription. Then, RNA is converted to proteins through a process called translation.

²⁴ "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

BRCA1/2 mutation, there is a 50% chance that his or her child will inherit the deleterious mutation.²⁵

If one inherits a harmful mutation, then there is a 45% chance (with a *BRCA2* mutation) and a 55-65% chance (with a *BRCA1* mutation) of developing breast cancer. These individuals also have an 11-17% chance (with a *BRCA2* mutation) and a 39% chance (with a *BRCA1* mutation) of developing ovarian cancer, compared to the average in the general population of 1.4%.^{26,27} These risk percentages are averages, and vary based on other factors such as age and race. For instance, individuals of Ashkenazi Jewish descent are much more likely to carry a *BRCA1/2* mutation than other populations. Whereas *BRCA1/2* mutations occur in 0.25% (1/400) of the general population, harmful mutations occur in 2.3 to 2.7% of the Ashkenazi Jewish population.^{28,29,30}

Though there is a significantly higher probability of developing breast cancer with a *BRCA1/2* mutation, very few women actually carry such a mutation. Thus, guidelines have emerged detailing which individuals would benefit from testing, and when they should consider it. Various organizations and societies have their own guidelines.³¹ In the United States, the most widely followed recommendations are those laid out by the United States Preventative Task

²⁵ "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

²⁶ "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

²⁷ **Note:** According to the National Cancer Institute, ovarian cancer is the ninth most common cancer in the United States and the fifth most deadly. In 2013, there was an estimated 22,240 newly diagnosed cases and 14,030 deaths. **Source:** "Genetics of Breast and Ovarian Cancer (PDQ®)," NCI, NIH.

²⁸ "Final Recommendation Statement - Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women," U.S. Preventive Services Task Force (USPSTF). <http://www.uspreventiveservicestaskforce.org/uspstf12/brcatest/brcatestfinalrs.htm>. December 2013. Accessed February 2, 2013.

²⁹ Roa, B. B., Boyd, A. A., Volcik, K., & Richards, C. S. (1996). Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nature Genetics* 14, no. 2: 185-187.

³⁰ Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., & Tucker, M. A. (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *New England Journal of Medicine* 336, no. 20: 1401-1408.

³¹ "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

Force (USPSTF) and the National Comprehensive Cancer Network (NCCN). These recommendations differ slightly (to be discussed in Chapter 3).

Generally, individuals who are thought to have a family history of breast and ovarian cancer are encouraged to seek genetic counseling (Figure 2). If a physician or genetic counselor recommends further exploration, then it is “most informative to first test a family member who has had breast or ovarian cancer.”^{32,33} If this affected family member tests positive for a harmful *BRCA1/2* mutation, then other family members (who have not had breast/ovarian cancer) may want to consider testing. Such testing for additional family members is cheaper than the initial test because researchers know precisely where the mutation is on the gene. Thus, instead of sequencing the full gene to look for a mutation, researchers can pinpoint specific regions where this ‘*known familial mutation*’ would be. If individuals are unaware of their family history, it is not recommended to get *BRCA1/2* testing unless he/she has early-onset breast or ovarian cancer. Additionally, because “no risk-reduction strategies for children exist,” children should not undergo *BRCA1/2* testing until they become adults.³⁴

³² "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

³³ **Note:** The logic of testing an affected family member first (before the patient), is that this affected family member (considering he/she has already developed breast or ovarian cancer) is the most likely to carry a *BRCA1/2* mutation.

³⁴ "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

Meet with Primary Care Physician

Goal: Identify individuals who have an increased risk of carrying a harmful *BRCA1/2* mutation

Method: Gather a detailed family history; use various screening tools (See Appendix 4)

Outcome: Recommend high-risk individuals for further counseling. If individuals receive a “low risk” result from the screening tools, there is little recognized benefit of continuing through the genetic testing process.



Meet with a Genetic Counselor

Goal: Identify individuals who are at a high risk of carrying a *BRCA1/2* mutation and guide them through the testing process

Method: Gather a detailed family history, complete additional risk assessments, genetic testing education (discuss possible test results and their respective implications), identify other high-risk family members, discuss risk-reduction strategies.

Outcome: Patients may choose to proceed with genetic testing, or to pursue other options



Genetic Testing

Goal: Identify if, and where, a mutation in *BRCA1/2* exists

Method: DNA sequencing; the particular type of analysis varies (will be discussed later). For instance, specific tests are recommended for Ashkenazi Jewish individuals and for individuals with a known familial mutation.

Outcome: Possible test results include: (A) Positive for a deleterious mutation (B) Negative test result (C) Variant of Unknown Significance (VUS)



Continued Genetic Counseling

Goal: Interpret genetic test results and implications for patients

Method: Discuss meaning of test results. Depending on the test result, additional education and continued counseling may be necessary.

Outcome: Patients may decide to pursue various options such as enhanced screening or prophylactic surgeries. Depending on the test result, relatives of patients may also be contacted and brought into the genetic testing and counseling process.

Figure 2 | Common Steps in the Genetic Testing Process for *BRCA1/2*. This figure was created by the author to illustrate the most common pathway to getting tested for a *BRCA1/2* mutation. These steps follow the USPSTF’s recommendations (see Chapter 3).

As Figure 2 illustrates, genetic counselors are central in the genetic testing process for *BRCA1/2*. Genetic counselors are particularly important because test results are not always straightforward. After getting tested, patients could receive one of a few different results. Individuals could test *positive* for a *known, deleterious mutation*. In such instances, patients may choose to undergo prophylactic surgeries to reduce their risk of developing cancer, or may want to increase the frequency of their screenings. Patients could also receive a *negative* test result, indicating that their *BRCA1/2* sequence does not contain a mutation. Lastly, patients can receive an *uninformative test result*, meaning that the patient has a *variant of unknown significance* (VUS). This uninformative result occurs when a *BRCA1/2* mutation is found, but researchers do not know whether the mutation is deleterious. Usually researchers do not know the clinical significance of these mutations because they lack enough data to understand how harmful the mutation is (if at all).

Testing for *BRCA1/2*

When genetic testing is ordered for *BRCA1/2*, a patient's DNA is collected, either from a buccal swab or a blood sample. This sample is then sent to a company for analysis. For the past 15 years, the only company that performed this test in the United States was a genetic testing company called Myriad Genetics. Researchers Mark Skolnick, Walter Gilbert, Peter Meldrum, and Kevin Kimberlin founded Myriad in 1991 to help Skolnick and his team at the University of Utah in the sequencing of, and subsequent development of a test for, *BRCA1*. In August of 1994, Skolnick's team won the race against many other research groups across the country to sequence *BRCA1*. Researchers quickly filed a patent application on *BRCA1*, and, in 1996, filed a patent application on *BRCA2*, the other major breast cancer susceptibility gene. Shortly afterwards, the

company released their first genetic test, called BRACAnalysis®, which tests for mutations in *BRCA1/2*.³⁵ Though Myriad was initially founded with the goal of developing this genetic test, the company now offers other diagnostic tests as part of their broader goal of “elucidating the role genes play in human disease.”³⁶ The different versions of the tests Myriad currently offers for *BRCA1/2* can be seen in Table II.

Table II | Myriad: *BRCA1/2* Testing Options

Test	Cost	Test Details
Integrated/ Comprehensive BRACAnalysis®	\$4,040	Complete <i>BRCA1/2</i> sequence; 5 common large rearrangements
BRACAnalysis®	\$3,340	Complete <i>BRCA1/2</i> sequence
Single Site BRACAnalysis® for <i>BRCA1</i>	\$475	Tests for known familial mutations
Single Site BRACAnalysis® for <i>BRCA2</i>	\$475	Tests for known familial mutations
Multisite BRACAnalysis®	\$575	3 Ashkenazi Jewish founder mutations
BRACAnalysis Large Rearrangement Test (BART)	\$700	Just large rearrangement testing, not sequencing
MyRisk®	\$4,000 - \$4,500	25 genes for 8 hereditary cancers (breast, ovarian, gastric, colorectal, pancreatic, melanoma, prostate, and endometrial). <i>Expected to be released in September 2014.</i>

³⁵ “Brief History of Myriad,” Myriad Genetics. <http://www.myriad.com/about-myriad/history/>. Accessed February 2, 2014.

³⁶ “Brief History of Myriad,” Myriad Genetics.

Myriad Genetics Controversy

Since developing a test for *BRCA1/2*, and filing patents on the two genes, Myriad Genetics has received a significant amount of negative publicity and attention. This attention is in large part (if not entirely) due to the controversial nature of gene patents and the company's business practices. Researchers and physicians have claimed that Myriad's patents on *BRCA1/2* have limited research and have prevented additional genetic testing companies from entering into the market. With a monopoly in the market, Myriad has been able to charge an extremely high price (over \$3,000) for its BRACAnalysis® test.³⁷

Motivated by the high testing cost (limiting access to the test) and the belief that human DNA should not be patent eligible, a group of researchers, physicians, patients, and advocacy groups came together in 2009 to file a lawsuit against Myriad (see Figure 3). The plaintiffs argued that Myriad's patents were invalid under Section 101 of the Patent Act, which states that, to obtain a patent, one must “invent or discover any new and useful ... composition of matter.”³⁸ The Supreme Court has previously stated that this provision contains an important implicit exception: “laws of nature, natural phenomena, and abstract ideas are not patentable,” as they “are the basic tools of scientific and technological work.”³⁹ Thus, plaintiffs argued that patents on the sequence of *BRCA1/2* are invalid for precisely this reason – DNA, as a natural phenomenon, cannot be patent eligible.

³⁷ **Note:** Given current sequencing costs, a price of over \$3,000 is quite high. However, the analysis and interpretation that comes with the test result is one of the main reasons for the high testing cost. As the only testing company for the past 15 years, Myriad has built up an extremely valuable database of data. This database contains information on the clinical significance of variants of unknown significance (VUS) and will give Myriad a competitive advantage over entering testing companies. A movement has begun, often referred to as Free the Data, that is trying to release this genetic information.

³⁸ “35 USC §101 – Inventions patentable,” Legal Information Institute, Cornell University. <http://www.law.cornell.edu/uscode/text/35/101>. Accessed February 2, 2014.

³⁹ Mayo Collaborative Services, Mayo Medical Laboratories, *et al.* v. Prometheus Laboratories, Inc., 566 U.S. 1 (2012). <http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf>.

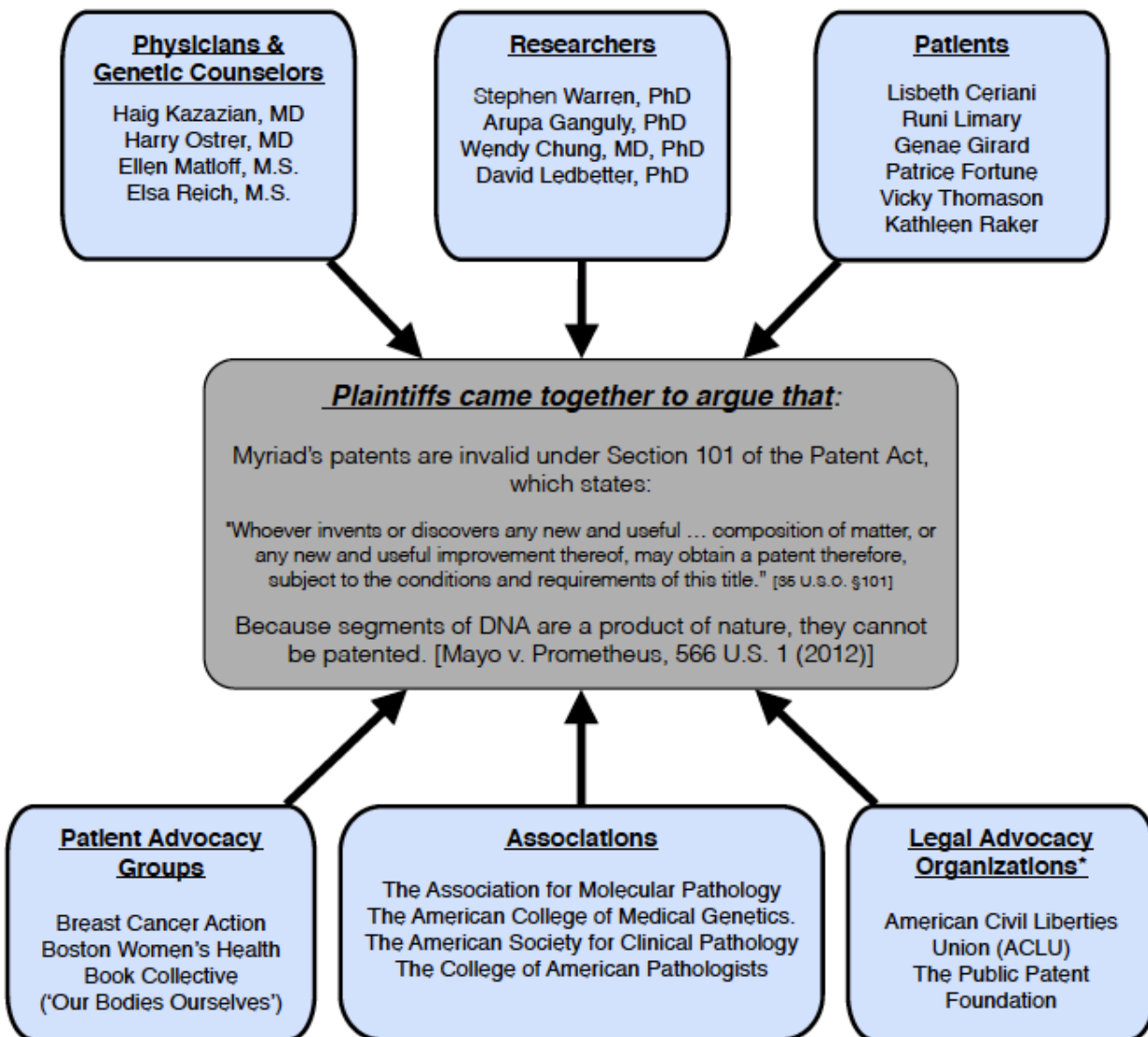


Figure 3 | Plaintiffs in AMP v. Myriad.

*The ACLU and The Public Patent Foundation were not plaintiffs, but provided legal counsel

Gene Patents

To understand the controversy surrounding gene patents and the importance of Association for Molecular Pathology (AMP) v. Myriad Genetics, it is helpful to review the historical context. The right to patent and to hold intellectual property arises from Article 1, Section 8, Clause 8 of the United States Constitution, which states that Congress shall have the power “to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries.”⁴⁰ The four main methods to protect one’s intellectual property (IP) are through owning patents, copyrights, trademarks, and trade secrets.⁴¹ Within the biotech field, patents are the most applicable because they protect ‘inventions.’ Essentially, a patent gives the ‘assignee’ the right to sue anyone who infringes upon his or her “exclusive right to make, use, and sell the patented innovation for a limited period of time.”⁴² Today, the U.S. Patent and Trademark Office (USPTO), a Federal agency, manages patent and trademark claims.

Historically, the USPTO *has* granted patents on human genes. A study published in 2005 found that over 4,000 of the approximately 23,000 human genes have been noted or claimed as intellectual property.⁴³ Another study found that the USPTO has “granted over 50,000 patents containing at least one DNA-related claim.”⁴⁴ With about 20% of the human genome patented (although estimates vary significantly), one could rightly wonder why Myriad has acquired so much negative attention. One potential reason is that the genes Myriad patented are not trivial; a

⁴⁰ “Constitution of the United States,” U.S. Constitution, Article 1, Section 8, Clause 8. National Archives and Records Administration. http://www.archives.gov/exhibits/charters/constitution_transcript.html. Accessed February 2, 2014.

⁴¹ “Office of Policy and International Affairs,” U.S. Patent and Trademark Office (USPTO), <http://www.uspto.gov/ip/global/index.jsp>. October 1, 2013. Accessed February 2, 2014.

⁴² “Patent,” Cornell University Law School: Legal Information Institute. <http://www.law.cornell.edu/wex/patent>. August 19, 2010. Accessed February 2, 2014.

⁴³ Jensen & Murray (2005). Intellectual property landscape of the human genome. *Science* 310 (5746): 239-240.

⁴⁴ Liang, G. (2012). Molecules or Carriers of Biological Information: A Chemist’s Perspective on the Patentability of Isolated Genes. *Albany Law Journal of Science and Technology* 22: 133-645.

mutation in *BRCA1/2* leads to a significantly increased risk of developing heritable breast cancer.⁴⁵ With pink ribbons covering anything from yogurts to charity walk banners, it is hard to deny that breast cancer is one of America's most visible diseases. Furthermore, like many scientific breakthroughs, Myriad's discovery relied heavily on the work of previous researchers. For example, Mary-Claire King, a geneticist at UC-Berkeley, was one of the first scientists to believe there was a heritable component to breast and ovarian cancer. After years of searching, she discovered the genetic link between breast cancer risk and chromosome 17 in the early 1990s.⁴⁶ Her discovery subsequently ignited a race among researchers to identify, sequence, and clone the gene(s) that accounted for this heritability. Lastly, perhaps the main reason Myriad has gathered so much negative attention is that, once the company won the race to sequence *BRCA1/2*, Myriad strictly enforced its patents in a manner that angered a wide range of individuals.⁴⁷

AMP v. Myriad Genetics (June 2013)

After the initial lawsuit in 2009, the case was passed through the courts and did not reach the Supreme Court until the spring of 2013 (Table III).⁴⁸ Though seven patents and intellectual

⁴⁵ **Note:** As discussed above, a woman's lifetime chance of developing breast cancer increases from 12% to 45% (with a *BRCA1* mutation) or 55-65% (with a *BRCA2* mutation). Similarly, a woman's lifetime chance of developing ovarian cancer is 1.4%, which increases to 11-17% (with a *BRCA2* mutation) and 39% (with a *BRCA1* mutation). **Source:** "BRCA1 and BRCA2: Cancer Risk and Genetic Testing," NCI, NIH.

⁴⁶ **Note:** To learn more about Dr. Mary Claire King's perspective on 'the race' to map, sequence, and test for *BRCA1/2*, consider reading her recent article: King, M.C. (2014). "The Race" to Clone BRCA1. *Science* 343, no. 6178: 1462-1465.

⁴⁷ **Note:** Myriad gathered negative attention from a variety of interest groups. These groups had similar goals, but differed slightly in their motivations. For example, civil rights and advocacy groups argued that Myriad's high testing cost limited access to the test. Patients believed they deserved access to second opinions before undergoing life-altering medical procedures. Researchers had received cease-and-desist letters and many fundamentally believed that genes should not be patentable material.

⁴⁸ **Table Sources:** (1) Association for Molecular Pathology (AMP) et al. v. Myriad Genetics, Inc., 569 U.S. 1 (2013). http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf. (2) "Association for Molecular Pathology v. Myriad Genetics – Timeline of Events," American Civil Liberties Union. <https://www.aclu.org/timelines/association-molecular-pathology-v-myriad-genetics-timeline-events>.

property claims were in question, the critical point at stake was whether or not DNA (in its isolated form) can be patented.⁴⁹

Table III | AMP v. Myriad Timeline

Date	Event
May 2009	American Civil Liberties Union (ACLU) and Public Patent Foundation (representing more than 20 plaintiffs) file suit against Myriad.
March 2010	Judge Robert Sweet, of the Southern District of NY (Federal District Court), rules that DNA is not patent eligible.
July 2011	Defendants appeal to the Court of Appeals for the Federal Circuit (CAFC). CAFC rules that gene patents are valid.
March 2012	Supreme Court sends the case back to the CAFC for further review.
August 2012	CAFC again rules that patents on genes are valid.
September 2012	Plaintiffs appeal to the Supreme Court.
April 2013	Supreme Court hears oral arguments.
June 13, 2013	Supreme Court invalidates gene patents (AMP v. Myriad Genetics)

Accessed February 2, 2014. (3) Cook-Deegan *et al.*, “BRCA Briefing Page,” Duke University: Institute for Genome Sciences & Policy. <http://www.genome.duke.edu/centers/cpg/Myriad/>. Accessed February 2, 2014.

⁴⁹ (1) Skolnick *et al.*, U.S. Patent No. 5,747,282 (2) Shattuck-Eidens *et al.*, U.S. Patent No. 5,693,473 (3) Tavtigian *et al.*, U.S. Patent No. 5,837,492).

On June 13, 2013, the Supreme Court ruled loosely in the plaintiff's favor.⁵⁰ As the Opinion of the Court reads, "Myriad's principal contribution was uncovering the precise location and genetic sequence of the *BRCA1* and *BRCA2* genes within chromosomes 17 and 13."⁵¹ The Court found that while Myriad "found an important and useful gene, separating that gene from its surrounding genetic material is not an act of invention." If Myriad's patents were methods patents, detailing an innovative new procedure for isolating *BRCA1/2* or for manipulating the genes, then the patents might have been found valid. However, given that "the claims focus on the genetic information encoded in the *BRCA1* and *BRCA2* genes," and this information is determined by nature, the Supreme Court ruled that the claims were not valid.⁵²

Summary

Genetics plays an important role in the development of many diseases. One of these diseases is breast cancer. Mutations in two genes, *BRCA1* and *BRCA2*, increase one's chances of developing heritable breast cancer. Though mutations in *BRCA1/2* are rare, the probability of developing breast cancer increases so significantly with a harmful mutation in these genes that they have become two of the most widely studied human genes. In 1996, Myriad Genetics was the first company to develop a test (called BRACAnalysis®) for mutations in these genes. Since

⁵⁰ **Note:** The actual case was much more complicated. While the Supreme Court did rule in the plaintiff's favor by saying that isolated DNA is not patentable, the Court upheld Myriad's cDNA patents. cDNA stands for 'complementary DNA.' The logic behind this ruling is that isolated DNA (or gDNA) is not patent eligible because it is a product of nature and not an act of invention (i.e., simply isolating a gene is not new and noteworthy). However, the Supreme Court did *not* consider cDNA to be a product of nature, as it involves significant manipulation by man. This cDNA decision is also controversial. Because all of Myriad's cDNA patents were upheld, the company still believes they hold a strong enough patent portfolio to prevent other testing companies from entering the market. However, as the next chapter shows, many companies did enter the market and claim that they are not infringing upon Myriad's patents. Myriad has sued many of these companies, but the cases are still ongoing and, in the meantime, these companies will continue to offer *BRCA1/2* testing.

⁵¹ Association for Molecular Pathology (AMP) *et al.* v. Myriad Genetics, Inc., 569 U.S. 1 (2013). http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf.

⁵² AMP *et al.* v. Myriad Genetics, Inc.

the release of this test, thousands of women have benefitted from the information, and subsequent analysis, that Myriad has provided.

Though Myriad has helped thousands of women personalize their breast cancer prevention and treatment strategies, the company has gained a significant amount of negative attention due to their intellectual property (IP) and business practices. The controversy surrounding Myriad's patents and high testing costs provided the impetus for a lawsuit challenging the validity of gene patents. Twenty plaintiffs (representing a variety of interest groups, from patients to physicians and research organizations) filed suit against Myriad in 2009, arguing that DNA, as a naturally occurring material, is not patent eligible. On June 13, 2013, the Supreme Court sided with the plaintiffs by unanimously declaring gene patents invalid.⁵³ The Court's decision was widely considered to be one of the most important alterations to U.S. patent policy in recent history. Immediately following the Court decision, many academic institutions and private companies announced their plans to develop genetic tests for *BRCA1/2*. Though Myriad still has a significant competitive advantage over these companies, there is no doubt that the genetic testing landscape for *BRCA1/2* will be dramatically different going forward.⁵⁴

⁵³ **Note:** The Supreme Court ruled that Myriad's patents on the isolated genes *BRCA1* and *BRCA2* were invalid; however, they upheld Myriad's patents on cDNA.

⁵⁴ **Note:** This court case is particularly important for Myriad because a majority of the company's earnings are from its BRACAnalysis® test. According to Myriad's 2013 Annual Report, the BRACAnalysis® test "accounted for 75.1% of total revenue." Myriad's BART test (large rearrangement analysis) accounted for another 9.6%. **Source:** "Annual Report," Myriad Genetics. August 14, 2014. <http://investor.myriad.com/secfiling.cfm?filingID=1193125-13-334245>. Accessed April 17, 2014.

A Changing Genetic Landscape

Outline

- A. Aftermath of the Supreme Court Case
- B. New Competitors
 - i. Research Methods
 - ii. Overview
- C. Cost on Decision Making
- D. Summary

Aftermath of the Supreme Court Case

The effects of the Supreme Court's ruling in June of 2013 could be seen immediately. On June 13, 2013, the same day that the decision was released, the Deputy Commissioner for Patent Examination Policy, A.H. Hirshfeld, released a memorandum to all Patent Examining Corps explaining the new policy change. As Hirshfeld writes, *AMP v. Myriad* “significantly changes the Office’s examination policy regarding nucleic acid-related technology.”⁵⁵ The letter calls on examiners to “reject product claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, as being ineligible subject matter under 35 U.S.C. §101.”⁵⁶

Within a week of the ruling many biotech companies and medical centers announced plans to develop *BRCAl/2* tests, claiming that they would offer them at significantly lower prices than Myriad. Though each of the new testing companies will be summarized in the table below, readers should consult Appendix 2 for more details regarding the pricing and technical details of each of these tests.

⁵⁵ Hirshfeld, A. H., “Memorandum: Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc.,” United States Patent and Trademark Office (USPTO). June 13, 2013. http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf. Accessed February 6, 2014.

⁵⁶ Hirshfeld, United States Patent and Trademark Office.

New Competitors

Research Methods

The following table on current *BRCA1/2* testing companies and costs was primarily drawn from company websites. This information was gathered to investigate how much (or how little) *BRCA1/2* testing costs have changed over the past 15 years and to aid in the analysis of payer policies. Company names were found from reading news articles following the June 2013 Supreme Court case. Since these companies and laboratories are interested in publicizing their new *BRCA1/2* tests, it was not difficult to compile a list of them. Company websites differed in the amount of information publically available. In most instances, especially when company websites provided unclear, contradictory, or insufficient information, company representatives were contacted by phone and email. Please note that this information is time sensitive. New companies may be entering the market and test prices may have changed since the latest revision.⁵⁷

⁵⁷ **Note:** In addition to the companies listed in Appendix 2, there are a couple academic centers that offer *BRCA1/2* testing, but just for their own patients. For instance, the University of North Carolina's Molecular Genetics Lab offers testing only for individuals referred from its Cancer Genetics Clinic. The Institute of Genomic Medicine (New Jersey's Medical School) also offers *BRCA1/2* testing, but not commercially. Furthermore, due to "insurance restrictions," the lab "does not provide testing for most patients through the NJMS lab anyways." Baylor Medical Genetics Laboratories does not yet have an in-house sequencing test for *BRCA1/2* and sends all samples to Counsyl for analysis. Though there has been speculation that the University of Pennsylvania and Washington University in St. Louis would offer tests, as of April 20, 2014, these institutions have not released a test. Private companies, such as DNA Direct, Inc. and Pathway Genomics, have also expressed interest in entering the testing market but have not developed tests yet.

Overview

The following table lists the current *BRCA1/2* testing options in the United States. Companies and academic institutions are presented in chronological order, with the first company to offer testing presented first (Myriad Genetics). The date each company entered the *BRCA1/2* testing market is listed underneath each company name, along with company's VUS rate. Then, test titles, costs, descriptions, and turn around times (TATS) are provided. Full-gene sequencing is abbreviated as "seq" and duplication/deletion analysis is abbreviated as "dup/del." CPT codes for each of the tests are listed in Appendix 6.

Readers should consult Appendix 2 for further details on each of these new testing companies. Appendix 2 provides a brief description of the company, states the sequencing technology used, and, if the company offers multi-gene panels, then these genes are listed as well.

Table IV Summary of New <i>BRCA1/2</i> Testing Options				
Company (Date of Entrance) (VUS rate)	Test Title	Cost	Test Description	TATs
Myriad Genetics 1996 <i>BRCA1</i> VUS: 0.6%. <i>BRCA2</i> VUS: 1.6%	Integrated/ Comprehensive BRACAnalysis®	\$4,040	Complete <i>BRCA1/2</i> sequence; 5 common large rearrangements	14 days
	BRACAnalysis® (not comprehensive)	\$3,340	Comprehensive BRACAnalysis® now recommended for most patients	14 days
	BRCA1 or BRCA2 Single Site BRACAnalysis®	\$475	Known familial mutations in <i>BRCA1</i> or <i>BRCA2</i>	14 days
	Multisite BRACAnalysis®	\$575	3 Ashkenazi Jewish founder mutations	14 days
	BRACAnalysis Large Rearrangement Test (BART)	\$700	Offered as an add-on to BRACAnalysis®	14 days
	MyRisk®	B/w \$4,000 and \$4,500	25 genes for 8 hereditary cancers (breast, ovarian, gastric, colorectal, pancreatic, melanoma, prostate, and endometrial). <i>Expected to be released in September.</i>	TBD
UCLA Diagnostic Molecular Pathology Lab May 2012 VUS: n/a	BRCA1 & 2 Ashkenazi Jewish Mutations	approx. \$500	3 Ashkenazi Jewish founder mutations	3-28 days
Ambry Genetics June 13, 2013 VUS: 4.4%	<i>BRCA1</i> or <i>BRCA2</i> site specific analysis	\$400	Detection of a known familial mutation in <i>BRCA1</i> or <i>BRCA2</i>	7-14 days
	<i>BRCA</i> Ashkenazi Jewish panel	\$500	3 founder mutations	7-10 days
	<i>BRCA1/2</i> Deletion/ Duplication Only	\$500	Del/dup analysis	14 days

	<i>BRCA1/2</i> Sequence + Deletion/Duplication	\$2,200	Full gene sequencing and del/dup analysis	14-21 days
	BRCA Ashkenazi Jewish 3-site mutation panel w/ reflex to <i>BRCA1/2</i> analysis	\$2,250	3 founder mutations. If test comes back negative, it reflexes to full sequencing of <i>BRCA1/2</i> .	14-21 days
	<i>BRCA1/2</i> analysis w/ reflex to <i>BRCPlus</i> ® if negative	\$3,350	Full gene sequencing of <i>BRCA1/2</i> . If test comes back negative, it reflexes to del/dup analysis and analysis of 4 other high-risk genes.	14-21 days
	<i>BRCPlus</i> ®	\$3,300	Sequence and del/dup analysis of 6 clinically actionable genes for breast cancer	21 days
	BreastNext®	\$3,900	Del/dup analysis of 18 genes for breast cancer	6-10 weeks
	OvaNext®	\$3,900	Full gene sequencing and del/dup analysis of 23 genes for breast, ovarian and/or uterine cancers.	8-12 weeks
	CancerNext®	\$4,250	Full gene sequencing and del/dup analysis of 28 genes for cancer susceptibility.	8-12 weeks
University of Washington June 14, 2014 VUS: 15%	Single Gene Analysis	\$1,350	Sequencing for any gene, such as <i>BRCA1</i> or <i>BRCA2</i>	12 weeks
	Known Familial Mutation	\$450	Point mutation analysis	12 weeks
	<i>BRCA1/2</i> Ashkenazi Jewish 3-site	n/a	Test not performed by Washington; Samples sent to Mayo for testing and analysis	12 weeks
	<i>BRCA1/2</i> Complete Analysis	\$2,200	Sequencing and dup/del	12 weeks
	BROCA - Cancer Risk Panel	\$3,350	Complete seq. of genes and detection of large del/dup and mosaicism. Genes for breast or ovarian cancer, colorectal, endometrial, pancreatic, endocrine, or melanoma.	12 weeks
Ethigen June 19, 2013 VUS: 5-7%	Hereditary Breast and Ovarian Cancer Testing	\$1,250	Sequence and rearrangement analysis of <i>BRCA1/2</i> .	20-30 days
	<i>Rapid</i> Hereditary Breast and Ovarian Cancer Testing	\$1,950	Sequence and rearrangement analysis of <i>BRCA1/2</i> .	< 15 days

	Expanded Cancer Panel	\$2,250	Multigene panel (sequencing and del/dup analysis) for <i>BRCA1/2</i> and 17 other genes	20-30 days
Fulgent Therapeutics, LLC mid-June 2013 VUS: 6%	Breast Ovarian Cancer NGS Panel	\$1450 (institutional) \$1950 (3rd party)	Sequencing of 30 genes involved in hereditary breast and ovarian cancer predisposition.	4-6 weeks
	BRCA1 and BRCA2 deletion/duplication analysis	\$500 (institutional only)		2 weeks
	BRCA1 and BRCA2 gene sequence analysis	\$500 (institutional only)		2 weeks
	Hereditary Cancer Panel (HCP)	\$1450 (institutional) \$1950 (3rd party)	Sequencing (no del/dup) of 49 genes involved in susceptibility for many cancers	4-6 weeks
Gene DX August 28, 2013 VUS: 5% (will have an updated VUS rate within the next month)	BRCA1/2 Sequencing	\$1,850		2 weeks
	BRCA1/2 Del/Dup	\$1,000		7-10 days
	BRCA1/2 Familial Variant	For 1: \$350 For 2: \$500		2-3 weeks
	BRCA1/2 Sequencing and Del/Dup Analysis	\$2,200		2 weeks
	BRCA1/2 Ashkenazi Founder Mutation Panel	\$450		7-10 days
	OncoGeneDx Comprehensive Cancer Panel	\$4,530	Sequence and Del/Dup Analysis for 35 genes for cancer susceptibility	10 weeks
	Breast Cancer High Risk Panel	\$3,700	Sequence and Del/Dup Analysis for 6 genes for breast cancer	10 weeks
	Breast/Ovarian Cancer Panel	\$3,850	Sequence and Del/Dup Analysis for 26 genes for breast and ovarian cancer	10 weeks
Quest Diagnostics	BRCAVantage® Comprehensive Evaluation	\$2,495	Sequencing and del/dup analysis in <i>BRCA1/2</i>	14 days

mid-October 2013 VUS: 1.9% (VUS rate based off only 500 samples. Will update in May 2014 w/ 2000 more samples; expected to increase)	BRCAVantage® Ashkenazi Jewish Evaluation	\$500	3 founder mutations	7 days
	BRCAVantage® Single Site	\$500	Detection of a known familial mutation in <i>BRCA1/2</i> .	14 days
	BRCAVantage® Rearrangement Evaluation	\$500	Detection of dup/del in <i>BRCA1/2</i> .	14 days
The University of Chicago Genetic Services November 20, 2013 VUS: n/a	BRCA1 and BRCA2 familial testing	\$415	Testing for known familial BRCA1/2 mutations just by sequence analysis.	2-4 weeks
	Custom del/dup testing	\$650	Custom deletion/duplication testing by quantitative PCR. Test costs \$450 for additional family members.	4-6 weeks (2nd family member: 3- 4 weeks)
	BRCA1 and BRCA2 founder mutations	\$475		2-4 weeks
LabCorp December 2, 2013 VUS: 4.6%	BRCA1 or BRCA2 Targeted Analysis	\$500	Just sequencing of <i>BRCA1</i> or <i>BRCA2</i> .	14 days
	BRCA1/2 Comprehensive Analysis (BRCAssure®)	\$2,895	Sequencing and del/dup analysis of <i>BRCA1/2</i> .	21 days
	BRCA1/2 Del/Dup Analysis	\$700	Just del/dup analysis of <i>BRCA1/2</i> .	14 days
	BRCA1/2 Ashkenazi Jewish Profile	\$600	Just sequencing of <i>BRCA1/2</i> .	10-12 days
InVitae December 2013 VUS: 6%	Hereditary breast and ovarian cancer	\$1,500	Full-gene seq. and del/dup analysis for breast and ovarian cancer	2 weeks
	High-Risk Hereditary Breast Cancers	\$1,500	Full-gene seq. and del/dup analysis of 6 genes for cancer susceptibility & other syndromes	2 weeks
	Women's Hereditary Cancers	\$1,500	Full-gene seq. and del/dup analysis of 17 genes for cancer susceptibility	2 weeks

	Hereditary Cancer Syndromes	\$1,500	Full-gene seq. and del/dup analysis of 29 genes for 16 different cancers and disorders	2 weeks
	Family Testing Services	\$200	Targeted mutation analysis	2 weeks
Center for Human Genetics January 2014 VUS: n/a	3 founder mutations	\$450		---
Counsyl Spring 2014 VUS: 5.3%	Counsyl Inherited Cancer (BRCA) Screen	\$999	Sequence and dup/del analysis	2 weeks
University of Michigan State Testing Lab Spring 2014 VUS: TBA	BRCA Mutation Panel	Won't disclose	Full gene sequencing and del/dup analysis;	28 days
	BRCA Ashkenazi Jewish Founder Mutations	Won't disclose		
	BRCA1/2 Targeted Sequencing, Familial	Won't disclose		28 days
	BRCA1/2 Gene Sequencing	Won't disclose		
	BRCA1/2 del/dup analysis	Won't disclose		21-28 days

As Table IV demonstrates, many new testing companies have entered the *BRCA1/2* testing market since June 2013. The following graphs help to illustrate these market changes. Figure 4 demonstrates that many new testing companies have entered the market with cheaper tests. This graph compares *comprehensive BRCA1/2* analysis test costs (so full gene sequencing and large rearrangement testing). Not all companies offer this particular version of *BRCA1/2* testing, so only those companies with comparable tests were included. Figure 5 shows how *BRCA1/2* testing companies (except for the University of Washington) have extremely similar turn-around-times (TATs); most companies return a patients' test results in under 20 days. Lastly, Figure 6 illustrates how Myriad has the lowest VUS rate of all *BRCA1/2* testing companies. Ambry, with a rate of 4.4%, and LabCorp, with a rate of 4.6%, are the next lowest companies.⁵⁸ The University of Washington has the highest VUS rate at 15%. Though these graphs display general market trends since June 2013, they should be viewed holistically and in conjunction with Table IV and Appendix 2. These *BRCA1/2* testing companies all offer slightly different tests, and each test is then associated with its unique VUS rate and turn-around-time, so it is difficult to directly compare each of the companies.

⁵⁸ **Note:** Technically, Quest Diagnostics has reported a VUS rate of 1.9%. However, this is only based off 500 samples. Company representatives expect this rate to increase soon as they are about to recalculate the VUS rate with 2,000 more samples.

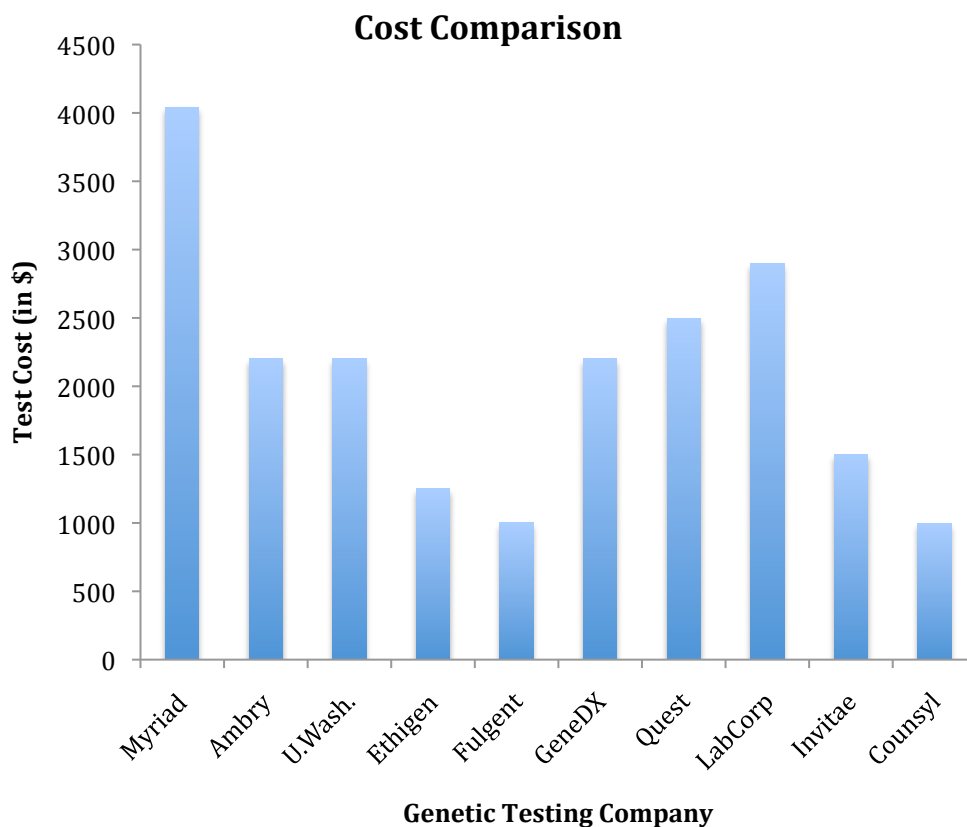


Figure 4 | Cost Comparison. This figure displays the drop in test cost following the June 2013 Supreme Court case. This particular figure displays the costs for *comprehensive BRCA1/2* analysis (so both full gene sequencing and rearrangement analysis). Only those companies that offered this particular test were included in this figure. Readers should consult Table IV and Appendix for other companies that offer *BRCA1/2* testing.

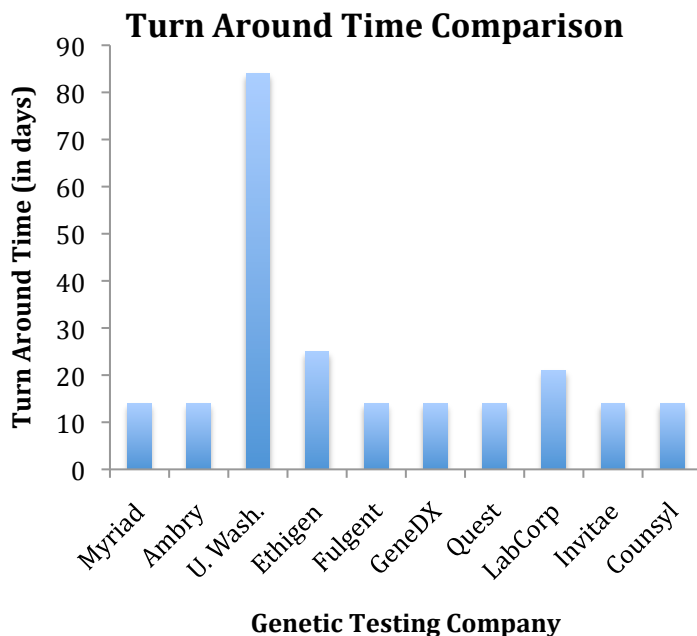


Figure 5 | Turn Around Time Comparison. This figure displays the turn around times (TATs) of the existing *BRCA1/2* testing companies for their sequencing and large rearrangement test. All companies have extremely similar TATs, except for the University of Washington with a TAT of 12 weeks.

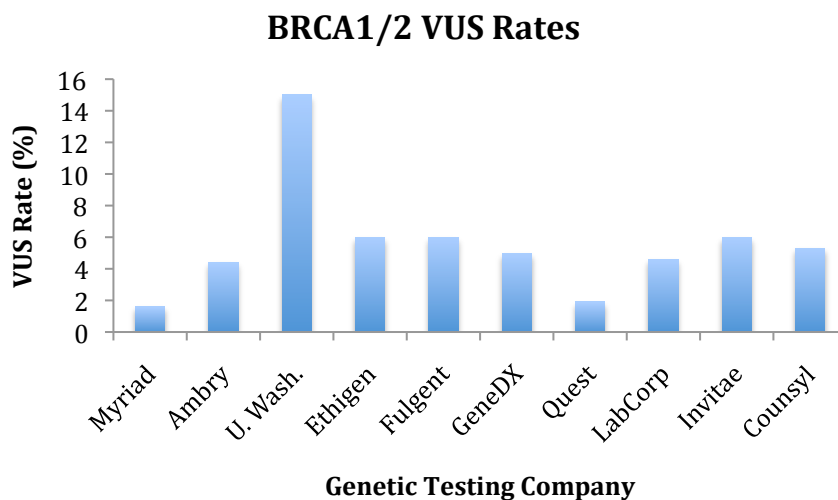


Figure 6 | VUS Rate Comparison. This figure displays the VUS rates of each existing *BRCA1/2* testing company. Myriad has the lowest rate (at 1.6%) and the University of Washington has the highest (at 15%). Most companies have rates in the 4-6% range.

Cost on Decision Making

After presenting new *BRCA1/2* test options (made possible by the 2013 Supreme Court decision), it is helpful to examine the literature on how important cost is for patients' considering *BRCA1/2* testing. Several studies have aimed to determine the significance of reimbursement for patients, and, more broadly, to examine the various motivations behind genetic testing decision-making.

For instance, in 2000 and 2001, Velicer and Taplin explored awareness of *BRCA1/2* testing and breast cancer survivors' intention of getting tested. To this end, researchers conducted a "population-based survey of 276 female survivors between the ages of 40 and 49 and living 5 to 10 years post-diagnosis."⁵⁹ They found that only 26% of these women would be willing to get tested if they had to pay for it. Of these women, only 7% would be willing to pay more than \$200 for the test. However, if insurance did cover testing, then 67% of women would be willing. Researchers also found that the most commonly cited benefit for getting tested (according to the patients) was learning more about their children's or relative's risk. However, the most commonly cited disadvantage was a concern about losing insurance. Overall, Velicer and Taplin concluded that most women seem to have a positive attitude towards *BRCA1/2* testing, but that their study demonstrates "how strongly [breast cancer survivors'] intent to obtain genetic testing is tied to insurance coverage."⁶⁰

A similar study by Peterson *et al.* aimed to determine the impact of concerns such as cost, confidentiality, and insurance discrimination on *BRCA1/2* testing decisions.⁶¹ Peterson worked with a group of 384 patients who were part of a Breast and Ovarian Cancer Risk Evaluation

⁵⁹ Velicer, C.M. and Taplin, S. (2001). Genetic testing for breast cancer: Where are health care providers in the decision process?. *Genetics in Medicine* 3: 112-119.

⁶⁰ Velicer and Taplin, *Genetics in Medicine*.

⁶¹ Peterson, E.A., Milliron, K.J., Lewis, K.E., Goold, S.D., *et al.* (2002). Health insurance and discrimination concerns and *BRCA1/2* testing in a clinic population. *Cancer Epidemiol Biomarkers Prev* 11: 79-87.

Program in Ann Arbor and Grand Rapids, Michigan. Within this group, 184 individuals met the qualifications for *BRCA1/2* testing and 58% of them chose to proceed with testing. The remaining 42% of individuals declined testing, and over half of them “cited concerns about cost and insurance discrimination as their reason.”⁶² Peterson *et al.* estimated that “approximately half of the patients [who] declined testing because of insurance coverage concerns would be positive for a *BRCA1/2* mutation,” indicating that (at least in this study) cost was prohibiting many women from finding out valuable health information. Concerns over cost were intensified in individuals with lower incomes. Though there was not a “significant difference between the higher and lower income groups for the importance attached to test result confidentiality,” there was a “significant difference [P-value of 0.003] based on income in the importance attached to insurance coverage for testing between the two income groups.”⁶³ While this conclusion is to be expected, it nevertheless reinforces the importance of cost for low-income individuals considering testing.

⁶² Peterson *et al.*, *Cancer Epidemiol Biomarkers Prev.*

⁶³ Peterson *et al.*, *Cancer Epidemiol Biomarkers Prev.*

Summary

Since the 2013 Myriad Supreme Court case, many new companies have entered the *BRCA1/2* testing market. While some of these companies are long-established diagnostic testing companies (Quest and LabCorp), most are smaller labs that specialize in testing for a few hereditary disorders. These new companies offer a variety of test options. Small tests, such as for a known familial mutation, can cost as low as \$200 (Invitae), and large multi-gene panels cost anywhere from \$1,000 to \$4,000.

Given less than a year has passed since the court case (in June of 2013), it is likely that the market has not reached equilibrium and test prices will continue to fluctuate. Test options may also change. For example, as will be discussed in the next section, insurance companies do not currently cover multi-gene panels. Yet, most of the new *BRCA1/2* testing companies have many multi-gene test offerings. If insurance companies continue to not cover multi-gene tests, then lower costs could help to incentivize out-of-pocket purchase. If demand gets even lower, such tests may need to be removed from a company's test portfolio entirely. Further research is needed on when (if ever) physicians prefer to order multi-gene panels rather than single gene sequencing. Additionally, because the literature overviewed here focused on patient opinions from the early 2000s, future research should investigate the effect of cost on decision-making today.

Rules for Coverage and Reimbursement

Outline

- A. *BRCA1/2* Testing Recommendations
- B. New Competitors (Insurance Information)
 - i. Research Methods
 - ii. Overview
- C. Insurance Policies
 - a. Research Methods
 - b. Overview
- D. Privacy Regulations and Insurance
- E. Other Coverage Issues
- F. Summary

***BRCA1/2* Testing Recommendations**

In order to consider insurance coverage of *BRCA1/2* tests, it is important to first understand the medical guidelines for *when* an individual should get tested. In the United States, there are two main *BRCA1/2* testing recommendations – those by the United States Preventative Services Task Force (USPSTF) and by the National Comprehensive Cancer Network (NCCN) (see Tables V, VI). The major difference between the two sets of recommendations is that the NCCN lays out *specific* criteria for who should seek *BRCA1/2* testing, whereas the USPSTF lays out a general process.

The National Comprehensive Cancer Network (NCCN) is a "not-for-profit alliance of 25 of the world's leading cancer centers." Clinical professionals from these top cancer centers regularly create "clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers."⁶⁴ For *BRCA1/2*, the NCCN first provides a list of 'Criteria for Further Genetic Risk Evaluation.' If an individual meets one or more of the criteria in that

⁶⁴ "About NCCN," National Comprehensive Cancer Network. <http://www.nccn.org/about/default.aspx>. Accessed March 29, 2014.

category, then the NCCN recommends referral to a cancer genetics professional (see Table V).^{65,66} This professional will offer the proper genetic counseling, and review over the ‘Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria.’ Meeting “one or more of these testing criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.”⁶⁷

The NCCN now also recognizes how “certain large genomic rearrangements are not detectable by primary sequencing assays, thereby necessitating supplementary testing, in some cases.” Thus, the NCCN recommends “comprehensive testing, which encompasses full *BRCA1/2* sequencing and detection of large gene rearrangements” for individuals who “meet the testing criteria for *BRCA1/2* and have no known familial *BRCA1/2* mutations.”⁶⁸ Most of the *BRCA1/2* testing companies outlined in the previous chapter offer this test (usually referred to as dup/del analysis).

⁶⁵ Bevers, T. B., Anderson, B. O., Bonaccio, E., Buys, S., Daly, M. B., Dempsey, P. J., ... & Yankeeelov, T. (2009). Breast cancer screening and diagnosis. *Journal of the National Comprehensive Cancer Network* 7, no. 10: 1060-1096.

⁶⁶ "Genetic/Familial High-Risk Assessment: Breast and Ovarian," NCCN Clinical Practice Guidelines in Oncology, National Comprehensive Cancer Network, Inc. 2014.

http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. Accessed March 21, 2014.

⁶⁷ "Genetic/Familial High-Risk Assessment: Breast and Ovarian," NCCN Clinical Practice Guidelines.

⁶⁸ "Medical Policy: Genetic Testing for HBOC," United HealthCare Services.

Table V | National Comprehensive Cancer Network *BRCA1/2* Testing Guidelines

Criteria for Further Genetic Risk Evaluation

A. An affected individual with one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- Early-age-onset breast cancer
- Triple negative (ER-, PR-, HER2-) breast cancer
- Two breast cancer primaries in a single individual
- Breast cancer at any age, and
 - ≥ 1 close blood relative with breast cancer ≤ 50 years, or
 - ≥ 1 close blood relative with epithelial ovarian cancer at any age, or
 - ≥ 2 close blood relatives with breast cancer and/or pancreatic cancer at any age
 - From a population at increased risk
- ≥ 1 family member on the same side of the family with a combination of breast cancer and \geq of the following (especially if early onset): pancreatic cancer, prostate cancer (Gleason score ≥ 7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer
- Ovarian cancer
- Male breast cancer

B. An unaffected individual with a family history of one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- ≥ 2 breast primaries in single individual
- ≥ 2 individuals with breast primaries on the same side of the family
- ≥ 1 ovarian cancer primary from the same side of the family
- First- or second-degree relative with breast cancer ≤ 45 years
- ≥ 1 family member on same side of family with a combination of breast cancer and ≥ 1 of the following (especially if early onset): pancreatic cancer, prostate cancer (Gleason score ≥ 7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polyps of GI tract; diffuse gastric cancer
- Male breast cancer

Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria.

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer and one of more of the following:
 - Diagnosed ≤ 45 years
 - Diagnosed ≤ 50 years with:
 - An additional primary
 - ≥ 1 close blood relative with breast cancer at any age
 - An unknown or limited family history
 - Diagnosed ≤ 60 years with:
 - Triple negative breast cancer
 - Diagnosed at any age with:
 - ≥ 1 close blood relative with breast cancer diagnosed ≤ 50
 - ≥ 2 close blood relatives with breast cancer at any age
 - ≥ 1 close blood relative with epithelial ovarian cancer
 - ≥ 2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥ 7) at any age
 - A close male blood relative with breast cancer
 - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required
- Personal history of epithelial ovarian cancer
- Personal history of male breast cancer

-
- Personal history of pancreatic cancer or prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age
 - Family history only (Significant limitations of interpreting test results for an unaffected individual should be discussed)
 - First- or second-degree blood relatives meeting any of the above criteria
 - Third degree blood relative with breast cancer and/or ovarian cancer with ≥ 2 close blood relatives with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian cancer
 - Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.
 - Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

The U.S. Preventive Services Task Force (USPSTF) is an "independent panel of non-Federal experts in prevention and evidence-based medicine," composed mostly of primary care providers. The panel conducts "scientific evidence reviews of a broad range of clinical preventive health care services (such as screening, counseling, and preventive medications) and develops recommendations for primary care clinicians and health systems." For *BRCA1/2* testing, the USPSTF recommends individuals with a family history of breast or ovarian cancer to first speak with their primary care provider (PCP) (see Table VI).^{69,70,71} PCPs are encouraged to screen women with one of several recommended screening tools (see Appendix 4). Then, if a woman tests positive with one of these screening tools, she should "receive genetic counseling and, if indicated after counseling, BRCA testing."⁷²

⁶⁹ "Preventive Services Panel Advises Against Broad BRCA Testing: 'Family History' Should Guide Testing," *GenomeWeb*. December 27, 2013. <http://www.genomeweb.com/clinical-genomics/preventive-services-panel-advises-against-broad-brca-testing-family-history-shou>. Accessed March 21, 2014.

⁷⁰ Moyer, V.A. (2014) Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine* 160, no. 4: 271-281.

⁷¹ Nelson, H.D., Pappas, M., Zakher, B., Mitchell, J.P., Okinaka-Hu, L., Fu, R. (2013). Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: A systematic review to update the U.S. Preventive Services Task Force recommendation. Published online on December 24, 2013.

⁷² Moyer, *Annals of Internal Medicine*.

Table VI | United States Preventative Task Force (USPSTF) *BRCA1/2* Testing Guidelines⁷³

Annals of Internal Medicine



**RISK ASSESSMENT, GENETIC COUNSELING, AND GENETIC TESTING
FOR BRCA-RELATED CANCER IN WOMEN
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

Population	Women who have not been diagnosed with BRCA-related cancer and who have no signs or symptoms of the disease	
Recommendation	Screen women whose family history may be associated with an increased risk for potentially harmful BRCA mutations. Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing. Grade: B	Do not routinely recommend genetic counseling or BRCA testing to women whose family history is not associated with an increased risk for potentially harmful BRCA mutations. Grade: D
Risk Assessment	Family history factors associated with increased likelihood of potentially harmful BRCA mutations include breast cancer diagnosis before age 50 years, bilateral breast cancer, family history of breast and ovarian cancer, presence of breast cancer in ≥1 male family member, multiple cases of breast cancer in the family, ≥1 family member with 2 primary types of BRCA-related cancer, and Ashkenazi Jewish ethnicity. Several familial risk stratification tools are available to determine the need for in-depth genetic counseling, such as the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, and FHS-7.	
Screening Tests	Genetic risk assessment and BRCA mutation testing are generally multistep processes involving identification of women who may be at increased risk for potentially harmful mutations, followed by genetic counseling by suitably trained health care providers and genetic testing of selected high-risk women when indicated. Tests for BRCA mutations are highly sensitive and specific for known mutations, but interpretation of results is complex and generally requires posttest counseling.	
Treatment	Interventions in women who are BRCA mutation carriers include earlier, more frequent, or intensive cancer screening; risk-reducing medications (e.g., tamoxifen or raloxifene); and risk-reducing surgery (e.g., mastectomy or salpingo-oophorectomy).	
Balance of Benefits and Harms	In women whose family history is associated with an increased risk for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention is moderate.	In women whose family history is not associated with an increased risk for potentially harmful BRCA mutations, the net benefit of genetic testing and early intervention ranges from minimal to potentially harmful.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on medications for the reduction of breast cancer risk and screening for ovarian cancer. These recommendations are available at www.uspreventiveservicestaskforce.org .	

FHS-7 = Family History Screen 7.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

⁷³ **Note:** The USPSTF assigns to their recommendations various letter “grades” (A, B, C, D, or I). These grades correspond to the following descriptions: **A.** The USPSTF recommends the service. There is high certainty that the net benefit is substantial. **B.** The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. **C.** The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. **D.** The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. **I.** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. **Source:** “Grade Definitions,” U.S. Preventive Services Task Force (USPSTF). July 2012. <http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm>. Accessed April 7, 2014.

Readers should note that the USPSTF's recommendations apply only to women, and specifically only those who have *not* been diagnosed with breast cancer. The USPSTF encourages women who *have* been diagnosed with breast cancer and who have a family history of breast or ovarian cancer to "discuss further evaluation with their clinician." However, no specific recommendations are made because "that assessment is part of disease management," which is "beyond the scope" of the USPSTF."⁷⁴

New Competitors (Insurance Information)

Research Methods

The following information on current coverage policies for *BRCA1/2* testing was primarily drawn from company websites. The websites of the companies discussed in the previous chapter were explored for any and all insurance and payment information. Company websites differed in the amount of information publically available.

Overview

Most genetic testing companies offer free insurance pre-verification before proceeding with testing. Given the diversity and complicated nature of insurance plans, this step is extremely important for patients so that they can learn *their* specific *BRCA1/2* testing cost. Some companies have established out-of-pocket cost thresholds. For example, after a test is ordered, Myriad Genetics will check the patient's insurance coverage. If patients are expected to pay more than \$375 out-of-pocket for the test, then Myriad will re-contact the patient before proceeding (Table VII). However, if their expected contribution is less than this limit, testing

⁷⁴ Moyer, *Annals of Internal Medicine*.

will continue without notification. Other companies re-contact the patient after insurance verification, despite the patient's expected cost.

Table VII offers a summary of Appendix 3A. Testing companies were evaluated to see if they offered pre-verification services. If applicable, the cost thresholds at which companies will re-contact patients to ask if patients want to proceed with testing is also included. Lastly, it is noted if a company bills with Medicare, Medicaid, and commercial insurers and whether financial assistance programs exist. Cells with "---" implies that there was no mention of that service.

Table VII Insurance Information Offered by Testing Companies					
	Pre-verification and Cost thresholds	Medicare	Medicaid	Private	Financial Aid Programs
Myriad	Yes. >\$375	Yes, if conditions are met.	---	Yes	Yes
UCLA	---	---	---	---	---
Ambry	Yes. >\$100	Yes, if conditions are met.	Some states' Medicaid plans	"Majority of commercial insurers"	Yes. Medicare/Medicaid individuals not eligible.
University of Washington	Yes. Re-contact always.	Yes, if conditions are met.	Some states' Medicaid plans	---	Yes. Patients "may be eligible for a discount"
Ethigen	---	---	---	---	---
Fulgent	---	---	---	---	---
GeneDX	Yes. >\$100	Yes, if conditions are met.	No	All commercial insurances.	Yes. For those without commercial insurance.
Quest	Yes. Re-contact always.	Yes, if conditions are met.	Yes	Yes	---
University of Chicago	No mention of pre-verification services.	Yes, if conditions are met.	Some states' Medicaid plans	Most insurance plans.	No
LabCorp	Yes. Re-contact always	Yes, if conditions are met.	Yes	Yes	Yes
Invitae	Yes	No	No	Yes	Yes. For those without insurance.
Center for Human Genetics	---	---	---	---	---
Counsyl	Yes. >\$299	No	No	Most insurance plans.	Yes
University of Michigan	No mention of pre-verification services.	Yes, if conditions are met.	Some states' Medicaid plans	Most insurance plans. Not 3 rd party billing for outside facility's samples.	Yes, but many criteria must be met.

Insurance Policies

Research Methods

The following table on *BRCA1/2* reimbursement policies offers a summary of Appendix 3 (parts B & C). The information contained in Appendix 3 was found by searching individual insurance company websites for genetic testing policies and for policies related to the prevention and screening of breast cancer.

The insurance policies overviewed here should not be considered exhaustive of all *BRCA1/2* coverage policies. Rather, these companies represent some of the larger and better-known insurance companies in the country. A 2007 report by the Harvard School of Government cites that Aetna, Blue Cross Blue Shield, Cigna, Humana, Kaiser, UnitedHealth, and Wellpoint are the nation's largest insurers. According to these estimates, BCBS insures about 33% of the US population, followed by Medicare and Medicaid at 15%, Wellpoint at 12%, United Health at 6%, and Aetna at 5%. Humana, Cigna, and Kaiser each cover 3% of the population.⁷⁵ Due to their large size, all of these payers were analyzed to see if they had specific *BRCA1/2* coverage policies.

In addition to these large insurers, the reader consulted a 2012 report by the Kaiser Family Foundation, which listed the largest three private insurers (in terms of enrollment) for each state.^{76,77} The author supplemented the starting list (of BCBS, Medicare, Medicaid, Wellpoint, United Health, Aetna, Humana, Cigna, and Kaiser) with insurance companies on this

⁷⁵ "Health Care Delivery Covered Lives – Summary of Findings," John F. Kennedy School of Government, Harvard University. 2007. <http://www.hks.harvard.edu/m-rcbg/hcdp/numbers/Covered%20Lives%20Summary.pdf>. Accessed April 20, 2014.

⁷⁶ "Market Share and Enrollment of Largest Three Insurers- Large Group Market" <http://kff.org/other/state-indicator/market-share-and-enrollment-of-largest-three-insurers-large-group-market/>. Accessed April 20, 2014.

⁷⁷ **Note:** Data was originally drawn from the Center for Consumer Information & Insurance Oversight (CCIIO).

list that had memberships of over 100,000 people. The resulting list of 24 insurance companies are shown in Table VIII.⁷⁸ In many instances, specific policies could not be found. It is important to note that the lack of an available coverage policy does not necessarily imply a non-covered service, as payers may not publish all of their coverage determinations.

In future research it will be necessary to undertake a more systematic assessment of payer policies for *BRCAl/2* testing. Given there is little research in this field, there is not a widely adopted methodology for which payers to include in such an analysis. In 2013, Graf *et al.* wrote one of the “first known surveys of all major US private health insurers with publicly available genetic testing policies.”⁷⁹ These authors similarly relied on simple Internet searches to find insurance policies. However, they first acquired a list of insurers from Atlantic Information Services, Inc. and selected the insurance companies with 50,000 or more members.⁸⁰ Future research could expand upon the number of insurance companies analyzed.

Overview

For more details regarding each of the following policies, see Appendix 3C (where these policies are actually provided). Cells with “---“ implies that there was no mention of that service.

⁷⁸ **Note:** This list would have been much larger, but the author removed all subsidiaries of the BlueCross BlueShield (BCBS) Association. Instead of looking for a specific policy for each of these subsidiaries, the author analyzed one of the largest components of BCBS (Anthem). In future research, the other subsidiaries of BCBS should also be reviewed.

⁷⁹ Graf, M.D., Needham, D.F., Teed, N., & Brown, T. (2013). Genetic testing insurance coverage trends: a review of publicly available policies from the largest US payers. *Personalized Medicine* 10, no. 3: 235-243.

⁸⁰ Graf *et al.*, *Personalized Medicine*.

Table VIII BRCA1/2 Reimbursement Policies					
Insurance Company	BRCA1/2 testing covered?	Dup/Del Analysis covered?	Multi-gene Panels covered?	Genetic Counseling covered?	Only contracted with Myriad?
Aetna Inc	Yes, if NCCN criteria are met or >10% probability from accredited risk assessment tools. Claims to follow the USPSTF, ACOG, ACMG guidelines, but lists the NCCN criteria.	No.	---	Yes.	Indirectly requires Myriad for testing.
BlueCross BlueShield (Anthem)	No national coverage policy found. Anthem follows NCCN criteria.	Yes, if criteria are met.	No.	Yes. Required both pre-and post-test.	No. No mention of a specific testing company.
Centene	No national coverage policy found. Preauthorization required for genetic tests.	---	---	---	---
Cigna	Yes, if common criteria are met or >10% probability from accredited risk assessment tools.	Yes, if criteria are met.	No.	Yes. Required.	No. No mention of a specific testing company.
Coventry Corp. Group	Yes. Follow USPSTF recommendations that have an A or B rating	---	---	Yes.	---
Dean Health Group	Yes, listed, but no specific policy found. Covered w/ no member cost sharing	---	---	Yes.	---
Emblem Health	Yes, if listed criteria are met.	Yes, if criteria are met.	---	Covered pre-and post-testing, but not required	Indirectly requires Myriad for testing.
Geisinger Health Plan	Yes, if NCCN criteria are met.	Yes, if criteria are met.	---	Yes.	No. No mention of a specific testing company.
Group Health Cooperative	Yes, but testing criteria not publicly available.	Yes, but criteria not available.	No	---	---
Harvard Pilgrim Health Care Group	Yes, listed, but no specific policy found. Covered w/ no member cost sharing.	---	---	Yes	---

Health Alliance Midwest	No policy found.	---	---	---	---
Health Net	Yes, if NCCN criteria are met.	Yes, if criteria are met.	---	Responsibility of care provider.	Indirectly requires Myriad for BART testing.
Health New England	Yes, if NCCN criteria are met.	---	---	Only pre-test counseling required.	Unclear.
Health Partners Group	Yes, if NCCN criteria are met.	Yes, if criteria are met.	---	Yes. Required pre-testing	Indirectly requires Myriad for testing.
Humana	Yes, if NCCN criteria are met. Preauthorization required.	Yes, if criteria are met.	No.	Yes. Part of their Genetic Guidance Program.	No. No mention of a specific testing company.
Kaiser Foundation Group	No national policy found.	---	---	Yes. Required both pre-and post-test.	No. No mention of a specific testing company.
Medica Group	Yes, if NCCN criteria are met. Preauthorization required.	Yes, if criteria are met.	---	Yes. Required pre-testing	Indirectly requires Myriad for BART testing.
Medicaid	No national policy found.	---	---	---	---
Medical Mutual of Ohio	Yes, listed, but no specific policy found.	---	---	Yes.	---
Medicare	No national coverage policy. LCDs follow NCCN criteria, but only for people w/ a personal history of breast and ovarian cancer	Yes, if criteria are met.	---	Yes. Required both pre-and post-test.	No. No mention of a specific testing company.
Select Health	Yes, listed, but no specific policy found.	---	---	Yes	---
Spectrum Health	No policy found.	---	---	---	---
Tufts Health Plan	Yes, if listed criteria are met. Covered w/ no member cost sharing.	Yes, if criteria are met.	---	Yes.	Indirectly requires Myriad for BART testing.
United Health Care	Yes, if NCCN criteria are met.	Yes, if criteria are met.	---	Strongly recommended.	No. No mention of a specific testing company.

Privacy Regulations and Insurance

As the literature review on the importance of cost on decision making illustrated (see previous chapter), patients also have a significant fear of losing their health insurance as a result of genetic testing. In the United States, there are two main regulations in place to protect the privacy of patients and their health care information.^{81,82}

First, the **Federal Policy for the Protection of Human Subjects** (known colloquially as ‘The Common Rule’) was established in June of 1991.⁸³ The Common Rule draws heavily from ethical considerations set forth by the Belmont Report in 1976.⁸⁴ Enforced by the Office for Human Research Protections (OHRP), the Common Rule defines human subjects, details what types of research are exempt or nonexempt, and sets forth guidelines for informed consent and Institutional Review Boards.

The Privacy Rule of the **Health Information Portability and Accountability Act (HIPAA)** establishes “a set of national standards for the protection of certain health information.”⁸⁵ (Thus, HIPAA pertains more to privacy in health care, whereas the Common Rule helps guide research that involves human subjects). The Department of Health and Human Services states that “a major goal of the Privacy Rule is to assure that individuals’ health information is properly protected while allowing the flow of health information needed to

⁸¹ Lowrance, W.W., “Privacy, Confidentiality, and Identifiability in Genomic Research,” National Human Genome Research Institute (NHGRI), October 3, 2006.

⁸² **Note:** For a comparison of the Common Rule and HIPAA, see: Williams, E.D. "Federal Protection for Human Research Subjects: An Analysis of the Common Rule and Its Interactions with FDA Regulations and the HIPAA Privacy Rule," The Library of Congress: Congressional Research Service. <http://www.fas.org/sgp/crs/misc/RL32909.pdf>. June 2, 2005. Accessed March 19, 2014.

⁸³ "Federal Policy for the Protection of Human Subjects ('Common Rule')," U.S. Department of Health & Human Services. <http://www.hhs.gov/ohrp/humansubjects/commonrule/>. Accessed March 19, 2014.

⁸⁴ "The Belmont Report," U.S. Department of Health & Human Services. <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>. Accessed March 19, 2014.

⁸⁵ "Health Information Privacy," U.S. Department of Health & Human Services. <http://www.hhs.gov/ocr/privacy/>. Accessed March 19, 2014.

provide and promote high quality health care and to protect the public's health and well being.”

The rule (enforced by the Office for Civil Rights) protects ‘individually identifiable health information,’ which includes demographic data as well as past, present, and future health conditions (and the payment associated with these conditions).

The **Genetic Information Nondiscrimination Act (GINA)** was passed in 2008 to further the protections guaranteed through the Common Rule and HIPAA. GINA prohibits genetic discrimination in employment and prevents group health plans and insurers from altering premiums based on genetic information. GINA also expands upon HIPAA's regulations by providing "additional underwriting protections, prohibit[ing] requesting or requiring genetic testing, and restrict[ing] the collection of genetic information."⁸⁶

Though GINA has alleviated many concerns related to employment and health insurance discrimination, it does have its limitations. Most notably, GINA's protections "do not extend to life insurance, disability insurance, and long-term care insurance."⁸⁷ However, researchers at the University of Pennsylvania claim that "the few cases of people being charged more or denied access to life insurance appear to be based on family history information and not based on results from genetic testing."⁸⁸ Another limitation is that GINA's provisions regarding employment discrimination do not apply to employers with fewer than 15 people. Lastly, though health insurance cannot be denied due to a genetic test result, eligibility and insurance premiums *can be* altered based on "manifestation of a disease or disorder."⁸⁹ Thus, someone could not be denied

⁸⁶ "FAQs on the Genetic Information Nondiscrimination Act," United States Department of Labor. <http://www.dol.gov/ebsa/faqs/faq-GINA.html>. Accessed March 19, 2014.

⁸⁷ "GINA: The Genetic Information Nondiscrimination Act of 2008 - Information for Researchers and Health Care Professionals," Department of Health and Human Services (HHS). April 6, 2009. <https://www.genome.gov/Pages/PolicyEthics/GeneticDiscrimination/GINAInfoDoc.pdf>. Accessed March 19, 2014.

⁸⁸ "Insurance FAQ," Bassler Research Center for BRCA, University of Pennsylvania. <http://www.penncancer.org/bassler/education-and-support/insurance-faq/>. Accessed April 7, 2014.

⁸⁹ "GINA: The Genetic Information Nondiscrimination Act of 2008," HHS.

health insurance due to a genetic susceptibility to breast cancer, but if he or she actually presents with the cancer, then insurance can be affected.⁹⁰

Other Coverage Issues

In 2006, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) wrote a report addressing problems in the coverage and reimbursement of genetic tests. The SACGHS was created in 2002 to help serve as a "public forum for deliberations on the broad range of human health and societal issues raised by the development and use of genetic tests and, as warranted, to provide advice on these issues."⁹¹ After a year of research and consultations, authors created "nine steps to alleviate the barriers and improve current mechanisms for coverage and reimbursement of genetic tests and services." Details of the nine steps are provided in the report, but Table IX overviews these nine steps.

⁹⁰ "Insurance FAQ," Bassett Research Center for BRCA, University of Pennsylvania.

⁹¹ "Coverage and Reimbursement of Genetic Tests and Services," Secretary's Advisory Committee on Genetics, Health, and Society. February 2006. <http://depts.washington.edu/genpol/docs/SACGHS-ReportDraftApril2005.pdf>. Accessed March 20, 2014.

Table IX | Overview of Nine Steps to Improve Coverage of Genetic Tests (SACGHS)

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- (1) *Evidence-Based Coverage Decision Making.*
 - Encourage “payers to reassess how they make decisions about which tests and services to cover and under what conditions they will reimburse them”
 - (2) *Insurance Market.*
 - Many private insurance companies look to Medicare for guidance because it is the largest provider of health insurance in the US. However, Medicare’s target population is much older than that of private companies and genetic tests are usually “used for preventive, reproductive, or life planning purposes.” Thus, “it may not be appropriate for private health insurance plans to follow Medicare’s lead in making coverage decisions for predictive and predispositional genetic tests and services.”
 - (3) *Medicare Coverage Decision Making Process.*
 - Reduce inconsistencies between Medicare coverage decisions at the national and local level
 - (4) *Medicare Screening Exclusion.*
 - There is a need to reassess Medicare’s screening exclusion, which limits coverage for genetic tests and genetic counseling.
 - (5) *Medicaid Coverage of Genetic Tests and Services.*
 - Genetic tests and genetic counseling are “optional” services under Medicaid, which makes them susceptible to state budget cuts. Furthermore, “variation in Medicaid coverage across States can result in disparate access to genetic tests and services.”
 - (6) *Medicare Clinical Laboratory Fee Schedule.*
 - Some health care providers have argued that “Medicare laboratory fees often do not reflect a genetic test’s true cost.”
 - (7) *Billing and Reimbursement for Genetic Counseling Services.*
 - Genetic counseling is extremely important, but often not reimbursed. CPT billing codes also need updating.
 - (8) *Provider Education and Training.*
 - Health providers should have a working knowledge of genetics and should be adequately trained to use and interpret genetic tests.
 - (9) *Public Awareness.*
 - Increased public awareness has the potential to facilitate coverage, but could also result in the “misinformation and inappropriate demand for genetic tests and services”

Given this report was written in 2006, some of these recommendations are not applicable today. For instance, Current Procedural Terminology (CPT) codes have been updated (see Appendix 6). Code stacking has been eliminated and, now, instead of focusing on the laboratory test method used, CPT codes reflect the purpose of the test (in this case, the gene being analyzed). Physicians and insurers have generally responded favorably to the new coding system. However, it would be helpful to conduct a review, similar to that by Harrison *et al.*, to

study the impact of, and issues in implementation, of the current coding system.⁹² The SACGHS report also calls for increased reimbursement of genetic counseling. Fortunately, as the previous chapter demonstrates, coverage for genetic counseling has also improved - *most* insurance companies now recognize the importance of counseling both pre- and post-testing.

Despite the decrease in relevance of some of these recommendations, the SACGHS report does highlight one of the major remaining issues regarding testing to this day – there are still many inconsistencies in testing and coverage policies. Though research is limited, many other studies have reached this conclusion. For instance, Wang *et al.* found large differences in payer policies between public versus private payers.⁹³ On average, private payers “had more detailed coverage policies for genetic services” than public payers. Whereas Medicare does not cover testing for individuals who have not had cancer, most private payers studied by Wang *et al.* covered *BRCA1/2* testing for all women (with or without cancer), assuming they met the testing criteria.⁹⁴

Graf *et al.* also concluded that there is significant “variation between payers on the number and scope of policies” and that many “challenges remain in ensuring consistency.” However, authors did acknowledge that reimbursement of genetic tests could be expected to vary given “payers have varying coverage philosophies and decision-making strategies.” Nevertheless, additional research should focus on how payers are “approaching genetic testing: what general limits they place on the scope of genetic services, what genetic tests they address and when they reimburse for those tests.”⁹⁵

⁹² Harrison T.A., Doyle D.L., McGowan C., *et al.* (2010). Billing for medical genetics and genetic counseling services: a national survey. *Journal of Genetic Counseling* 19, no. 1: 38–43.

⁹³ Wang, G., Beattie, M.S., Ponce, N.A., Phillips, K.A. (2011). Eligibility criteria in private and public coverage policies for BRCA genetic testing and genetic counseling. *Genetics in Medicine* 13, no. 12: 1045–1050.

⁹⁴ **Note:** Different private payers have different testing criteria. Most roughly follow the NCCN guidelines.

⁹⁵ Graf *et al.*, *Personalized Medicine*.

By conducting a national survey of private health insurers, Schoonmaker *et al.* aimed to examine the factors influencing insurance coverage of *BRCA1/2* testing and of other new genetic technologies.⁹⁶ Schoonmaker concluded that the primary factors influencing coverage of new genetic tests were the "validity of the test" and its "safety and effectiveness." Secondary factors included the cost of the test and "approval of professional groups."⁹⁷ Given Schoonmaker's analysis was completed in 2000, it would be worthwhile to repeat a similar study now.

The SACGHS report also highlighted the need for greater physician education. Many studies have detailed the confusion among physicians regarding who is at risk for a *BRCA1/2* mutation and when testing should occur. For instance, in 2011 Bellcross *et al.* investigated awareness of *BRCA1/2* testing among primary care physicians (PCPs). While the majority (87%) of PCPs were aware of testing, only 19% of PCPs "consistently recognized the family history patterns identified by the USPSTF as appropriate indications for *BRCA* evaluation."⁹⁸ Such results led Bellcross *et al.* to conclude that knowledge of genetic tests and existing recommendations must be improved among care providers, "particularly in this era of increased *BRCA* direct-to-consumer marketing."⁹⁹

Though their research was conducted much earlier (and thus may be less representative of the current state of physician education), Sandhaus *et al.* and Doksum *et al.* reached similar conclusions. Sandhaus *et al.* found that "32% of PCPs did not demonstrate sufficient knowledge of Mendelian inheritance," indicating that physicians could easily misinterpret a patient's risk of

⁹⁶ Schoonmaker, M.M., Bernhardt, B.A., Holtzman, N.A. (2000). Factors influencing health insurers' decisions to cover new genetic technologies. *International Journal of Technology Assessment in Health Care* 16, no. 1: 178–189.

⁹⁷ Schoonmaker *et al.*, *International Journal of Technology Assessment in Health Care*

⁹⁸ Bellcross C.A, Kolor K., Goddard K.A.B., Coates R.J., Reyes M., Khoury M.J. (2011). Awareness and Utilization of *BRCA1/2* Testing Among U.S. Primary Care Physicians. *American J. of Preventive Medicine* 40, no. 1: 61-66.

⁹⁹ Bellcross *et al.*, *American Journal of Preventive Medicine*.

breast cancer.¹⁰⁰ Consequences of risk misinterpretation also spill over to relatives of patients. Overestimates of risk can lead to increased anxiety, inappropriate surveillance, and extreme medical decisions, whereas underestimates of risk are associated with missed opportunities for intervention in high-risk women.¹⁰¹ Doksum *et al.* studied how physicians' knowledge of, and experience ordering, *BRCA1/2* tests varied by discipline. His research team found that oncologists answered the most knowledge questions correctly, followed by OB-GYNs, followed by internists.¹⁰² Doksum *et al.* did not find an association between knowledge of the test, and ordering of the test, suggesting that though knowledge of the test is low, physicians are still discussing it with, and ordering it for, patients.¹⁰³ Both groups of researchers concluded that there is a need for continued medical education (CME) programs for physicians to increase knowledge of genetics, epidemiology, and cumulative risk interpretation.

¹⁰⁰ Sandhaus, L.M., Singer M.E., Dawson N.V., Wiesner G.L. (2001). Reporting *BRCA* test results to primary care physicians. *Genetics in Medicine* 3: 327-334.

¹⁰¹ Sandhaus *et al.*, *Genetics in Medicine*.

¹⁰² Doksum T., Bernhardt B.A., Holtzman N.A. (2003). Does knowledge about the genetics of breast cancer differ between nongeneticist physicians who do or do not discuss or order BRCA testing? *Genetics in Medicine* 5: 99-105.

¹⁰³ Doksum *et al.*, *Genetics in Medicine*.

Summary

Though other organizations have slightly different recommendations, most physicians and insurers follow either the U.S. Preventative Services Task Force's (USPSTF) or the National Comprehensive Cancer Network's (NCCN) guidelines when determining who should get tested for a mutation in *BRCA1/2*. Once a genetic test is ordered, testing companies usually pre-verify with a patient's insurance to determine coverage. Some genetic testing companies, such as Myriad, Ambry, Quest, and LabCorp claim to be contracted with the majority of private (commercial) insurers, Medicare, and some states' Medicaid plans. Others, such as Invitae, only bill some (usually just private) insurers.

Individual insurance companies were chosen for analysis based on the number of covered lives (also referred to as enrollment or membership). Of these 24 insurers, which together represent the largest insurance companies in the country, four insurers did not mention any coverage for *BRCA1/2* testing. Of payers that did cite *BRCA1/2* test coverage, most referenced the USPSTF or the NCCN in their coverage determinations. While there is general consensus on the medical necessity of large rearrangement testing, payer policies still vary in their recognition of genetic counseling.

In addition to these insurance discrepancies for *BRCA1/2* testing, other coverage issues exist. Studies have shown that many patients have a fear of losing health insurance after genetic testing. Additional research should investigate if patients' still have this fear considering the Genetic Information Nondisclosure Act (GINA) was passed in 2008 with the goal of alleviating insurance discrimination concerns. Knowledge among physicians of genetic testing criteria and genetic risk should improve and Medicare and Medicaid's coverage should be clarified and re-assessed.

Policy Recommendations

Overview

- A. Test Costs and Data Sharing Efforts
- B. Ambiguity & Inconsistencies among Public Payers
- C. Variation in Private Insurance
- D. Clarifications in Testing Guidelines
- E. Broader Implications: Technology Access and Research Disparities
- F. Limitations & Future Research
- G. Conclusions

Test Costs and Data Sharing Efforts

The cost of testing for *BRCA1/2* has dropped significantly since the June 2013 Supreme Court case. Myriad's Comprehensive BRACAnalysis® test costs \$4,040 and includes analysis of five large rearrangements in *BRCA1/2*. Counsyl offers a similar test for a quarter of the cost (\$999). Ambry, Quest, LabCorp, Fulgent, Invitae, Ethigen, and GeneDX also all have comprehensive *BRCA1/2* tests for under \$3,000. In addition to having lower testing prices, these newer companies offer a variety of multi-gene panels. Invitae gives care providers and researchers the opportunity to include as many genes as they want on a panel, all for the low price of \$1,500.

These decreases in test costs are significant, especially considering that cost has been shown to be an extremely important factor in genetic test decision making (and even more so for low-income patients). However, there are other aspects of a *BRCA1/2* test that entering companies must adequately address. For instance, entering companies will need to focus on

achieving low rates of variants of unknown significance (VUS).¹⁰⁴ Though difficult to substantiate given they stopped publically reporting their data, Myriad claims to have a VUS rate of 0.6% for *BRCA1* and 1.6% for *BRCA2*.¹⁰⁵ Most of the new testing companies have VUS rates in the 4 to 6% range (Appendix 2).

Though these VUS rates are all *roughly* similar, there is extraordinary value in achieving very low rates. Most patients who receive *BRCA1/2* testing receive the straightforward results that either they have no variation from the wild type (WT) sequence or that a deleterious mutation is present. However, in a “significant minority of results,” variants of unknown significance exist.¹⁰⁶ These mutations are the result of genetic variations (mutations) in, or close by, the *BRCA1/2* genes that are difficult to interpret. It is challenging for researchers to learn the clinical significance of these mutations because not many people have been identified with these rare variations. As more patients are tested, and more health information is gathered about these individuals and their families, the number of VUSs will decrease.

Researchers, physicians, patients, and policy makers should be especially eager to share VUS data (such as Myriad’s) given how significantly patients have been shown to respond to such test results. It is already a difficult decision to undergo *BRCA1/2* testing. However, once having decided to undergo testing, receiving news of a VUS seems to provide more psychological distress for patients than either a ‘positive’ or ‘negative’ test result.¹⁰⁷

¹⁰⁴ **Note:** As was discussed earlier, VUSs are mutations in *BRCA1/2* that researchers do not know the clinical significance of. VUS analysis relies on large data sets, giving Myriad an advantage over entering companies because they have built up a database over the past 15 years of thousands of patients’ DNA.

¹⁰⁵ **Note:** Myriad’s last “major deposit of data” in the public domain (to the Breast Cancer Information Core, maintained by the National Human Genome Research Institute) was in November of 2004. Ever since, the company has “adopted a deliberate policy of retaining data as a trade secret.” **Source:** Cook-Deegan *et al.*, *EJHG*.

¹⁰⁶ Cook-Deegan, R., Conley, J.M., Evans, J.P., Vorhaus, D. (2013). The next controversy in genetic testing: clinical data as trade secrets? *European Journal of Human Genetics* 21: 585-588.

¹⁰⁷ Brédart, A., Kop, J.L., DePauw, A., Caron, O., *et al.*, (2013). Short-term psychological impact of the *BRCA1/2* test result in women with breast cancer according to their perceived probability of genetic predisposition to cancer. *British Journal of Cancer* 108: 1012-1020.

In a recent study, Brédart *et al.* investigated patients' perceived control over cancer risk after a *BRCA1/2* gene test. Researchers hoped to learn about how patients respond to VUSs, as they argued that research has disproportionately focused on the psychological impact of 'positive' or 'negative' *BRCA1/2* test results, rather than on unclassified variants. In Brédart's study, 15% of the women tested received VUS results and, after receiving these results, many of these women felt high levels of anxiety, depression, and intrusion. Authors hypothesized that the effect of receiving a VUS result, over a positive result, on depression "may be related to the lack of clearly defined risk management recommendations, leaving women uncertain about the actions to be taken to cope with increased cancer-related anxiety." Additionally, because some of these women were "not informed of the possibility of receiving a [VUS] result, they only expected to receive either a positive or a negative result," leading them to view their VUS results as "puzzling."¹⁰⁸

Many additional researchers have found that receiving ambiguous test results can trigger a false sense of alarm in women (referred to as the 'genetic-uncertainty-causes-distress-hypothesis' by researcher Joël Vos). However, other research has noted that women *are* making appropriate risk management techniques. Vos' work supports the notion that the "disclosure of a UV-test [VUS] result is associated neither with the feeling of certainty nor with the feeling of uncertainty about the heredity of the cancer." Interestingly, he finds that, though patients correctly recalled a VUS test result as "non-informative," they interpreted this result as "pathogenic at the same time." This perception made patients more likely to undergo prophylactic interventions. Vos hypothesized that choosing to undergo such surgeries could help fulfill patients' "strong wish for certainty and control."¹⁰⁹

¹⁰⁸ Brédart *et al.*, *British Journal of Cancer*.

¹⁰⁹ Vos, J., Otten, W., van Asperen, C., Jansen, A., Menko, F., Tibben, A. (2008). The counsellors' view of an

Though varied in their conclusions, studies on the psychological distress patients endure after a VUS test result demonstrate the significance of decreasing the frequency of receiving such an ambiguous result. There are many possible policy solutions that would help lower VUS rates. Most of these proposals rely on the idea that data sharing is necessary for progressing research and for improving healthcare outcomes. Of course, when data sharing initiatives arise, there are many ethical and legal factors to consider. Complete anonymity is impossible to guarantee when DNA sequence data is involved. ***Thus, policy makers and researchers must first determine what level of risk is acceptable.*** Such a determination would be helpful in guiding de-identification efforts and privacy regulations. Further engagement with the community and additional research on how to fine-tune the informed consent process would also be beneficial. ***Lastly, insurance companies, individual payers, genetic testing registries, national health systems, and granting agencies could all help influence research groups and private companies to upload data into a shared space.*** For instance, payers could recommend the use of companies that engage in data sharing efforts over testing companies that do not.

Ambiguity & Inconsistencies among Public Payers

Aside from the drop in *BRCA1/2* test costs, this analysis has revealed a large amount of inconsistency and ambiguity in payer policies for *BRCA1/2* testing. Yet, there is little explanation for why this variation occurs. One of the major questions that should be addressed going forward is why Medicare's coverage policies exclude individuals who have not had breast or ovarian cancer. One could argue that the sole purpose of the test is to help women, who are at a very high risk of developing breast and ovarian cancer, manage their screening, prevention, and

unclassified variant in *BRCA1/2*: recall, interpretation, and impact on life. *Psycho-Oncology* 17: 822–830.

treatment options so that they will not develop the disease. Thus, refusing to reimburse for the test unless the individual *has* breast and ovarian cancer, makes little sense. In some cases, a patient's family member has been identified as having a *BRCA1/2* mutation. If this patient has Medicare, *even though* there is a known mutation in the family, her genetic test will not be covered. ***Given Medicare officials have not come forward with any kind of explanation for this policy, the Centers for Medicare & Medicaid Services (CMS) should consider removing this screening exclusion as soon as possible.***

Policy makers should also encourage CMS to establish clear, national coverage determinations for *BRCA1/2* testing. Unfortunately, their lack of a specific policy for *BRCA1/2* testing is not a unique problem, but instead spreads to *many* diagnostic, screening and preventive services. In fact, only two National Coverage Determinations (NCDs) exist for any type of genetic test, and there is little explanation for the wide variety in state reimbursement levels (see Appendix 3). Data collected in 2012 by the Kaiser Family Foundation indicate that Medicaid offices from **6 of the 50 states** do not cover *any* "Diagnostic, Screening and Preventive Services."^{110,111,112} Furthermore, **23 of the 50 states** that do cite coverage of these services "do

¹¹⁰ **Note:** Diagnostic, Screening, and Preventive Services are defined, by the Kaiser Foundation (reflecting Federal regulations) as followed: ***Diagnostic Services*** are medical procedures or supplies recommended by a physician or other licensed practitioner of the healing arts, within the scope of his or her practice under state law, to identify the existence, nature, or extent of illness, injury, or other health deviation in an individual. Examples include radiological or laboratory tests indicated by the presence of specific signs or symptoms. ***Screening Services*** are defined as the use of standardized tests given under medical direction in the mass examination of a designated population to detect the existence of one or more particular diseases or health deviations or to identify for more definitive studies individuals suspected of having certain diseases. ***Preventive Services*** are defined as services provided by a physician or other licensed practitioner of the healing arts within the scope of his or her practice under state law to prevent disease, disability, and other health conditions or their progression; to prolong life; and to promote physical and mental health and efficiency.

¹¹¹ "Medicaid Benefits: Diagnostic, Screening and Preventive Services," Kaiser Commission on Medicaid and the Uninsured (KCMU) Medicaid Benefits Database. 2012. <http://kff.org/medicaid/state-indicator/diagnostic-screening-and-preventive-services/>. Accessed April 20, 2014.

¹¹² **Note:** The states that do not offer any diagnostic, screening or preventive services are: Alabama, Arkansas, Kansas, New Mexico, Wisconsin, Wyoming

so in various ways." For example, some states only cover certain immunizations or have specified age criteria for preventive services.¹¹³

If CMS is unwilling to establish a NCD for *BRCA1/2* testing, then state policies should at least be made readily accessible to the public. According to section 1903(i)(7) of the Social Security Act, "State Medicaid programs are prohibited from paying for lab tests that exceed the Medicare payment amount."¹¹⁴ *Medicaid's dependence on Medicare's pricing levels should be clarified and, if such dependence exists, then it is even more important for Medicare officials to make clearer and readily accessibly coverage policies.*

A recent report by CMS titled "Payments for Laboratory Test: Comparing Medicare, State Medicaid, and Federal Employees Health Benefits Programs" also testifies to the little information available regarding what genetic tests Medicaid covers. CMS undertook this study, in which surveys were sent to State Medicaid and Federal Employee Health Benefit programs, to learn more about genetic laboratory test coverage and to receive feedback on establishing payment rates.¹¹⁵ In regards to State Medicaid coverage, CMS found that "officials from all but one State [New Mexico] described some level of coverage for genetic tests." However, "officials from 17 States stated that their States have no specific policy addressing them." The remaining states used a variety of factors to influence coverage decisions. For instance, Arizona's Medicaid contractor does not cover genetic testing if it is used "to determine whether a

¹¹³ **Note:** The states that cite various exclusions to their coverage for diagnostic, screening or preventive services are: Alaska, Arizona, Colorado, DC, Florida, Hawaii, Idaho, Illinois, Iowa, Kentucky, Louisiana, Maine, Michigan, Nebraska, Nevada, New Jersey, Ohio, Oklahoma, Pennsylvania, South Carolina, Texas, Utah, Virginia, Washington

¹¹⁴ "Memorandum Report: Coverage and Payment for Genetic Laboratory Tests, OEI-07-11-000 11," Department of Health and Human Services. June 12, 2013. <https://oig.hhs.gov/oei/reports/oei-07-11-00011.pdf>. Accessed March 22, 2014.

¹¹⁵ "Memorandum Report: Coverage and Payment for Genetic Laboratory Tests, OEI-07-11-000 11," DHHS

member carries a hereditary predisposition to cancer or other diseases."¹¹⁶ When officials from State Medicaid programs were asked to provide payment rates for genetic tests (including *BRCA1/2* analysis), only 8 state Medicaid programs were able to provide specific payment rates. These payment rates varied widely, "\$1,000 in Pennsylvania to nearly \$4,500 in Iowa." See Appendix 3B for the prices of the remaining states.¹¹⁷ ***Ideally, CMS should establish a national coverage determination for BRCA1/2 testing. However, if they are unable to, then policy makers should at least try to harmonize state coverage policies so that there are not such great disparities in test cost.*** According to Kaiser estimates, in the years 2010 and 2012 (respectively) there were over 66 million total Medicaid enrollees and 49 million Medicare enrollees. Considering the immense number of people affected, revisions to Medicaid and Medicare *BRCA1/2* testing policies should be given high priority.^{118,119}

Variation in Private Insurance

Another downside of Medicare's policy is that it sets a poor example for private insurance companies. As the 2006 SACGHS report highlights, Medicare has a unique place in the insurance market because other, smaller, private insurance companies look to it as a model.¹²⁰ Yet, Medicare's target population is much older than that of the general population. Thus, genetic testing, which is predominately used in a younger population, is not an area in

¹¹⁶ "Chapter 300: Medical Policy for AHCCCS Covered Services," AHCCCS Medical Policy Manual (AMPM), Arizona's Medicaid Agency. March 1, 2011.

<http://www.azahcccs.gov/shared/Downloads/MedicalPolicyManual/Chap300.pdf>. Accessed April 7, 2014.

¹¹⁷ "Memorandum Report," Department of Health and Human Services. June

¹¹⁸ "Total Medicaid Enrollment, FY2010," Kaiser Commission on Medicaid and the Uninsured and Urban Institute. 2010. <http://kff.org/medicaid/state-indicator/total-medicare-enrollment/>. Accessed April 20, 2014.

¹¹⁹ "Total Number of Medicare Beneficiaries," Kaiser Family Foundation. 2012. <http://kff.org/medicare/state-indicator/total-medicare-beneficiaries/>. Accessed April 20, 2014.

¹²⁰ "Coverage and Reimbursement of Genetic Tests and Services," Secretary's Advisory Committee on Genetics, Health, and Society. February 2006. <http://depts.washington.edu/genpol/docs/SACGHS-ReportDraftApril2005.pdf>. Accessed March 20, 2014.

which Medicare would be expected to have an exemplary plan. Therefore, SACGHS authors argue that private companies should not necessarily look to Medicare for guidance on how to form their own private policies.

Fortunately, the private payers analyzed here have not adopted Medicare's coverage exclusion. Nevertheless, there is still some variation among private payer policies. First, there are still disparities in recognition and coverage of the test. For instance, Centene, a large insurer with over 2.7 million members, does not have a national *BRCA1/2* coverage policy available online and the insurer hardly mentions covering any genetic tests.¹²¹ ***There should not be such differential recognition of BRCA1/2 testing among insurers, especially among some of the nation's largest payers.***

As was recommended for public payers, large insurance companies should also be encouraged to develop comprehensive national policies for BRCA1/2 testing. BlueCross BlueShield is a national association with 37 different state and regional companies within the national group. To determine coverage policies, patients and care providers must contact their local offices. If patients are trying to determine their particular coverage policy for genetic testing, then they have already been identified as being at high-risk for a mutation. This is a stressful point in these patients' lives and it should not be this difficult to track down a coverage policy. Establishing national coverage policies would, hopefully, reduce the confusion among payers and patients and aid in harmonization.

Variation was also found in coverage for genetic counseling. Whereas for most companies genetic counseling is a required (and covered) service both pre-and post-testing, for a few it is only recommended. Cigna has been especially vocal about the importance of genetic

¹²¹ "2013 Annual Review: Reaching for the Summit," Centene Corporation.
Centene: <http://www.centene.com/wp-content/uploads/2014/03/AnnualReport-2013.pdf>. Accessed March 22, 2014.

counseling - the insurer even stipulates that patients' genetic counselors have certain credentials, illustrating the company's commitment to ensuring that patients receive proper guidance and education throughout the testing process. Alternatively, HealthNew England only requires genetic counseling pre-testing, HealthNet considers counseling to be the responsibility of the care provider, and United Healthcare only strongly recommends counseling. ***Given the well-established merits of genetic counseling, payers should (uniformly) require it both pre-and post-testing.***

Private payers also differ in the specificity of their coverage policies for *BRCA1/2*. For instance, some policies imply that testing must be completed with Myriad, while others do not specify which laboratory must be used. It is not clear how deliberate these requirements are. For instance, Aetna necessitates the use of Myriad within the "BRCA Test Authorization Workflow" section of their medical coverage policy. Within this policy, Myriad is listed as the only testing site. The policy states that a "'Prior Authorization' request for BRCA Molecular Testing is to be sent along with the TRF form from Myriad Genetics." Thus, given these particular authorization requirements, only requests that are reported through Myriad will be deemed eligible. HealthNet, and other payers analyzed, also specify that Myriad's BRCAAnalysis Large Rearrangement Test (BART)[®] be used for dup/del analysis.

It is possible that these two insurance companies view there to be too much risk in partnering with newer companies. After all, though many disapprove of Myriad's business practices, most researchers and physicians agree that Myriad runs a well-respected and high quality laboratory. However, the most likely reason that some payers have specified the use of Myriad for testing is that these payers have simply not responded to the market change yet. For the past 15 years, Myriad has been the only company to offer *BRCA1/2* testing. Thus, when

insurance policies dictate the use of Myriad for testing, these policies could require Myriad simply because there have been no other options for so long. Some of the insurance policies analyzed were internally reviewed more recently than others, which would make them more likely to reflect the current consensus on what tests should and should not be reimbursed. Perhaps, in a year or two, especially after these new testing companies are more established, coverage policies will be made broader.

There is general consensus among private payers regarding reimbursement for rearrangement (del/dup) analysis and the small variation in coverage that does exist is most likely attributable to timing.¹²² Myriad argues that because the NCCN only recently added large rearrangement testing to be included with general *BRCA1/2* sequencing, “many insurance companies have not yet adopted it as a covered test.”¹²³ While some payers do not mention large rearrangement in their coverage policies, only one payer (Aetna) explicitly declared rearrangement analysis as *not* medically necessary. Aetna’s policy was scheduled to be reviewed in February of 2014, so it is possible a new policy will be released soon that covers rearrangement analysis.¹²⁴

Another one of the few areas of harmonization among private payer policies is that no insurance policy was found that covers multi-gene panels. However, there is also a noticeable trend among testing companies to include these larger panels in their test offerings. Almost all of the new testing companies described in this analysis have developed multi-gene panels that look for mutations in *BRCA1/2*, as well as for mutations in many more genes. As Ethigen’s

¹²² **Note:** To clarify, there are several types of *BRCA1/2* testing. There are point mutation tests, full gene sequencing tests, and also large rearrangement (duplication and deletion) analysis tests. Rearrangement analysis is now recommended by the NCCN and most private insurers also cover this additional method of testing. Aetna is the only policy that was analyzed here that did not consider dup/del testing to be medically necessary.

¹²³ "Understanding BART," Myriad Genetics. June 2012. <http://d1izdzz43r5o67.cloudfront.net/brac/BART-PT-Aid.pdf>. Accessed March 22, 2014.

¹²⁴ **Note:** As of March 20, 2014, no revised policy was found.

website states, improved sequencing technologies have allowed for a “breadth of testing not previously possible, at little to no additional cost ... providing us with a much more detailed analysis of cancer risk than has historically been available.”¹²⁵ Though testing companies appear to be quite optimistic about these larger panels, no payer policies were found that acknowledge the medical utility of such tests.

Clarifications in Testing Guidelines

In addition to the variety of insurance policies for *BRCA1/2* testing, there are also many guidelines for who should get tested in the first place. As discussed in Chapter 3, the NCCN and USPSTF’s guidelines are the most commonly referenced. The NCCN lays out specific guidelines, and the USPSTF recommends that patients first use a screening tool, and then (if positive), patients should seek genetic counseling to determine if they should proceed with testing. Many screening tools exist (see Appendix 6), and the USPSTF does not recommend one over the others.

The USPSTF recommendations do not include individuals who have already had cancer. This discrepancy is explained by the USPSTF’s role as a *preventative services* task force; the agency states that screening for cancer patients is not within its scope. Given the organization’s focus, such an exclusion makes sense. However, unfortunately, this exclusion complicates the recommendation and reimbursement process because many insurance companies follow USPSTF guidelines. Additionally, there is a glaring contradiction between the USPSTF’s and Medicare’s guidelines. Medicare will not cover testing unless the individual has had breast cancer. So, by the USPSTF recommendations, individuals should seek genetic testing and

¹²⁵ “Expanded Cancer Panel,” Ethigen. <http://ethigen.net/index.php/services/expanded-cancer-panel>. Accessed March 20, 2014.

counseling before developing breast cancer, but it is only after they have manifested with the disease that will Medicare pay for the test.

Going forward, it would be helpful to receive clarity on why so many different recommendations exist. In addition to the NCCN and the USPSTF, many other organizations and societies have developed their own recommendations governing who should get testing for a *BRCA1/2* mutation. These include: The American Congress of Obstetricians and Gynecologists,¹²⁶ The American Society of Clinical Oncology,¹²⁷ The National Society of Genetic Counselors,¹²⁸ and The Society of Gynecologic Oncologists.¹²⁹ The presence of so many different guidelines leads one to wonder how there could be such a diverse set of opinions on an issue that should be evidence-based.

Further clarification is also needed regarding how physicians or insurers choose which guidelines to follow, those by the USPSTF or the NCCN. Many of the private payers included in this paper cite that they follow USPSTF criteria for *BRCA1/2* testing. However, when the specific policies are analyzed, the guidelines resemble NCCN criteria rather than USPSTF guidelines. This technicality may not be extremely significant because one would assume that patients and physicians reading the policies would just follow the actual guidelines. However, it is important to be accurate and consistent. ***All payers should clearly state which***

¹²⁶ American College of Obstetricians and Gynecologists. (2009). ACOG Practice Bulletin No. 103: hereditary breast and ovarian cancer syndrome. *Obstetrics and Gynecology* 113, no. 4, 957.

¹²⁷ Robson, M. E., Storm, C. D., Weitzel, J., Wollins, D. S., & Offit, K. (2010). American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. *Journal of Clinical Oncology* 28, no. 5, 893-901.

¹²⁸ Berliner, J. L., Fay, A. M., Cummings, S. A., Burnett, B., & Tillmanns, T. (2013). NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. *Journal of Genetic Counseling* 22, no. 2, 155-163.

¹²⁹ Lancaster, J. M., Powell, C. B., Kauff, N. D., Cass, I., Chen, L. M., Lu, K. H., ... & Herzog, T. J. (2007). Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecologic Oncology* 107, no. 2, 159-162.

recommendations they follow when determining BRCA1/2 coverage, and the recommendations they cite should be consistent with the ones they list later on in the policy.

Broader Implications: Technology Access and Research Disparities

When analyzing new technology and diagnostic tools, especially tools with a significant impact on human health, it is necessary to consider the social implications of such research. Access to, and equitable distribution of, technology is one of the largest areas of concern in science, technology, and society research. Generally speaking, the Supreme Court case has been acclaimed as a ‘win’ for patients because it opened up the market for new testing companies to enter. Breaking Myriad’s monopoly then drove down the test price, theoretically increasing access. Though increased access to new technology should not automatically be viewed as a positive change, in this instance, greater access to *BRCA1/2* testing is a positive social goal *as long as* the testing is properly administered. (Meaning that the test should only be given to those who could stand to benefit from its results, which is a *very* small percentage of the general population).

Despite the decrease in test cost, there are still many access issues related to *BRCA1/2* testing. For example, the significant variation in insurance coverage for the test has been discussed in this paper. Hall and Olopade have written an extensive review of other disparities in genetic testing, highlighting the inequality of *BRCA1/2* testing in their analysis.¹³⁰ Specifically, Hall and Olopade discuss how the majority of research on *BRCA1/2* has been conducted on Western, European populations. Low testing volumes and small data sets

¹³⁰ Hall, M.J. & Olopade, O.I. (2006). Disparities in Genetic Testing: Thinking Outside the BRCA Box. *Journal of Clinical Oncology* 24, no. 14: 2197-2203.

compromise the interpretation of genetic variants in minority populations – explaining why there are disproportionately high variants of unknown significance (VUS) rates among African Americans. Unfortunately, despite having a lower incidence of breast cancer, African American women in the United States actually “have a higher mortality rate from breast cancer than white counterparts.”^{131,132} Hall and Olopade argue that “differential access to and utilization of genetic counseling and cancer predisposition testing among underserved racial and ethnic minorities compared with the white population has led to growing health care disparities in clinical cancer genetics.”¹³³ Similarly, Armstrong *et al.* found that, “even after adjusting for cancer risk, women who sought *BRCA1/2* testing were significantly less likely to be African-American.”¹³⁴ Though Hall and Olopade acknowledge that the NIH has many initiatives to “increase minority recruitment into clinical research,” they maintain that “as long as testing remains limited to Western, predominantly white populations, the preventive potential of genetic testing to reduce cancer incidence worldwide will not be realized.”¹³⁵

In addition to efforts to achieve more equal access to improvements in genetic testing, broader research on the ethical consequences of genetic testing and research should be encouraged. Fortunately, this research has been very well supported by the Federal government. When the Human Genome Project began in the 1990s, the National Human Genome Research Institute (NHGRI) established an Ethical, Legal and Social Implications (ELSI) Research Program to “foster basic and applied research on the ethical, legal and social

¹³¹ Hall & Olopade, *Journal of Clinical Oncology*.

¹³² Chu, K.C., Lamar, C.A., Freeman, H.P. (2003) Racial disparities in breast carcinoma survival rates: separating factors that affect diagnosis from factors that affect treatment. *Cancer* 97, no. 11: 2853-60.

¹³³ Hall & Olopade, *Journal of Clinical Oncology*.

¹³⁴ Armstrong, K., Weber, B., Stopfer, J., Calzone, K., Putt, M., Coyne, J., Schwartz, J.S. (2003) Early use of clinical *BRCA1/2* testing: associations with race and breast cancer risk. *American Journal of Medical Genetics* 117A, no. 2: 154-60.

¹³⁵ Hall & Olopade, *Journal of Clinical Oncology*.

implications of genetic and genomic research for individuals, families and communities.”¹³⁶

This research program “funds and manages studies, and supports workshops, research consortia and policy conferences related to these topics.”¹³⁷ Another idea, advocated by Professor

Langdon Winner, is to incorporate public deliberations into the research process early on.¹³⁸

Winner argues that such public participation is a great way to integrate research on social and ethical concerns with research and development (R&D) efforts.¹³⁹

¹³⁶ "The Ethical, Legal and Social Implications (ELSI) Research Program," The National Human Genome Research Institute (NHGRI). February 14, 2014. <http://www.genome.gov/elsi/>. Accessed March 20, 2014.

¹³⁷ "The Ethical, Legal and Social Implications (ELSI) Research Program," NHGRI.

¹³⁸ **Note:** In his testimony to the House’s Committee on Science, Professor Langdon Winner was specifically discussing nanotechnology. However, many parallels can be drawn to molecular diagnostic tools.

¹³⁹ "Langdon Winner's testimony to the Committee on Science of the U.S. House of Representatives on The Societal Implications of Nanotechnology," The Loka Institute. April 9, 2003. http://www.loka.org/Documents/Winner_nano_testimony.pdf. Accessed March 20, 2014.

Limitations & Future Research

One of the main improvements to this research would be to expand its scope. Only 24 insurance company policies were reviewed in this analysis. These insurance companies are among the largest payers in the country.¹⁴⁰ Nevertheless, conclusions could be strengthened by a broader analysis.

In future research, it would be interesting to look at any effects the Affordable Care Act (ACA) may have on genetic test reimbursement. Given the timing of the ACA's implementation, it is too early to see its effects on genetic test reimbursement. Future research should also examine the *consequences* of this variability in payer policies for patients, providers, and society at large. For instance, though there appears to be a significant amount of ambiguity in coverage policies, it is possible these discrepancies have little effect on clinical practice. Once a more thorough understanding of coverage policies for *BRCA1/2* is reached, it would also be helpful to expand such an analysis to genetic testing coverage in general. There is little research on payer policies for genetic tests and a comprehensive analysis on the current state of affairs may be helpful for policy makers and care providers. This work should aim to learn how these payer policies are influencing access to *BRCA1/2* testing and what kinds of policy tools would aid in equitable use of these diagnostic tools.

¹⁴⁰ **Note:** Wang *et al.* estimated that his analysis (of only a few insurance plans) included over “50 million privately insured lives, 1.5 million lives under a local Medicare carrier, and 18.7 million lives under four state Medicaid programs.” This report analyzed many more private insurance companies, so 50 million would be an extremely conservative estimate.

Conclusions

This paper has provided an overview of the genetic testing landscape for *BRCA1/2* following the June 2013 Myriad Supreme Court case. Since the case, many new genetic testing companies have entered the market and the cost of *BRCA1/2* testing has decreased significantly. However, many access issues remain. To survey these access issues, this paper examined current payment methods, analyzed variation among testing guidelines and payers, and suggested ways in which access to *BRCA1/2* testing could improve. To this end, the author has provided the following policy recommendations:

- Maximize the leverage of national health agencies and payers to encourage the safe and secure sharing of VUS data.
- Uniformly require all payers to cover genetic counseling, both pre-and post-testing.
- Revisit the major genetic testing recommendations (NCCN, USPSTF) and consider creating one uniform 'testing criteria.'
- Increase transparency from insurers, especially public payers
 - ⇒ Encourage the Centers of Medicaid and Medicare (CMS) to create a National Coverage Determination (NCD) for *BRCA1/2* testing.
 - If unable to develop a NCD, then local offices must develop clear coverage policies and make such policies apparent on state websites.
 - ⇒ Remove Medicare's screening exclusion. Provided that women meet the 'testing criteria,' they should receive coverage for *BRCA1/2* testing even if they have not been diagnosed with breast cancer.

This paper has demonstrated that guidelines for, and insurance coverage of, *BRCA1/2* vary widely. Given genetic testing for *BRCA1/2* is a relatively new market, some discrepancies are expected to exist. However, policy makers and payers must still develop clear, concise, and thoughtful testing guidelines and reimbursement policies. The need to properly address these policies is heightened by the test's position to serve as a model for the commercialization of genetic tests going forward.

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Appendix 1

Abbreviations

ABMD	American Board of Medical Genetics
ABN	Advance Beneficiary Notice of Noncoverage
ACA	Affordable Care Act
ACGC	American Board of Genetic Counseling
ACLU	American Civil Liberties Union
ACMG	American College of Medical Genetics
ACOG	American College of Obstetricians and Gynecologists
AMP	Association for Molecular Pathology
BRCA1/2	Breast Cancer Genes 1 and 2
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
Del/Dup	Deletion and Duplication Analysis
HBOC	Hereditary Breast and Ovarian Cancer syndrome
HMO	Health Maintenance Organizations
IP	Intellectual Property
LCD	Local Coverage Determination
LOA	Letter of Agreement
LOMN	Letter of Medical Necessity
NCD	National Coverage Determination
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NGS	Next Generation Sequencing (or Next-Gen)
NIH	National Institutes of Health
NHGRI	National Human Genome Research Institute
NLA	National Limit Amounts
PCP	Primary Care Physician
USPTF	United States Preventative Task Force
USPTO	United States Patent and Trademark Office
SEER	Surveillance, Epidemiology, and End Results
TRF	Test Requisition Form

Appendix 2

BRCA1/2 Testing Companies

Note to Reader: This Appendix provides a description of each of the companies that now offer *BRCA1/2* testing. Short descriptions of these tests, their costs, and turn around times are provided in Chapter 3: A Changing Genetic Landscape. Thus, the purpose of this Appendix is to elaborate upon the information presented in Chapter 3. For example, each company's sequencing technology is listed, as well as all of the genes in their multigene panels (if they offer multigene panels).

Myriad Genetics

See discussion of Myriad as a company in Chapter 2: Historical & Scientific Background.^{141,142}

Genes on the upcoming MyRisk® test: BRCA1, BRCA2, MLH1, MLH2, PMS2, EPCAM, APC, MUTYH, CDKN2A, PALB2, STX11, PTEN, TP53, CDH1, BMPR1A, SMAD4, ATM, BARD1, BRIP1, CDK4, CHEK2, NBN, RAD51C, RAD51D

UCLA Diagnostic Molecular Pathology Laboratory

UCLA has offered *BRCA1/2* sequencing for the three Ashkenazi Jewish founder mutations since May 2012.¹⁴³ A few academic labs were given rights by Myriad to test for these three mutations, which explains why UCLA has been able to offer this test since 2012. According to their website, all other samples (for full gene sequencing) are sent to Myriad for analysis. UCLA's Ashkenazi panel relies on Sanger sequencing.

Ambry Genetics

The same day that the Supreme Court released its decision (June 13, 2013), Ambry Genetics, a clinical genetic testing company based out of Aliso Viejo, California, announced their entrance into the *BRCA1/2* testing market. Ambry was founded in 2001 and now has a test menu of over 300 different genes. Many of these genes (75 of ~300 genes) are involved in the development of hereditary cancer, which establishes Ambry as one of the largest cancer testing companies in North America.¹⁴⁴ Ambry was also one of the first labs to introduce next generation sequencing (NGS) technology into the clinical setting and to offer multi-gene hereditary cancer panels.

¹⁴¹ **Note:** Myriad uses multiplexed quantitative PCR and microarray-CGH analysis for seq. and dup/del analysis.

¹⁴² **Note:** For more information regarding Myriad's VUS rate and classification programs, visit: "MyVision: Myriad Variant Classification Program," Myriad Genetics. 2013. <https://s3.amazonaws.com/myriad-library/brochures/Myriad+VCP+Brochure.pdf>. Accessed April 21, 2014.

¹⁴³ **Note:** UCLA may have started to offer this testing earlier than May 2012; however, this is the date they appeared on the National Genetic Testing Registry (GTR). No information was available online regarding their start date.

¹⁴⁴ "BRCA1/BRCA2 Test Logistics," Ambry Genetics.

http://www.ambrygen.com/sites/default/files/pdfs/forms/most_updated/cancer/BRCA_Test_Information_sheet_1.14.pdf. Accessed February 7, 2013.

Ambry offers many hereditary cancer panels, which vary in their level of analysis.¹⁴⁵ For instance, Ambry's BreastNext® analyzes 18 genes, while the larger CancerNext® panel analyzes 28 genes. Though Ambry offered a breast and ovarian cancer panel before June 2013 (without *BRCA1/2* included), the Supreme Court case allowed the company to add *BRCA1/2* (the most important genes for hereditary breast and ovarian cancer) into the panel. Ambry uses NGS or Sanger sequencing for their multi-gene panels and multiplex ligation-dependent probe amplification (MLPA) for dup/del analysis. All mutations and VUS's are confirmed through Sanger sequencing.

Genes on the BRCAplus® test: BRCA1, BRCA2, CDH1, PTEN, STK11 and TP53

Genes on the BreastNext® test: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11 and TP53

Genes on the OvaNext® test: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, and TP53.

Genes on the CancerNext® test: APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11, and TP53

The University of Washington

The University of Washington announced on June 14, 2013 that they would add the *BRCA1/2* genes to their BROCA testing panels.¹⁴⁶ The Department of Laboratory Medicine at the University of Washington now offers five different *BRCA1/2* tests: the BROCA cancer risk panel, sequencing and rearrangement analysis, an Ashkenazi Jewish panel, single gene testing, and known familial mutation testing. These tests are performed on an Illumina HiSeq2000.

Note: The clinical lab and the King lab are separate entities. The King Lab offers free BROCA testing for families who meet its testing criteria, so this free test is only for subjects in King's genetic research studies. The clinical lab at UW provides commercial BROCA panel testing for patients who are referred by their providers - "specimens come from all over the country and from some international clients."

Genes on the BROCA Cancer Risk Panel: AKT1, APC, ATM, ATR, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK1, CHEK2, CTNNA1, FAM175A (Abraxas), GALNT12, GEN1, GREM1, HOXB13, MEN1, MLH1, MRE11A, MSH2 (+EPCAM), MSH6, MUTYH, NBN, PALB2, PIK3CA, PPM1D, PMS2, POLD1, POLE, PRSS1, PTEN, RAD50, RAD51, RAD51C, RAD51D, RET, SDHB, SDHC, SDHD, SMAD4, STK11, TP53, TP53BP1, VHL, and XRCC2

¹⁴⁵ "2014 CPT Codes and Client Pricing," Ambry Genetics. January 17, 2014. http://www.ambrygen.com/sites/default/files/Master_Pricelist_testCode_1_17_2014_0.pdf. Accessed February 6, 2014.

¹⁴⁶ "Genetics and Solid Tumor Diagnostic Testing: BRCA1 and BRCA2 added to BROCA Cancer Risk Panel," Department of Laboratory Medicine, University of Washington Medical Center. <http://depts.washington.edu/labweb/Divisions/MolDiag/MolDiagGen/index.htm>. Accessed April 18, 2013.

Ethigen

Ethigen is a genetic testing company based out of Salt Lake City, Utah that emphasizes the importance of having a certified genetic counselor involved in the genetic testing process. The company began with a focus on genetic testing for hereditary breast and ovarian cancer, Lynch syndrome, and polyposis syndromes, but hopes to expand their scope into other hereditary conditions.¹⁴⁷ On June 19, 2013, Ethigen announced the addition of *BRCA1/2* sequencing and rearrangement analysis to their list of services. *BRCA1/2* sequencing is offered as an individual test, or as part of a larger hereditary cancer panel.¹⁴⁸ Illumina NGS platforms are used.

Genes on the Expanded Cancer Panel: BRCA1/2, MLH1, MSH2, MSH6, APC, MUTYH (MYH), PTEN, TP53, CDK4, STK11, SMAD4, BMPR1A, CDH1, MET, FH, FLCN, PDGFRA, and KIT. Rearrangements are also included for BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EpCAM, APC, and MYH.

Fulgent Therapeutics, LLC

Fulgent Therapeutics, LLC is pharmaceutical company based in Temple City, CA that specializes in "developing and commercializing innovative cancer therapeutics and companion diagnostics."¹⁴⁹ Founded in 2011, Fulgent currently offers single gene and multi-gene panels for breast, lung, ovarian, colon, and pancreatic cancer. In June of 2013, Fulgent added *BRCA1/2* to its hereditary cancer panels and established a tiered pricing structure for institutional versus third party billing.¹⁵⁰ Fulgent uses an Illumina MiSeq® for its multi-gene panels and now for *BRCA1/2* analysis as well. Mutations are confirmed with Sanger sequencing, or sometimes with an Ion Proton® Life Technologies machine. MLPA is used for dup/del analysis. If a VUS result is given, Fulgent offers free of charge sequencing for any additional family members.

Genes on the Breast Ovarian Cancer NGS Panel: ATM, ATR, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, CTNNB1, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51, RAD51C, RAD51D, STK11, TP53, XRCC3

Genes on the Hereditary Cancer Panel (HCP): APC, ATM, ATR, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, EXO1, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, GALNT12, MEN1, MLH1, MRE11A, MSH2, MSH3, MSH6, MUTYH, NBN, PALB2, PDGFRA, PMS1, PMS2, PRSS1, PTCH1, PTEN, RAD50, RAD51, RAD51C, RAD51D, RBBP8, RET, SMAD4, STK11, TP53, VHL, XRCC3

¹⁴⁷ "About Us," Ethigen. 2014. <http://ethigen.net/>. Accessed February 19, 2014.

¹⁴⁸ "Ethigen Launches Next Generation (NGS) BRCA Testing With Expanded Hereditary Cancer Panel," PR Web. June 19, 2013. <http://www.prweb.com/releases/Ethigen/BRCA/prweb10843704.htm>. Accessed February 19, 2014.

¹⁴⁹ "About Fulgent Therapeutics," Fulgent Therapeutics. 2012. <http://fulgent-therapeutics.com/our-company/about-us/>. Accessed February 19, 2014.

¹⁵⁰ "Fulgent Therapeutics Announces Their Comprehensive Hereditary Cancer Test Including BRCA1 and BRCA2 Analysis," PR Web. June 14, 2014. <http://www.prweb.com/releases/2013/6/prweb10833921.htm>. Accessed February 19, 2014.

GeneDX

GeneDX is a genetic testing company, based out of Gaithersburg, MD, that specializes in testing for rare hereditary disorders. The company was founded in 2000 and is a subsidiary of Bio-Reference Laboratories, Inc., which is the fourth largest publicly traded clinical laboratory in the U.S.¹⁵¹ As part of GeneDX's mission to "make clinical testing available to people with rare genetic conditions and their families," the company offers a variety of *BRCA1/2* test options.¹⁵² GeneDX also offers many multi-gene panels, such as a breast and ovarian cancer panel that evaluates 26 genes and a larger OncoGene panel that analyzes 35 genes. GeneDX's cancer panels use an Illumina MiSeq®. If a VUS result is given, GeneDX will test additional family members for free.¹⁵³

Genes on the OncoGeneDx Comprehensive Cancer Panel: APC, ATM, AXIN2, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FAM175A, FANCC, HOXB13, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, PALB2, PALLD, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, XRCC2

Genes on the Breast Cancer High Risk Panel: BRCA1, BRCA2, CHH1, PTEN, STK11, TP53

Genes on the Breast/Ovarian Cancer Panel: ATM, BARD1, BLM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FAM175, FANCC, HOXB13, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2

Quest Diagnostics

Quest Diagnostics was another one of the most vocal companies to declare entrance into the *BRCA1/2* testing market. In contrast to companies such as Ambry, Fulgent, and Ethigen, Quest is one of the largest diagnostic and laboratory information companies in the US. With a workforce of approximately 41,000 employees, Quest's diagnostic tests serve 50% of U.S. physicians and 30% of American adults.¹⁵⁴ When Quest released its test in October of 2013, they became the "largest clinical laboratory company to introduce a BRCA test since the U.S. Supreme Court's human gene patent ruling in June."¹⁵⁵ The company's test, called *BRCAVantage*®, uses next-generation sequencing methods and multiplex ligand-dependent probe amplification (MLPA) to detect deletions, duplications, and rearrangements. Patients and care providers can order four different versions of the test, each of which vary in level of analysis and cost.

¹⁵¹ "GeneDx to Launch Comprehensive Breast Cancer Genetic Test," GeneDX. June 13, 2013.

<http://www.genedx.com/genedx-to-launch-comprehensive-breast-cancer-genetic-test/>. Accessed February 9, 2014.

¹⁵² "About," GeneDX. <http://www.genedx.com/about-genedx/>. Accessed February 9, 2014.

¹⁵³ **Note:** GeneDX's VUS rate is expected to change by May 2014. Readers can call GeneDX's main number and ask to speak with a customer service genetic counselor for an updated number.

¹⁵⁴ "Fact Sheet," Quest Diagnostics. <http://www.questdiagnostics.com/home/about/facts>. Accessed February 6, 2014.

¹⁵⁵ "Quest Diagnostics Introduces BRCAVantage™, Broadly Expanding Patient Access to BRCA Genetic Testing for Inherited Breast and Ovarian Cancers," Quest Diagnostics. October 15, 2013.

<http://newsroom.questdiagnostics.com/2013-10-15-Quest-Diagnostics-Introduces-BRCAVantage-Broadly-Expanding-Patient-Access-to-BRCA-Genetic-Testing-for-Inherited-Breast-and-Ovarian-Cancers>. Accessed February 6, 2014.

University of Chicago

The University of Chicago Genetic Services Lab began to offer *BRCA1/2* testing in November of 2013. The lab focuses on "testing of rare orphan genetic diseases for which testing is not readily available elsewhere."¹⁵⁶ Chicago offers two different *BRCA1/2* tests - familial mutation sequence analysis testing or founder mutation testing. These tests are \$415 and \$475, respectively. Though the lab does not specifically market a large rearrangement test for *BRCA1/2*, if individuals want dup/del analysis, they can order custom analysis for \$650. The lab works "works closely with research groups to develop new tests for genetic disorders as their genetic bases become identified," and all tests are available commercially.¹⁵⁷ Sequencing is done with Sanger sequencing.

LabCorp®

On December 2, 2013, Laboratory Corporation of America® Holdings (LabCorp®) announced they would offer *BRCA1/2* testing.¹⁵⁸ Based out of Burlington, NC, LabCorp® is an extremely large laboratory network that offers "more than 4,000 tests ranging from routine blood analyses to reproductive genetics to companion diagnostics."¹⁵⁹ LabCorp uses Sanger sequencing for sequencing and a multiplex ligation-dependent probe amplification (MLPA) platform for dup/del analysis.

Invitae

Invitae is a genetic testing company, specializing in diagnostics for hereditary disorders, based in San Francisco, CA. The company has the mission of "reinvent[ing] genetic testing by making it more affordable and accessible than ever before." The company announced in early December that they would offer *BRCA1/2* testing and multi-gene panels including *BRCA1/2* for a flat price of \$1,500.¹⁶⁰ Invitae offers full gene sequencing (using NGS methods) for 218 genes and their associated disorders. However, the most unique aspect of Invitae is that the company allows for personalized panels. Patients can work with their physician to compose a gene panel that includes the one to 218 genes that Invitae offers. All numbers and combinations of genes, disorders, and panels are offered for the price of \$1,500.¹⁶¹

¹⁵⁶ "About Us," University of Chicago Genetic Services Laboratory. <http://dnatesting.uchicago.edu/about-us/overview>. Accessed April 20, 2014.

¹⁵⁷ "About Us," University of Chicago Genetic Services Laboratory.

¹⁵⁸ "LabCorp to Offer BRCA Assure Breast Cancer Mutation Tests," Laboratory Corporation of America® Holdings. December 2, 2013.

<https://www.labcorp.com/wps/wcm/connect/IntGeneticsLib/integratedgenetics/resources/pdfs/other/brcassure+press+release>. Accessed February 11, 2014.

¹⁵⁹ "About LabCorp," Laboratory Corporation of America® Holdings.

https://www.labcorp.com/wps/portal/!ut/p/c0/04_SB8K8xLLM9MSSzPy8xBz9CP0os_hACzO_QCM_IwMLo1ALAyNj1yBnQxNfAwMDY_2CbEdFANq6iRA!/. Accessed February 11, 2014.

¹⁶⁰ "Invitae Offers BRCA1/BRCA2 Testing, Providing Clinicians with a Reliable, Fast, Affordable Option for Patients," Invitae. December 11, 2013. <https://www.invitae.com/en/news/2013/12/11/invitae-offers-brca1brca2-testing-providing-clinicians-reliable-fast-affordable-option-patients/>. Accessed February 11, 2014.

¹⁶¹ "Support," Invitae. <https://www.invitae.com/en/faq/>. Accessed February 11, 2014.

Genes on the High-Risk Hereditary Breast Cancers Panel: BRCA1, BRCA2, , PTEN, TP53, STK11, CDH1

Genes on the Women's Hereditary Cancers Panel: BRCA1, BRCA2, PTEN, TP53, MLH1, MSH2, MSH6, EPCAM, PMS2, STK11, CDH1, CHEK2, RAD51C, BRIP1, PALB2, NBN, ATM

Genes on the Hereditary Cancer Syndromes Panel: BRCA1, BRCA2, PTEN, TP53, MLH1, MSH2, MSH6, EPCAM, PMS2, APC, BMPR1A, SMAD4, STK11, MUTYH, CDH1, CDK4, CDKN2A, PALLD, MET, MEN1, RET, PTCH1, VHL, CHEK2, BRIP1, PALB2, RAD51C, NBN, ATM

Center for Human Genetics

The Center for Human Genetics is a small non-profit based in Cambridge, MA that offers *BRCA1/2* testing for the three Ashkenazi Jewish founder mutations. Though the lab uses targeted variant analysis (PCR with RFLP) for their current mutation analysis, they hope to offer full-gene sequencing and dup/del analysis in the future. The Center first began to publicize their test in January of 2014; most of the center's patients are referred by physicians in New England.

Counsyl

In the spring of 2014, Counsyl released the cheapest *BRCA1/2* sequencing test available today. This test offers sequencing and dup/del analysis using a NGS Illumina-based assay, but Counsyl has also developed their own hardware and software. Patients who use Counsyl for testing are eligible for a complimentary phone consultation with a genetic counselor.

Michigan

The University of Michigan also released a *BRCA1/2* sequencing test in the Spring of 2014, but has not released their prices. According to the lab's website, bi-directional Sanger Sequence Analysis is used with an Applied Biosystems 3730 capillary sequencing instrument. The lab just started testing, so they do not have an established VUS rate and are also not sure what the breakdown of their client base will be (i.e., samples sent in from throughout the country or just from physicians at the University's clinics).

Appendix 3A

Coverage Policies

Testing Company Overviews

Myriad

Though patients can choose to cover the test price on their own, Myriad claims that most insurance plans cover BRCAAnalysis®, allowing most patients to pay “less than 10% of the test price.”¹⁶² If a patient chooses to bill with insurance, Myriad first verifies coverage. Then, if the projected cost is greater than \$375, Myriad will re-contact the patient before proceeding with the sequencing analysis. Medicare will cover BRCAAnalysis® if the specific medical criteria are met, but otherwise, “test cost is the patient’s responsibility.”

UCLA

The UCLA Clinical Laboratory does not have any information available online about their insurance coverage for *BRCA1/2* testing.¹⁶³

Ambry Genetics

Ambry performs free pre-verification for patients and interested clients as part of their commitment to “improving patient access to medically necessary genetic testing.” The company is contracted with the “majority of commercial insurance companies” and is also a Medicare provider.¹⁶⁴ However, in order for patients to be covered under Medicare for the BRCAPlus, BreastNext, and OvaNext tests, they must meet the Medicare testing criteria and must not have had *BRCA1/2* testing previously. Thus, Medicare patients will not receive reimbursement if they order testing purely based on family history.¹⁶⁵

Ambry is also contracted with some Medicaid plans, which usually require pre-verification for genetic testing. If patients are expected to pay more than \$100 out of pocket for a test, Ambry will contact the patient for verbal approval before continuing.¹⁶⁶ The company’s Financial Assistance Program (or ‘Hardship Payment Plan’) allows for non-insured and under-insured individuals to receive a “significant discount off [Ambry’s] Institutional Rates, often limiting the patient out-of-pocket expenses to only \$100.” Individuals with Medicare or Medicaid are not eligible for Ambry’s Financial Assistance program.

¹⁶² “Insurance Company Information,” Myriad Genetics. <https://www.myriadpro.com/insurance-company-information/>. Accessed December 12, 2013.

¹⁶³ “Molecular Pathology,” UCLA Clinical Laboratory and Pathology Services. April 24, 2014. <http://pathology.ucla.edu/body.cfm?id=103>. Accessed April 24, 2014.

¹⁶⁴ “Billing & Insurance Information,” Ambry Genetics. January 20, 2014. <http://www.ambrygen.com/billing-insurance-information>. Accessed February 10, 2014.

¹⁶⁵ “Billing & Insurance Information,” Ambry Genetics.

¹⁶⁶ “BRCA1/BRCA2 Test Logistics,” Ambry Genetics.

University of Washington

The University of Washington offers pre-verification services for all patients, and all patients are re-contacted after the “pre-authorization team obtains benefit information and out of pocket estimates.”¹⁶⁷ The lab can bill Medicaid in some states, so patients and care providers are encouraged to contact the pre-authorization team. The BROCA risk panel is covered for Medicare patients, provided that patients meet Medicare's testing criteria for *BRCA1/2*, Lynch syndrome, or APC and MUTYH testing. If patients are "covering the entire cost of testing, out of pocket," they "may be eligible for a discount, if they pay for services in advance."¹⁶⁸

Ethigen

Ethigen does not have any information available online about their insurance coverage for *BRCA1/2* testing.

Fulgent Therapeutics, LLC

Though Fulgent does not have much information on their website, they do cite “institutional, insurance, and patient out-of-pocket” as their three billing options. Prepayment is required for patient billing and all Health Maintenance Organizations (HMO) submissions must be pre-authorized.¹⁶⁹

GeneDX

For oncology tests, such as *BRCA1/2* testing, GeneDX accepts all commercial insurances. If a patient is expected to pay more than \$100 out-of-pocket, then GeneDX will contact the patient to see how he or she would like to proceed. GeneDX also offers a financial assistance program “for patients who do not have commercial insurance and cannot afford to pay out of pocket.”¹⁷⁰ GeneDX is a Medicare provider and requires an Advance Beneficiary Notice of Noncoverage (ABN) prior to testing for Medicare patients. Though GeneDX is *not* a participating provider with any state’s Medicaid plan, company representatives will still try to “negotiate a price and arrange [for] individual contract.” The company warns on their website that Medicaid coverage for diagnostic tests varies greatly from state to state; many state plans have “refused to negotiate with and/or pay GeneDx for services,” including NY, Maryland, Arizona, and California.¹⁷¹

¹⁶⁷ "UW Laboratory Medicine Clinical Test Information: Pre-Authorization for Next-Generation Sequencing Panels," University of Washington. March 31, 2014.

<http://web.labmed.washington.edu/tests/genetics/preauthorization>. Accessed April 18, 2014.

¹⁶⁸ "UW Laboratory Medicine Clinical Test Information," University of Washington.

¹⁶⁹ "Billing," Fulgent Therapeutics. <http://fulgent-therapeutics.com/testing/billing/>. Accessed February 22, 2014.

¹⁷⁰ "Oncology Genetics Billing Policy," Gene DX. <http://www.genedx.com/oncology-genetics-billing-policy/>. Accessed on February 9, 2014.

¹⁷¹ "FAQs," GeneDX. <http://www.genedx.com/faqs/>. Accessed February 9, 2014.

Quest Diagnostics

Quest Diagnostics has “more than 2,100 patient service centers located across the United States.”^{172,173} In addition to making submitting DNA samples “geographically convenient” and quick, Quest’s large size (especially compared to other upcoming *BRCA1/2* testing companies) is particularly advantageous because it means the majority of insurance companies are partnered with the company. Patients can visit Quest's website, and click on their state of residence, to see if their insurance company is contracted with Quest.¹⁷⁴ In addition to providing financial assistance to qualified patients, Quest offers a “concierge insurance preauthorization” service as part of their commitment to “work with health plans on [a patient’s] behalf to determine if the test will be covered.” After evaluating a patient’s insurance plan, Quest will re-contact the patient before moving forward with testing.

The University of Chicago

The University of Chicago offers three main billing methods: institutional billing, self-pay, and insurance. The lab does not offer discounts for institutional billing and self-pay, so costs reflect those listed in Chapter 3. The lab "accepts most insurance plans, with the exception of Illinois and out-of-state Medicaid."¹⁷⁵ Medicare is also accepted. Most of the commercial insurance plans that Chicago accepts are listed on their website, though patients are "advised to contact their insurance company to confirm the University of Chicago's participation prior to scheduling an appointment."¹⁷⁶

LabCorp®

Similar to Quest Diagnostics, LabCorp is one of the largest diagnostic testing companies in the United States, which is advantageous for patients who hope to receive insurance coverage. LabCorp files with an extremely large list of insurance providers and patients are encouraged to visit LabCorp’s website, enter their state of residence, and see if their company is one of LabCorp’s most commonly billed insurance carriers. LabCorp also has a financial assistance program, and offers preauthorization services for all patients.¹⁷⁷

¹⁷² "Quest Diagnostics Introduces BRCAVantage..." Quest Diagnostics.

¹⁷³ Ray, T., "With BRCAVantage Launch, Quest Becomes Largest US Lab to Enter BRCA Testing Space," *GenomeWeb*. October 16, 2013. <http://www.genomeweb.com/clinical-genomics/brcavantage-launch-quest-becomes-largest-us-lab-enter-brca-testing-space>. Accessed February 11, 2014.

¹⁷⁴ "Insurance Lists & Third Party Payors," Quest Diagnostics. 2014.

<https://www.questdiagnostics.com/home/patients/insurance.html>. Accessed February 11, 2014.

¹⁷⁵ "Billing," University of Chicago Genetic Services Laboratory. <http://dnatesting.uchicago.edu/billing>. Accessed April 20, 2014.

¹⁷⁶ "Insurance Plans," University of Chicago Genetic Services Laboratory.

<http://www.uchospitals.edu/billing/managed-care.html>. Accessed April 20, 2014.

¹⁷⁷ "LabCorp to Offer BRCAssure Breast Cancer Mutation Tests," Laboratory Corporation of America® Holdings.

Invitae

Invitae is not contracted with Medicare or Medicaid, but does bill third party insurance providers and pre-authorization services exist. To bill insurance, patients must submit a letter of medical necessity (LOMN) from their doctor. To help patients who are paying out of pocket, Invitae offers a patient payment plan. For those with significant financial need, assistance plans exist, which ensure that qualified patients pay no more than \$100 for testing. However, given New York and Utah's additional laboratory standards, Invitae does not accept patient samples from these states.¹⁷⁸

Center for Human Genetics

The Center for Human Genetics does not have any information available online about their insurance coverage for *BRCA1/2* testing.¹⁷⁹

Counsyl

Counsyl is contracted with "most commercial insurance plans" and will re-contact any patients whose testing costs exceed \$299 after insurance. Though the company is contracted with most large private payers, such as Aetna, Cigna, Anthem, Highmark BCBS, and some Kaiser plans, they are not contracted with government plans, such as Medicaid. Counsyl does offer payment plans and also has a financial aid system to assist those who meet the qualifications.¹⁸⁰

University of Michigan

The University of Michigan does not have third party billing for outside facility's sample(s) – they will only bill the third payer for "established University of Michigan patients."¹⁸¹ For such patients, a list of accepted insurance plans, including a few Medicare and Medicaid plans, is available online.¹⁸² Though a financial assistance program exists, many qualifications must be met.

¹⁷⁸ "Support," Invitae. <https://www.invitae.com/en/faq/>. Accessed February 11, 2014.

¹⁷⁹ "Human Genetics," Center for Human Genetics, Inc. <http://chginc.org/>. Accessed April 24, 2014.

¹⁸⁰ "Help Center," Counsyl. <https://help.counsyl.com/home>. Accessed April 24, 2014.

¹⁸¹ "Billing Information," Michigan Medical Genetics Laboratories (MMGL). http://sitemaker.umich.edu/michigan.medical.genetics.laboratories/billing_information. Accessed April 24, 2014.

¹⁸² "Insurance," University of Michigan Health System. <http://www.uofmhealth.org/insurance>. Accessed April 24, 2014.

Appendix 3B

Coverage Policies

Insurance Company Overviews

Note to Reader: Insurance Companies are listed alphabetically. See Appendix 3C for specific policies. See research methodology described in Chapter 4.

AETNA GROUP.

Aetna Group considers *BRCA1/2* testing medically necessary according to the guidelines set forth in Table 1.^{183,184} The company's policy for *BRCA1/2* testing has not been updated since the June 2013 Supreme Court case. Thus, it is not necessarily surprising that Aetna's policy indirectly necessitates the use of Myriad for *BRCA1/2* testing. For example, within the "BRCA Test Authorization Workflow" section of Aetna's medical policy, only Myriad is listed as a testing site. The policy states that a "'Prior Authorization' request for BRCA Molecular Testing is to be sent along with the Myriad Genetics TRF form from Myriad Genetics."

Aetna will not cover large rearrangement testing or re-testing. The company's medical policy states that "there is inadequate information regarding the frequency of large genomic rearrangements in the United States populations to indicate that use of [large rearrangement analysis]" is medically necessary. Therefore, the company considers del/dup analysis, and re-testing for specific mutations, to be "experimental and investigational."¹⁸⁵ Aetna's policy states that it is "essential" for patients "to undergo adequate education and counseling because molecular susceptibility testing raises important medical, psychological, and social issues for patients and their families." Thus, genetic counseling is a "covered benefit in all Aetna products," and considered "medically necessary" for familial cancer disorders.¹⁸⁶

Though Aetna's current policies necessitate the use of Myriad and do not cover del/dup analysis, it is possible that these policies may change with time. The next scheduled review date is February 27, 2014.¹⁸⁷

¹⁸³ **Note:** Aetna's medical policy for *BRCA1/2* testing is "based on the guidelines from the American College of Obstetricians and Gynecologists (2009), the American College of Medical Genetics (1999) and the U.S. Preventive Services Task Force (2005)."

¹⁸⁴ "Clinical Policy Bulletin: BRCA Testing, Prophylactic Mastectomy, and Prophylactic Oophorectomy," Aetna. Policy Number: 0227. March 14, 2013. Aetna. http://www.aetna.com/cpb/medical/data/200_299/0227.html. Accessed February 25, 2014.

¹⁸⁵ "Clinical Policy Bulletin: BRCA Testing..." March 14, 2013. Aetna.

¹⁸⁶ "Clinical Policy Bulletin: Genetic Counseling," Aetna. Policy Number: 0189. January 31, 2014. http://www.aetna.com/cpb/medical/data/100_199/0189.html. Accessed March 4, 2014.

¹⁸⁷ "Clinical Policy Bulletin: BRCA Testing..." March 14, 2013. Aetna.

BLUE CROSS / BLUE SHIELD (BC/BS)

The Blue Cross and Blue Shield Association does not have a national coverage policy for *BRCA1/2* testing. Thus, individuals seeking reimbursement information should contact their local Blue Cross Blue Shield (BCBS) company. There are 37 different state and regional companies within the national group (see Table 2).^{188,189}

BCBS Anthem is an independent subsidiary of the BCBS Association and provides health insurance for 14 states.¹⁹⁰ Given its large size, BCBS Anthem was chosen by the author to be representative of BCBS's policies toward *BRCA1/2* testing; however, readers should consult their local BCBS organization for particular policies.^{191,192}

BCBS Anthem covers *BRCA1/2* testing in accordance with the common guidelines (see Table 3). All genetic testing must be accompanied by "appropriate pre- and post-test counseling" by "adequately trained health care professionals."¹⁹³ Anthem will cover rearrangement analysis for individuals who meet the testing criteria and received a negative result with an initial sequence analysis. However, multi-gene panels, such as BreastNext®, BREVAGgen, DeCode BreastCancer®, OvaNext®, and CancerNext®, are not considered to be medically necessary unless "all components of the panel have been determined to be medically necessary based on [previously stated testing] criteria."¹⁹⁴

¹⁸⁸ "About the Blue Cross and Blue Shield Association," BlueCross BlueShield Association. <http://www.bcbs.com/about-the-association/>. Accessed March 4, 2014.

¹⁸⁹ "About the Blue Cross and Blue Shield Companies," BlueCross BlueShield Association. <http://www.bcbs.com/about-the-companies/>. Accessed March 4, 2014.

¹⁹⁰ "Genetic Testing for Breast and/or Ovarian Cancer Syndrome," Anthem, BCBS. January 14, 2014. http://www.anthem.com/medicalpolicies/policies/mp_pw_c166602.htm. Accessed March 4, 2014.

¹⁹¹ **Note:** For instance, North Carolina's policy can be found here: https://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/genetic_testing_for_breast_and_ovarian_cancer.pdf.

¹⁹² **Note:** For instance, Mississippi's policy can be found here: http://www.bcbsms.com/index.php/index.php?q=provider-medical-policy-search.html&action=viewPolicy&source=emed&path=/policy/emed/Genetic%20Testing%20for%20Hereditary%20Breast%20and_or%20Ovarian%20Cancer.html.

¹⁹³ "Genetic Testing for Breast and/or Ovarian Cancer Syndrome," Anthem, BCBS.

¹⁹⁴ "Genetic Testing for Breast and/or Ovarian Cancer Syndrome," Anthem, BCBS.

CENTENE CORPORATION

Centene Corporation is a national insurance company composed of local health plans for 19 different states.¹⁹⁵ A national policy could not be found, and individual states did not seem to have specific *BRCA1/2* coverage policies either. The only comment related to genetic testing that was available online was a press statement discussing how prior authorization forms are required for genetic testing.¹⁹⁶

CIGNA HEALTH GROUP.

Cigna considers single site analysis medically necessary for individuals with a known familial mutation.^{197,198} Otherwise, if one has a personal history of breast, ovarian, or pancreatic cancer (and meets any of a long list of indications), then Cigna will cover full sequence analysis and dup/del analysis (see Table 4). Large rearrangement testing is considered medically necessary when initial criteria are met, but conventional testing (i.e., just sequence analysis) returned a negative result. Unlike most insurance companies, Cigna considers *BRCA1/2* testing medically necessary if an individual has at least a 10% probability of carrying a mutation as determined by a validated risk assessment tool (such as BRCAPro, University of Pennsylvania [UPenn I or UPenn II], BOADICEA, or Tyrer-Cusick).¹⁹⁹

In regards to multigene panels, such as BreastNext and BRCAplus by Ambry or BROCA by the University of Washington, Cigna argues that the use of these testing methods is “still preliminary and not yet recommended in guidelines from professional organizations.” Thus, because there is “insufficient evidence in the published scientific literature to establish the diagnostic and clinical utility” of these multi-gene panels, they are considered “investigational”.²⁰⁰

Cigna has received press coverage recently for requiring genetic counseling to accompany all major genetic tests. This announcement, which took effect on September 16, 2013, established

¹⁹⁵ **Note:** These state plans are: Arizona (Bridgeway Health Solutions), Massachusetts (CeltiCare Health Plan), Arkansas (NovaSys Health), Mississippi (Magnolia Health Plan), California (California Health & Wellness), Missouri (Home State Health Plan), Florida (Sunshine Health), New Hampshire (Granite State Health Plan), Georgia (Peach State Health Plan), Ohio (Buckeye Community Health Plan), Illinois (IlliniCare Health Plan), South Carolina (Absolute Total Care), Indiana (Managed Health Services), Texas (Superior Health Plan), Kansas (Sunflower Health Plan), Washington (Coordinated Care), Kentucky (Kentucky Spirit Health Plan), Wisconsin (Managed Health Services), Louisiana (Louisiana Healthcare Connections. Source: "Health Plans," Centene Corporation. <http://www.centene.com/health-plans/>. Accessed March 3, 2014.

¹⁹⁶ "Prior Authorization Changes for Genetic Testing Codes," May 1, 2013. Peach State Health Plan, Centene Corporation. <http://www.pshpgeorgia.com/2013/05/01/prior-authorization-changes-for-genetic-testing-codes/>. Accessed March 3, 2014.

¹⁹⁷ "Medical Necessity Guidelines: Genetic Testing for Susceptibility to Breast and Ovarian Cancer," CareAllies, Cigna. September 15, 2013.

http://www.cigna.com/sites/careallies/pdf/CA0001_BRCA1_BRCA2_Breast_Ovarian.pdf. Accessed March 3, 2014.

¹⁹⁸ "Cigna Medical Coverage Policy: Genetic Testing for Susceptibility to Breast and Ovarian Cancer," Cigna. February 15, 2014.

https://cignaforhpc.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0001_coveragepositioncriteria_genetic_testing_for_breast_and_ovarian_cancer.pdf. Accessed March 3, 2014.

¹⁹⁹ "Cigna Medical Coverage Policy," Cigna.

²⁰⁰ "Medical Necessity Guidelines," CareAllies, Cigna.

Cigna as the first major insurance company to require genetic counseling for *BRCA1/2*.²⁰¹ Cigna's emphasis on genetic counseling and education is also apparent in their medical policy. In addition to meeting the following accreditations, the care provider ordering testing must have "evaluated the individual, completed a three generation pedigree, and intend to engage in post-test follow-up counseling."²⁰²

1. An independent Board-Certified or Board-Eligible Medical Geneticist
2. An American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
3. A genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

COVENTRY CORPORATION GROUP

Coventry Health Care primarily follows the "U.S. Preventive Services Task Force (USPSTF) evidence-based recommendations that have in effect a rating of "A" or "B" ... for clinical preventive services."²⁰³ Thus, their policy for breast and ovarian cancer screening is that "women whose family history is associated with an increased risk for deleterious mutations in *BRCA1* or *BRCA2* genes be referred for genetic counseling and evaluation for BRCA testing." However, Coventry notes that their "preventive health guidelines do not reflect reimbursement or payment practices." No mention of multi-gene panels or dup/del analysis was made.²⁰⁴

DEAN HEALTH GROUP

The Dean Health Group lists "BRCA counseling about genetic testing for women at higher risk" as a "Covered Preventive Services for Women." Additionally, this service is "covered in full without being applied to co-insurance." No further details are given.²⁰⁵

²⁰¹ "Cigna Demands Counseling for Breast Test in Myriad Threat," Bloomberg Technology. August 19, 2013. <http://www.bloomberg.com/news/2013-08-19/cigna-demands-counseling-for-breast-test-in-myriad-threat.html>. Accessed March 3, 2014.

²⁰² Cigna Medical Coverage Policy," Cigna.

²⁰³ "Coventry Health Care Clinical Preventive Services 2013," Coventry Health Care. 2013. http://www.mhnet.com/web/groups/public/@cvty_regional_chcmo/documents/document/c045215.pdf. Accessed April 22, 2014.

²⁰⁴ "Coventry Health Care Clinical Preventive Services 2013," Coventry Health Care.

²⁰⁵ "Covered Preventive Services," Dean Health Group. 2012. <http://www.deancare.com/insurance/members/preventivecarelist/>. Accessed April 22, 2014.

EMBLEM HEALTH

Emblem Health considers *BRCA1/2* testing (specified as BRACAnalysis) to be medically necessary when the “results of the genetic testing will directly impact surveillance or treatment.” Patients must meet one of the three criteria listed in Table 5. BART testing is covered if members meet the criteria for BRACAnalysis, but received a negative result.²⁰⁶ Emblem Health members are “eligible for pre- and post-test genetic counseling by a physician or a licensed, or certified, genetic counselor when recommended for EmblemHealth-covered tests.”²⁰⁷

GEISINGER HEALTH PLAN

The Geisinger Health Plan is a health insurance program that arose out of the Geisinger Health System - a healthcare system in northeastern and central Pennsylvania. The Health Plan has approximately 290,000 members and offers coverage for businesses of all sizes, individuals and families, Medicare beneficiaries, and children enrolled in the Children's Health Insurance Program (CHIP).²⁰⁸

Under the Geisinger Health Plan, *BRCA1/2* testing is covered both for individuals with a personal history of breast, ovarian, fallopian, or peritoneal cancer and for individuals who are at high risk for carrying a *BRCA1/2* mutation as defined by the provided criteria (Table 6).^{209,210} Rearrangement testing is considered medically necessary for individuals who met the *BRCA1/2* testing criteria, but received a negative point mutation result. Genetic counseling, by a certified ACGC or ABMD professional, must occur both pre-and post-genetic testing.

GROUP HEALTH COOPERATIVE

Group Health Cooperative is a health care system that serves more than 600,000 individuals in Washington and Idaho.²¹¹ A genetic testing policy was available online, but specific testing criteria are considered “proprietary,” and Group Health only shares specific coverage documents on an individual member basis.²¹²

²⁰⁶ "BRCA 1 and 2 Genetic Testing (BRACAnalysis) and BRACAnalysis Rearrangement Testing," Emblem Health. August 23, 2013. http://www.emblemhealth.com/~media/Files/PDF/_med_guidelines/MG_BRCA_Testing.pdf. Accessed April 22, 2014.

²⁰⁷ "Genetic Counseling and Testing," Emblem Health. February 27, 2013. http://www.emblemhealth.com/~media/Files/PDF/_med_guidelines/MG_Genetic_Counseling_Testing.pdf. Accessed April 22, 2014.

²⁰⁸ "Key Facts," Geisinger Health Plan. August 21, 2012. <http://www.thehealthplan.com/news/keyfacts.cfm#Background>. Accessed March 4, 2014.

²⁰⁹ "Medical Benefit Policy: Genetic Testing for BRCA1 or BRCA2 for Breast and Ovarian Cancer." Geisinger Health Plan. Policy: MP 97. July 2013. https://www.thehealthplan.com/providers_us/medpolicies/repository/4873.pdf. Accessed March 4, 2014.

²¹⁰ **Note:** Testing requires pre-authorization.

²¹¹ "About Group Health," GroupHealth. <https://www1.ghc.org/html/public/about>. Accessed March 22, 2014.

²¹² "Clinical Review Criteria," GroupHealth. March 4, 2014. http://www.ghc.org/all-sites/clinical/criteria/pdf/genetic_screening.pdf. Accessed March 22, 2014.

HARVARD PILGRIM HEALTH CARE GROUP

Harvard Pilgrim does not list a specific policy for *BRCA1/2* testing, but it does list breast cancer screening (“Genetic Counseling and Evaluation for BRCA Testing”) as a possible service and provides the CPT codes.²¹³ Additionally, Harvard lists “BRCA 1 or 2 genetic counseling, evaluation and testing for women with a family history associated with increased risk of mutation” as a preventive service that is covered with “no Member Cost Sharing.”²¹⁴

HEALTH ALLIANCE MIDWEST INC

No coverage policies were found for *BRCA1/2* testing, or for genetic testing in general.

HEALTH NET

For *BRCA1/2* testing, Health Net follows the guidelines detailed in Table 7.²¹⁵ Health Net considers Myriad’s BRCAAnalysis Large Rearrangement Test (BART)® “medically necessary to detect large genomic rearrangements in individuals who are at risk for *BRCA1/2* related cancers but have negative *BRCA1/2* genetic sequence tests and meet the criteria for *BRCA1/2* testing.”²¹⁶ Their coverage policy does not include *BRCA1/2* rearrangement testing by other testing companies. Health Net considers genetic counseling to be the responsibility of the care provider. Such counseling should include “risk assessment, pre-test education and post-test counseling” and can be completed by the care provider or a genetic counselor.²¹⁷

HEALTH NEW ENGLAND (HNE)

Health New England (HNE) is a Health Maintenance Organization (HMO) that serves over 137,000 members in Massachusetts.²¹⁸ HNE’s policy was last updated in June of 2013 and is separated into different sections for different types of insurance (see Table 8).²¹⁹ Patients with

²¹³ "Patient Protection and Affordable Care Act: Harvard Pilgrim Health Care—Provider Manual," Harvard Pilgrim. January 2014.

https://www.harvardpilgrim.org/pls/portal/docs/PAGE/PROVIDERS/MANUALS/MEMBER%20CARE/B%20PPACA_011514.PDF. Accessed April 22, 2014.

²¹⁴ "Preventive Care: Services Covered Under the Affordable Care Act," Harvard Pilgrim Health Care. April 2014. <https://www.harvardpilgrim.org/pls/portal/docs/PAGE/MEMBERS/WELLNESS/PREVENTIVE/PREVENTIVE-CARE-CC4297.PDF>. Accessed April 22, 2014.

²¹⁵ "National Medical Policy: Genetic Testing for BRCA1 and BRCA2," Health Net, Inc. September 2013. <https://www.healthnet.com/static/general/unprotected/pdfs/national/policies/GeneticTestingforBRCA1andBRCA2.pdf>. Accessed February 24, 2014.

²¹⁶ "National Medical Policy: Genetic Testing for BRCA1 and BRCA2," Health Net, Inc. September 2013.

²¹⁷ "National Medical Policy: Genetic Testing for BRCA1 and BRCA2," Health Net, Inc. September 2013.

²¹⁸ "HNE Facts at a Glance," Health New England. https://www.healthnewengland.com/HNEs_Story/facts.html. Accessed March 22, 2014.

²¹⁹ "Clinical Review Criteria for BRCA Genetic Testing," Health New England (HNE). May 11, 2013. http://www.healthnewengland.com/hne_providers/documents/BRCAforGeneticTesting-Criteria-External.pdf. Accessed March 22, 2014.

Medicare Advantage must follow the CMS criteria for *BRCA1/2* testing, while those with commercial insurance follow USPSTF and NCCN guidelines.²²⁰

HEALTH PARTNERS GROUP

Health Partners requires prior authorization for *BRCA1/2* testing, and the service is generally covered if all of the criteria listed in Table 9 are met. Health Partners' medical criteria are based off the 2013 NCCN guidelines for Genetic/Familial High-Risk Assessment, Breast and Ovarian.²²¹

HUMANA INC.

Humana has a 'Genetic Guidance Program,' which is designed to help patients and doctors decide when genetic testing is best (and which specific test should be ordered). The program also brings certified genetic counselors into the care process in the hope that inclusion of these professionals will lead to "more-informed healthcare decisions."²²² In addition to the option of setting a patient up with a genetic counselor, the Genetic Guidance Program allows physicians to call Humana to speak with a board-certified genetic counselor directly about preauthorizations. Preauthorization of molecular diagnostic and genetic tests is required for commercial, HMO, and PPO members. However, preauthorization is not required for Medicare Advantage Private Fee-for-Service (PFFS) plans, Risk groups, Medicaid members, CarePlus members, and HumanaOne members.²²³

Humana's Genetic Guidance Program covers a long list of genetic tests and *BRCA1/2* are among the genes included. Full *BRCA1/2* sequence analysis, known familial mutations, and del/dup analysis are all listed as possible testing options.²²⁴ Genetic counseling is to be performed with a physician or certified genetic counselor (before and after testing) for hereditary cancer syndromes.²²⁵ Humana considers genetic testing and genetic counseling for *BRCA1/2* medically necessary if individuals are over 18 years old and meet the following criteria (Table 10).²²⁶ These policies are in accordance with the NCCN's guidelines.²²⁷ Humana will cover large rearrangement testing if an individual has a known familial mutation only detectable by

²²⁰ **Note:** Medicare Advantage is a "type of Medicare health plan offered by a private company that contracts with Medicare to provide Part A and Part B benefits." **Source:** "Medicare Advantage Plans," Centers for Medicare & Medicaid Services. <http://www.medicare.gov/sign-up-change-plans/medicare-health-plans/medicare-advantage-plans/medicare-advantage-plans.html>. Accessed March 22, 2014.

²²¹ "Genetic testing for breast/ovarian cancer predisposition (BRCA genetic testing)," HealthPartners. March 11, 2014. <https://www.healthpartners.com/public/coverage-criteria/brca-testing/>. Accessed April 22, 2014.

²²² "Molecular Diagnostic and Genetic Testing (MD/GT)," Humana. <https://www.humana.com/provider/medical-providers/education/referral/dna-preauth>. Accessed March 4, 2014.

²²³ "Molecular Diagnostic and Genetic Testing (MD/GT)," Humana.

²²⁴ "Genetic Tests and Disease States Included in Humana's Genetic Guidance Program," Humana. <http://apps.humana.com/marketing/documents.asp?file=2088567>. Accessed March 4, 2014.

²²⁵ "Medical Coverage Policy: Genetic Testing and Genetic Counseling for Hereditary Cancer Syndromes," Humana. January 1, 2014. http://apps.humana.com/tad/tad_new/home.aspx. Accessed March 4, 2014.

²²⁶ "Medical Coverage Policy," Humana.

²²⁷ Shah, A., Harris, H., Brown, T., Graf, M.D., Sparks, L., Mullins, T., Bruins, C., (2011). Analysis of Insurance Preauthorization Requests for BRCA1 and BRCA2 Genetic Testing. *Personalized Medicine* 8(5): 563-569.

rearrangement analysis, or if an individual meets the testing criteria for *BRCA1/2*, but full sequence analysis returned a negative result.²²⁸ If full sequence analysis produced a positive result, then rearrangement analysis is not covered.

Humana will not cover genetic testing for “hereditary multigene, next generation sequencing panels or pan-cancer panels (e.g., BRCAplus®, BreastNext®, CancerNext®, ColoNext®, FoundationOne®, OvaNext®) to determine susceptibility to hereditary cancers, to diagnose cancer, or determine treatment.”²²⁹ Additionally, Humana only covers testing once per lifetime per disease.

KAISER FOUNDATION

Kaiser Permanente does not have a national policy for *BRCA1/2* testing. Only one local policy was found (for the Mid-Atlantic Permanente Medical Group) and this policy dates back to 2009 (see Table 11). The policy covers *BRCA1/2* testing according to NCCN guidelines and requires genetic counseling both pre-and post-testing.²³⁰

MEDICA GROUP

Medica Group’s *BRCA1/2* testing policy follows the NCCN recommendations. Medica considers large rearrangement testing medically necessary if an individual met the criteria for *BRCA1/2* testing, but received a negative test result. However, Medica specifies that BART® testing must be performed, implying that only Myriad can be used for this service. Prior authorization is required for both *BRCA1/2* testing and BART® testing.²³¹

MEDICAID

See discussion in paper (Chapter 5: Policy Recommendations). There is little information available for what genetic tests Medicaid covers. This issue was addressed in a recent report by the Centers for Medicare & Medicaid Services (CMS) titled “Payments for Laboratory Test: Comparing Medicare, State Medicaid, and Federal Employees Health Benefits Programs.” The CMS undertook this study, in which surveys were sent to State Medicaid and Federal Employee Health Benefit programs, to learn more about genetic laboratory test coverage and to receive feedback establishing payment rates.²³² In regards to State Medicaid coverage, the CMS found

²²⁸ "Medical Coverage Policy," Humana.

²²⁹ "Medical Coverage Policy," Humana.

²³⁰ "BRCA Testing: Genetic Counseling and Testing for Inherited Susceptibility for Breast and/or Ovarian Cancer due to BRCA1/2 Defects," Kaiser Permanente, Mid-Atlantic Permanente Medical Group (MAPMG). 2009. https://www.mapmgonline.com/portal/documents/brca_testing.pdf. Accessed March 22, 2014.

²³¹ "Genetic testing for Hereditary Breast and / or Ovarian Cancer (BRCA1 and BRCA2 Genes and BRCAAnalysis Rearrangement Test [BART])," Medica. Utilization Management Policy. Medica Policy No. III-DIA.04. February 1, 2014.

²³² "Memorandum Report: Coverage and Payment for Genetic Laboratory Tests, OEI-07-11-000 11," Department of Health and Human Services. June 12, 2013. <https://oig.hhs.gov/oei/reports/oei-07-11-00011.pdf>. Accessed March 22, 2014.

that “officials from all but one State [New Mexico] described some level of coverage for genetic tests.” However, “officials from 17 States stated that their States have no specific policy addressing them.” The remaining states used a variety of factors to influence coverage decisions. When officials from State Medicaid programs were asked to provide payment rates for genetic tests (including *BRCA1/2* analysis), only 8 state Medicaid programs were able to provide payment rates. CMS found “great variation in test prices; for example, the payment rate for a *BRCA1* gene analysis ranged from \$1,000 in Pennsylvania to nearly \$4,500 in Iowa.” See the table below for the prices of the remaining states.²³³

Medicaid Payment Rates							
	CA	DE	IL	IA	MA	PA	VA
BRCA1 Gene Analysis	\$3,340	\$3,120	\$3,030	\$4,498	\$2,731	\$1,000	\$3,120
BRCA2 Gene Analysis	\$3,340	\$3,120	\$2,770	\$4,947		\$1,000	

Facing Our Risk of Cancer Empowered (FORCE), a non-profit advocacy group, has also testified to how widely states differ in their Medicaid coverage for *BRCA1/2* testing. According to FORCE, the states that most often cover testing are: Alaska, Arizona, California, Colorado, Connecticut, Delaware, Florida, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Montana, New Jersey, New York, New Mexico, Ohio, Oklahoma, Oregon, Tennessee, Texas, Utah, Virginia, Vermont, Washington, West Virginia, and Wyoming.²³⁴ According to Emory's genetic testing website, lab members are working "diligently with Georgia Medicaid and other government offices to address the issue of non-coverage for genetic testing."²³⁵ This statement implies that Georgia's Medicaid does not cover genetic testing.

MEDICAL MUTUAL OF OHIO

Medical Mutual does not have a specific *BRCA1/2* testing policy, but the test is listed as one that needs prior approval.²³⁶ Another page on the Medical Mutual website lists "counseling women at high risk of breast cancer" and "genetic screening and evaluation for the BRCA breast cancer gene" as covered services with no cost sharing, implying that Medical Mutual does cover the

²³³ "Memorandum Report," Department of Health and Human Services. June

²³⁴ "Insurance, Financial Assistance, Cost of Services," FORCE: Facing Our Risk of Cancer Empowered. http://www.facingourrisk.org/info_research/finding-health-care/financial-help/index.php?PHPSESSID=120896cb6d92db9dbab9c05549216c3b. Accessed February 10, 2014.

²³⁵ "Billing Options," Emory Genetics Laboratory. <https://genetics.emory.edu/egl/billing/index.php/1143>. Accessed March 22, 2014.

²³⁶ "Prior Approval and Investigational Services," Medical Mutual. April 14, 2014. <https://provider.medmutual.com/pdf/priorapprovallist.pdf>. Accessed April 22, 2014.

test.²³⁷ No mention was made in regards to rearrangement testing or specific laboratories that must be used.

MEDICARE

Medicare operates under a dual-system of national and local coverage determinations. Medicare does not have a National Policy for *BRCA1/2* testing. In fact, Medicare only has two national coverage determinations for any type of genetic test: (1) testing to predict patient responsiveness to the drug warfarin sodium and (2) cytogenetic studies.²³⁸ Thus, individuals should refer to Medicare's Local Coverage Determinations (LCDs) for Genetic Testing.²³⁹ Though Medicare does not have a NCD, most state's LCDs are quite similar. Generally, *BRCA1/2* testing is covered for people who meet the following guidelines laid out in Table 12.^{240,241} Because the CMS defines "comprehensive genetic testing of *BRCA1* and *BRCA2*" to include "full sequencing and detection of large genomic rearrangements," Medicare covers rearrangement (dup/del) analysis for affected individuals.²⁴² Medicare requires pre-test genetic counseling to be "provided by a qualified and appropriately trained practitioner." Additionally, before testing, patients must sign an informed consent form which states that they agree to post-test counseling.²⁴³ Medicare does *not* cover testing for people who have not *personally* had breast or ovarian cancer.²⁴⁴ Medicare views *BRCA1/2* testing for non-affected individuals as a type of "screening" and, therefore, ineligible for coverage.^{245,246}

In December of 2013, the Centers for Medicare and Medicaid Services (CMS) updated reimbursement levels for *BRCA1/2* testing by decreasing the National Limit Amounts (NLA).^{247,248} Previously, CMS reimbursed up to \$2,795 for *BRCA1/2* testing. However, effective after January 1, 2014, CMS will only cover up to \$1,438 for *BRCA1/2* testing (a 49%

²³⁷ "Women's Preventive Health Services," Medical Mutual. 2013. <https://www.medmutual.com/For-Employers/Healthcare-Reform/Affordable-Care-Act-Summary/HCR-Items/Womens-Preventive-Health-Services.aspx>. Accessed April 22, 2014.

²³⁸ "Memorandum Report," Department of Health and Human Services.

²³⁹ **Note:** Within Medicare's LCDs, individuals should refer to the section titled 'Genetic Testing and Molecular Diagnostic Tests (MDT).' **Source:** "Medical Policy: Genetic Testing for HBOC," United HealthCare Services.

²⁴⁰ **Note:** These Medicare coverage determinations were taken from Utah's LCD. Readers should consult their specific LCD to make sure coverage is the same.

²⁴¹ "Local Coverage Determination (LCD): Genetic Testing (L24308)," Centers for Medicare & Medicaid Services (CMS). Utah. October 31, 2013. <http://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=24308&ContrId=133&ver=62&ContrVer=1&bc=AAAAAAAAAQAAA&>. March 4, 2014

²⁴² "Local Coverage Determination (LCD): Genetic Testing (L24308)," CMS.

²⁴³ "Local Coverage Determination (LCD): Genetic Testing (L24308)," CMS.

²⁴⁴ "Insurance, Financial Assistance, Cost of Services," FORCE.

²⁴⁵ "Local Coverage Determination (LCD): Genetic Testing (L24308)," CMS.

²⁴⁶ **Note:** Medicare does cover some preventative services. For a list of such screenings that are covered, see: "Prevention - General Information," Centers for Medicare & Medicaid Services. April 25, 2013. <http://www.cms.gov/Medicare/Prevention/PrevntionGenInfo/index.html?redirect=/PrevntionGenInfo/>. Accessed March 4, 2014.

²⁴⁷ "CMS Cuts Reimbursement for BRCA1/2 Testing by 49 Percent; Analyst Downgrades Myriad Shares," GenomeWeb. December 30, 2013. <http://www.genomeweb.com/clinical-genomics/cms-cuts-reimbursement-brca12-testing-49-percent-analyst-downgrades-myriad-share>. Accessed February 10, 2014.

²⁴⁸ "Reimbursement for Breast-Cancer Risk Test to Be Cut," The WSJ. December 29, 2013. <http://online.wsj.com/news/articles/SB10001424052702304361604579288591617575358>.

decrease from 2013 levels).²⁴⁹ According to the CMS, the Supreme Court's decision in June of 2013 was influential in the reimbursement decrease because this decision allowed additional companies to enter the market and lower *BRCA1/2* testing costs.²⁵⁰

SELECT HEALTH

Select Health does not have a published *BRCA1/2* testing policy, but does list "BRCA counseling about genetic testing for women at higher risk" as a preventive service offered to women with no cost-sharing requirements.²⁵¹

SPECTRUM HEALTH

No policy found.

TUFTS HEALTH PLAN

Tufts Health Plan provides *BRCA1/2* testing and counseling, with no cost-sharing responsibilities, as a preventive service for women, provided that they meet the pre-authorization guidelines.²⁵² Tufts' Medical Necessity Guidelines state that testing is deemed medically necessary for members "at high risk for breast cancer."²⁵³ The policy then goes on to specify when women can be classified as "high risk," but generally, "Tufts Health Plan defines high risk as a greater than ten percent risk for a positive test result based upon either the Myriad or BRCAPRO model." Table 13 lists the coverage policy in more detail.

UNITED HEALTHCARE

UnitedHealthcare covers *BRCA1/2* testing in accordance with the guidelines laid out by the NCCN (see Table 14).²⁵⁴ When individuals meet the listed criteria, United Health also recognizes the clinical importance of large rearrangement analysis. Genetic counseling is "strongly recommended prior to genetic testing for BRCA mutations."²⁵⁵

²⁴⁹ **Note:** These new NLA amounts correspond to the CPT codes 81211 (full gene sequencing of *BRCA1/2*) and 81214 (full gene sequencing of just *BRCA1*). For more information about CPT codes, see Appendix 6.

²⁵⁰ "Gapfill Pricing Inquiries," Centers for Medicare and Medicaid Services (CMS). January 29, 2014. <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/Gapfill-Pricing-Inquiries.html>. Accessed February 24, 2013.

²⁵¹ "Preventive Care: At No Cost to You," Select Health. November 2010.

http://selecthealth.org/Forms%20and%20Documents/Reform/PreventiveCare_Reform.pdf. Accessed April 22, 2014.

²⁵² "Preventive Services," Tufts Health Plan. April 17, 2014.

http://www.tuftshealthplan.com/providers/pdf/payment_policies/preventive_services.pdf. Accessed April 22, 2014.

²⁵³ "Medical Necessity Guidelines: Genetic Testing for Multi-site BRCA3, Single Site BRCA1 or BRCA2, & BART," Tufts Health Plan. January 8, 2014.

http://www.tuftshealthplan.com/providers/pdf/mng/genetic_testing_brca.pdf. Accessed April 22, 2014.

²⁵⁴ "Medical Policy: Genetic Testing for Hereditary Breast and/or Ovarian Cancer Syndrome (HBOC)," United HealthCare Services. February 1, 2014. Inc.

https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Genetic_Testing_HBOC_Syndrome.pdf. Accessed February 10, 2014.

²⁵⁵ "Medical Policy: Genetic Testing for HBOC," United HealthCare Services.

Appendix 3C

Coverage Policies

Insurance Company Policies

Table 1 | Aetna’s Coverage of *BRCA1/2* Testing

Aetna considers molecular susceptibility testing for breast and/or ovarian cancer (“BRCA testing”) medically necessary in any of the following categories of high-risk adults with breast or ovarian cancer (adapted from guidelines from the U.S. Preventive Services Task Force (for screening indications) and from the American College of Obstetricians and Gynecologists and the American College of Medical Genetics (for testing persons with cancer)):

1. Women with a history of epithelial ovarian cancer
2. Women with personal history of breast cancer and any of the following:
 - a. Breast cancer is diagnosed at age 45 years or younger, with or without family history; or
 - b. Breast cancer is diagnosed at age 50 years or younger, with any of the following:
 - i. at least 1 close blood relative with breast cancer at age 50 years or younger; or
 - ii. at least 1 close blood relative with epithelial ovarian cancer; or
 - iii. bilateral breast cancer, or 2 primary breast cancers with 1st primary diagnosed at age 50 years or younger; or
 - iv. limited family structure, or no family history available because member is adopted.
 - c. Breast cancer is diagnosed at age 60 years or younger, and is triple negative.
 - d. Breast cancer is diagnosed at any age, with any of the following:
 - i. at least 2 close blood relatives on the same side of the family with breast cancer and/or epithelial ovarian cancer at any age; or
 - ii. the member has 2 breast primaries and also has at least 1 close blood relative with breast cancer diagnosed at age 50 years or younger; or
 - iii. the member has 2 breast primaries and also has at least 1 close blood relative with epithelial ovarian cancer; or
 - iv. close male blood relative with breast cancer; or
 - v. at least 1 1st-, 2nd-, or 3rd-degree blood relative with a known BRCA1 or BRCA2 mutation; or
 - vi. 2 close relatives on the same side of the family with pancreatic adenocarcinoma at any age; or
 - vii. if ethnicity is associated with higher mutation frequency (Ashkenazi Jewish), no additional family history is required.
3. Women with a personal history of pancreatic adenocarcinoma at any age with 2 close relatives on the same side of the family with breast cancer, epithelial ovarian cancer, and/or pancreatic adenocarcinoma at any age.
4. Women without a personal history of breast cancer, epithelial ovarian cancer, or pancreatic adenocarcinoma, and any of the following:
 - a. Women with 3 or more close blood relatives on the same side of the family with breast cancer, irrespective of age at diagnosis; or
 - b. Women with 1 or more close blood relatives on the same side of the family with breast cancer and 1 or more close blood relatives on the same side of the family with ovarian

-
- cancer; or
 - c. Women with 2 or more close blood relatives with epithelial ovarian cancer; or
 - d. Women with 1 or more male close blood relatives with breast cancer; or
 - e. Women with 2 or more 1st-degree relatives with breast cancer, 1 of whom was diagnosed at age 50 years and younger; or
 - f. Women with 1 or more 1st-degree relatives with bilateral breast cancer; or
 - g. Women with 1 or more close blood relatives with both breast and epithelial ovarian cancer; or
 - h. Women of Ashkenazi Jewish descent with 1 or more 1st-degree relatives or two or more 2nd-degree relatives with breast or ovarian cancer; or
 - i. Women with 1 or more 1st-, 2nd-, or 3rd-degree blood relatives with a known BRCA1 or BRCA2 mutation.
5. Women who do not meet any of the above criteria but are determined through both independent formal genetic counseling and validated quantitative risk assessment tool⁷ to have at least a 10% pre-test probability of carrying a BRCA1 or BRCA2 mutation. Note: In this category only, a 3-generation pedigree and quantitative risk assessment results must be provided to Aetna.
 6. Men with any of the following:
 - a. A 1st-, 2nd-, or 3rd-degree blood relative who has a known BRCA1 or BRCA2 mutation, where the results will influence clinical utility (i.e., reproductive decision-making); or
 - b. A personal history of breast cancer.

Table 2 | BCBS Structure

Publically traded companies:

1. Anthem for-profit (Became WellPoint, Inc. in 2004)
 - a. Anthem BlueCross BlueShield: Colorado, Connecticut, Indiana, Kentucky, Maine, Missouri, Nevada, New Hampshire, Ohio, Parts of Virginia, Wisconsin
 - b. Anthem Blue Cross: California
 - c. BlueCross BlueShield: Georgia
 - d. Empire BlueCross and BlueShield: New York

Multi state private companies:

1. CareFirst
 - a. District of Columbia
 - b. Maryland
 - c. Parts of Virginia
2. Health Care Service Corporation (HCSC)
 - a. BlueCross BlueShield of Illinois
 - b. BlueCross BlueShield of New Mexico
 - c. Blue Cross Blue Shield of Montana
 - d. BlueCross BlueShield of Oklahoma
 - e. BlueCross BlueShield of Texas
3. Highmark
 - a. Highmark BlueCross BlueShield (Western Pennsylvania)
 - b. Highmark BlueShield (Northeastern, Eastern & Central Pennsylvania)

-
- c. Highmark BlueCross Blue Shield Delaware (Delaware)
 - d. Highmark BlueCross BlueShield West Virginia (West Virginia)
 - 4. Premera
 - a. Premera BlueCross BlueShield of Alaska
 - b. Premera BlueCross (Washington)
 - 5. The Regence Group (Cambia Health Solutions)
 - a. Regence BlueShield of Idaho
 - b. Regence BlueCross BlueShield of Oregon
 - c. Regence BlueCross BlueShield of Utah
 - d. Regence BlueShield (Washington)
 - 6. Wellmark BlueCross Blue Shield
 - a. Iowa
 - b. South Dakota

Single state or regional companies:

- 1. BlueCross BlueShield of Alabama
- 2. BlueCross BlueShield of Arizona
- 3. Arkansas BlueCross BlueShield
- 4. Blue Shield of California
- 5. BlueCross BlueShield of Florida (branded as Florida Blue)
- 6. Hawaii Medical Service Association
- 7. BlueCross of Idaho
- 8. BlueCross BlueShield of Kansas
- 9. BlueCross BlueShield of Louisiana
- 10. Blue Cross Blue Shield of Massachusetts
- 11. Blue Cross Blue Shield of Michigan
- 12. Blue Cross Blue Shield of Minnesota
- 13. Blue Cross Blue Shield of Mississippi
- 14. Blue Cross and Blue Shield of Kansas City
- 15. Blue Cross Blue Shield of Nebraska
- 16. Horizon Blue Cross Blue Shield of New Jersey
- 17. Excellus BlueCross BlueShield (Central New York, Rochester and Utica/Watertown)
- 18. BlueShield of Northeastern New York (A division of HealthNow New York Inc.)
- 19. BlueCross BlueShield of Western New York (A division of HealthNow New York Inc.)
- 20. Blue Cross Blue Shield of North Carolina
- 21. Blue Cross Blue Shield of North Dakota
- 22. Blue Cross of Northeastern Pennsylvania
- 23. Capital Blue Cross (Central Pennsylvania)
- 24. Independence Blue Cross (Philadelphia, Southeastern Pennsylvania)
- 25. Blue Cross Blue Shield of Rhode Island
- 26. Blue Cross Blue Shield of South Carolina
- 27. BlueCross BlueShield of Tennessee
- 28. BlueCross BlueShield of Vermont
- 29. BlueCross BlueShield of Wyoming

Table 3 | BCBS Anthem: Coverage for *BRCA1/2* Testing

For individuals from a family with a **known deleterious** BRCA1/BRCA2 mutation, genetic testing for a BRCA1 or BRCA2 mutation, associated with genetic counseling, is considered medically necessary.

For individuals with a **personal history of cancer**, genetic testing for a BRCA1 or BRCA2 mutation, associated with genetic counseling, is considered medically necessary when ANY of the following criteria are met:

- The individual was diagnosed with breast cancer prior to age 50; OR
- The individual has a history of breast cancer diagnosed at any age and at least 1 first-, second- or third-degree relative with breast cancer diagnosed at age 50 years or less; OR
- The individual has multiple primary breast cancers or bilateral breast cancer; OR
- The individual is a male with breast cancer; OR
- The individual has triple negative breast cancer diagnosed at age 60 or less; OR
- The individual has a history of breast cancer and a first-, second- or third-degree male relative with breast cancer; OR
- The individual has a history of breast cancer and 2 or more first-, second- or third-degree relatives on the same side of the family with pancreatic cancer; OR
- The individual has a history of ovarian, fallopian tube or primary peritoneal cancer; OR
- The individual has a history of pancreatic cancer and 2 or more first-, second-, or third-degree relatives on the same side of the family with breast, ovarian, fallopian tube, primary peritoneal or pancreatic cancer; OR
- The individual has a history of breast cancer and at least 2 or more first-, second- or third-degree relatives on the same side of the family with breast cancer; OR
- The individual has a history of breast cancer and at least 1 first-, second- or third-degree relative with ovarian, fallopian tube, or primary peritoneal cancer; OR
- The individual has a history of breast cancer and belongs to a population at risk for specific mutations due to ethnic background (for example, Ashkenazi Jewish, Icelandic, Swedish, Hungarian or Dutch descent).

For individuals with a **family history of cancer**, genetic testing for a BRCA1 or BRCA2 mutation, associated with genetic counseling, is considered medically necessary when they have a relative who would meet ANY of the following criteria, but that relative is not available for testing:

- The individual for whom the test is requested, has a first- or second-degree relative who had breast cancer diagnosed prior to age 50; OR
- The individual for whom the test is requested, has a first- or second-degree relative with breast cancer diagnosed at any age and that relative has at least 1 first-, second- or third-degree relative with breast cancer diagnosed at age 50 years or less; OR
- The individual for whom the test is requested, has a first- or second-degree relative who had multiple primary breast cancers or bilateral breast cancer; OR
- The individual for whom the test is requested, has a first- or second-degree male relative who developed breast cancer; OR
- The individual for whom the test is requested, has a first- or second-degree relative who had triple negative breast cancer diagnosed at age 60 or less; OR
- The individual for whom the test is requested, has a first- or second-degree relative with breast cancer and that relative has a first-, second- or third-degree male relative with breast cancer; OR
- The individual has a first- or second-degree relative with a history of breast cancer and 2 or more first-, second-, or third-degree relatives on the same side of the family with pancreatic cancer; OR
- The individual has a first- or second-degree relative who has a history of ovarian cancer and 2 or more first-, second-, or third-degree relatives on the same side of the family with pancreatic cancer; OR
- The individual for whom the test is requested, has a first- or second-degree relative who has a history of ovarian, fallopian tube, or primary peritoneal cancer; OR
- The individual has a first- or second-degree relative with a history of pancreatic cancer, and 2 or more first-, second-, or third-degree relatives on the same side of the family with breast, ovarian, fallopian tube, primary

peritoneal or pancreatic cancer; OR

- The individual for whom the test is requested, has a first- or second-degree relative with history of breast cancer, and that relative has at least 2 or more first-, second- or third-degree relatives on the same side of the family with breast cancer; OR
- The individual for whom the test is requested, has a first- or second-degree relative with breast cancer, and that relative has at least 1 first-, second-, or third-degree relative with ovarian, fallopian tube or primary peritoneal cancer; OR
- The individual for whom the test is requested, has a first- or second-degree relative who has a history of breast cancer and that relative belongs to a population at risk for specific mutations due to ethnic background (for example, Ashkenazi Jewish, Icelandic, Swedish, Hungarian or Dutch descent).

For individuals with a **family history** of three or more first-, second- or third-degree relatives with ovarian, fallopian tube or primary peritoneal cancer or breast cancer, (at least one of which has breast cancer at or before age 50), genetic testing for a BRCA1 or BRCA2 mutation, associated with genetic counseling, is considered medically necessary.

Table 4 | Cigna Health Plan: Coverage for *BRCA1/2* Testing

Known Familial Mutation

Cigna covers BRCA1 and BRCA2 genetic testing for susceptibility to breast or ovarian cancer in adults as medically necessary with single site analysis for the known familial variant for a biologically-related individual from a family with a known BRCA1 or BRCA2 mutation.

Personal History of Breast Cancer

Cigna covers BRCA1 and BRCA2 genetic testing for susceptibility to breast or ovarian cancer in adults with full sequence analysis and duplication/deletion analysis of common variants as medically necessary when there is a personal history of breast cancer and for ANY of the following indications:

- diagnosed at age 45 or younger
- diagnosed at age 50 or younger with at least one close blood relative* with breast cancer at any age
- diagnosed with two breast primaries (includes bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) when the first breast cancer diagnosis occurred prior to age 50
- diagnosed at age 60 or younger with a triple negative breast cancer
- diagnosed at age 50 or younger with a limited family history (e.g., fewer than two first- or second degree female relatives or female relatives surviving beyond 45 years in the relevant maternal and/or paternal lineage)
- diagnosed at any age and there are at least two close blood relatives* with breast cancer at any age
- diagnosed at any age with at least one close blood relative* with breast cancer at age 50 or younger
- diagnosed at any age and there are at least two close blood relatives* with pancreatic cancer at any age
- diagnosed at any age with at least two close blood relatives* with aggressive prostate cancer (e.g., Gleason score ≥ 7) at any age
- diagnosed at any age with at least one close blood relative* with epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer
- close male blood relative* with breast cancer
- individual of Ashkenazi Jewish descent (testing in this situation is only covered for the three founder mutations [CPT code 81212] and not for full sequence analysis and duplication/deletion analysis of common variants)

Personal History of Cancer

Cigna covers BRCA1 and BRCA2 genetic testing for susceptibility to breast or ovarian cancer in adults with full sequence analysis and duplication/deletion analysis of common as medically necessary in an adult for any of the following indications:

- personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- personal history of male breast cancer
- personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥ 7) at any age with two or more close blood relatives* with breast, ovarian, pancreatic cancer, or aggressive prostate cancer (e.g., Gleason score ≥ 7) at any age

Family History of Breast, Ovarian or Pancreatic Cancer

Cigna covers BRCA1 and BRCA2 genetic testing for susceptibility to breast or ovarian cancer in adults with full sequence analysis and duplication/deletion analysis of common variants as medically necessary when there is no personal history of breast or ovarian cancer and for a family history of ANY of the following:

- first- or second-degree blood relative with a history of breast cancer and any of the following:
 - diagnosed at age 45 or younger
 - diagnosed at age 50 or younger with at least one additional close blood relative* with breast cancer at any age
 - diagnosed with two breast primaries (includes bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) when the first breast cancer diagnosis occurred prior to age 50
 - diagnosed at age 60 or younger with a triple negative breast cancer
 - diagnosed at age 50 or younger with a limited family history (e.g., fewer than two first- or second degree female relatives or female relatives surviving beyond 45 years in the relevant maternal and/or paternal lineage)
 - diagnosed at any age and there are at least two close blood relatives* with breast cancer at any age
 - diagnosed at any age with at least one close blood relative* with breast cancer at age 50 or younger
 - diagnosed at any age and there are at least two close blood relatives* with pancreatic cancer at any age
 - diagnosed at any age with at least two close blood relatives* with aggressive prostate cancer (e.g., Gleason score ≥ 7) at any age
 - diagnosed at any age with at least one close blood relative* with epithelial ovarian cancer, fallopian tube, or primary peritoneal cancer
 - lose male blood relative* with breast cancer
 - individual of Ashkenazi Jewish descent (testing in this situation is only covered for the three founder mutations (CPT code 81212) and not for full sequence analysis and duplication/deletion analysis of common variants) first- or second-degree blood relative with a history of epithelial ovarian, fallopian tube, or primary peritoneal cancer
- first- or second-degree blood relative with a history of male breast cancer
- first- or second-degree blood relative with a history of pancreatic cancer at any age with two or more close blood relatives* with breast, ovarian, or pancreatic cancer at any age
- third-degree blood relative with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer with two or more close blood relatives* with breast and/or ovarian cancer (with at least one close blood relative with breast cancer prior to age 50)

Table 5 | Emblem Health: Coverage for *BRCA1/2* Testing

Members are eligible for coverage of BRCA 1 and 2 Genetic Testing (BRACAnalysis when the results of the genetic testing will directly impact surveillance or treatment).

BRCA 1 and 2 genetic testing — 1, 2 or 3 must be met:

1. ≥ 3 close relatives on the same side of the family (including the member) have breast (either invasive or non-invasive) or ovarian cancer.
2. < 3 close relatives on the same side of the family with breast or ovarian cancer, but any of the following are present:
 - a. Member or close relative diagnosed with breast cancer at ≤ 45 years of age. .
 - b. Close relative identified with a detectable BRCA 1 or 2 mutation.
 - c. Member diagnosed with breast cancer ≤ 50 years of age and ≥ 1 close relative diagnosed with breast cancer at any age.
 - d. Member diagnosed with breast cancer at any age and ≥ 1 close relative diagnosed with breast cancer ≤ 50 years of age
 - e. Member or close relative diagnosed with 2 primary breast cancers (including bilateral disease or ≥ 2 more separate primary tumors in opposite breasts) and the first cancer was diagnosed at ≤ 50 years of age.
 - f. Member or close relative diagnosed with triple negative breast cancer at ≤ 60 years of age. (Breast cancer that is negative for Estrogen receptor [ER], Progesterone receptor [PR] and HER2)
 - g. Member was diagnosed with breast cancer ≤ 50 years of age and has a limited family history.
 - h. The member was diagnosed with breast cancer at any age and has ≥ 2 close blood relatives with pancreatic cancer or aggressive prostate cancer (Gleason score >7) at any age.
 - i. Member or close relative diagnosed with ovarian cancer at any age.
 - j. Member or close relative with breast cancer is male.
 - k. Member or close relative diagnosed with breast cancer at any age and at increased risk for specific mutation(s) secondary to ethnic background (e.g., Ashkenazi Jewish descent). (See Limitations/Exclusions)
- II. The member was diagnosed with pancreatic cancer or aggressive prostate cancer (Gleason score ≥ 7) at any age with ≥ 2 close relatives with breast and/or ovarian (including fallopian tube or primary peritoneal cancer) and/or pancreatic or aggressive prostate cancer (Gleason score ≥ 7) at any age.

Members are eligible for BRACAnalysis Rearrangement Testing (BART) if they meet criteria for Comprehensive BRACAnalysis and the analysis is negative

Limitations/Exclusions

Authorization should initially be for the mutation(s) specific to the ethnic group in question (e.g., Multisite 3 BRACAnalysis or equivalent for members of Ashkenazi descent). If multisite screening is negative, additional genetic testing (e.g., Comprehensive BRACAnalysis) would be warranted if the member meets the remainder of the criteria above. Requests that do not meet the testing criteria will be reviewed by a medical director.

Table 6 | Geisinger Health Plan: Coverage for *BRCA1/2* Testing

The Plan considers molecular susceptibility testing for hereditary breast and ovarian cancer (BRCA testing) medically necessary in ANY of the following indications:

- I. Individuals with a biologically related family member with a known *BRCA1/BRCA2* mutation and for whom the result will influence clinical decision making.
- II. Women with a personal history of breast cancer (including both invasive and ductal carcinoma in situ) and ANY of the following:
 - a. breast cancer diagnosed at age 45 or younger; or
 - b. breast cancer is diagnosed at age 50 or younger with one of the following:
 - i. At least one first, second, or third-degree relative with breast cancer at age 50 years or younger; or
 - ii. At least one first- second-, or third degree blood relative with epithelial ovarian cancer/fallopian tube/primary peritoneal cancer at any age
 - c. Documented evidence of two breast primaries (including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors) where first breast cancer diagnosed prior to age 50; or
 - d. Documented evidence of breast cancer at any age with two or more close first- or second-degree blood relatives with breast cancer and/or epithelial ovarian cancer/fallopian tube/primary peritoneal cancer at any age; or
 - e. First, second or third-degree male blood relative with documented evidence of breast cancer; or
 - f. Personal history of epithelial ovarian cancer/fallopian tube/primary peritoneal cancer; or
 - g. Certain ethnic descent associated with deleterious mutations (e.g. founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian, Dutch or other) or personal history of breast and/or ovarian cancer in first-, second- or third degree blood relative on the same side of the family; no additional family history required.
 - h. diagnosed at age 60 or younger with a triple negative breast cancer
- III. Women with a personal history of epithelial ovarian cancer/fallopian tube/primary peritoneal cancer
- IV. Women without a personal history of breast cancer but documented evidence of a first-, second-degree relative meeting any of the above criteria.
- V. Women without a personal history of breast cancer but documented evidence of a third degree relative with more than 2 close blood relatives with breast and/or ovarian cancer with at least one close blood relative with breast cancer at age 50 or younger.
- VI. Males with a personal history of breast cancer

Table 7 | HealthNet *BRCA1/2* Testing Guidelines

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1. Individuals with a family member with a known BRCA1/BRCA2 mutation; or
 2. Non-Ashkenazi Jewish women, age 18 or older, who have not been diagnosed with either breast or ovarian cancer, with any of the following high-risk family history patterns:
 - Two first-degree relatives* with breast cancer, one of whom was diagnosed at age 50 or younger; or
 - A combination of 3 or more first- or second-degree* relatives with breast cancer, regardless of age of diagnosis; or
 - A combination of both breast and ovarian cancer among first- and second –degree relatives; or
 - A first-degree relative with bilateral breast cancer; or
 - A combination of 2 or more first- or second-degree relatives with ovarian cancer, regardless of age of diagnosis; or
 - A first- or second-degree relative with both breast and ovarian cancer, at any age; or
 - A history of breast cancer in a male relative (father, sons, brothers, uncles, grandfathers); or
 - A family member has been identified with a detectable mutation
 3. Women of Ashkenazi Jewish heritage, (without a personal history of either breast or ovarian cancer), with any of the following high-risk family history patterns:
 - First-degree relative with breast or ovarian cancer, at any age; or
 - Two second-degree relatives on the same side of the family with breast or ovarian cancer, at any age.
 4. Women with a personal history of breast cancer (including invasive and ductal carcinoma in situ breast cancer) and one or more of the following:
 - Diagnosed age < 45y
 - Diagnosed at any age, with > 1 close blood relative with breast cancer diagnosed < 50 y
 - Diagnosed at any age with >1 close blood relative with epithelial ovarian cancer (including fallopian tubes and primary peritoneal cancer)
 - Two breast primaries when first breast cancer diagnosis occurred <age 50y [Two breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously]
 - Diagnosed age < 60 y with a triple negative breast cancer (i.e., ER-, PR-negative, and HER2-negative)
 - Diagnosed age < 50y with > 1 close blood relative with breast cancer at any age OR with a limited family history (Individuals with a limited family history, such as fewer than 2 first, or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation)
 - Diagnosed at any age, with > 2 close blood relatives with breast cancer at any age
 - Diagnosed at any age with > 2 close blood relatives with pancreatic cancer or aggressive prostate cancer (Gleason score >7) at any age
 - Close male blood relative with breast cancer
 - For an individual of ethnicity associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other), no additional family history may be required. Note: Testing for founder-specific mutation(s), if available, should be performed first. Full sequencing may be considered if other Hereditary Breast/Ovarian Cancer criteria is met.
 5. Women with a personal history of ovarian cancer (including fallopian tubes and primary peritoneal cancer).

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- For an individual of ethnicity associated with deleterious mutations (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other), no additional family history may be required. Note: Testing for founder-specific mutation(s), if available, should be performed first. Full sequencing may be considered if other hereditary breast and ovarian cancer (HBOC) criteria is met.

6. Males with a personal history of breast cancer

7. Individuals with a personal history of pancreatic cancer or aggressive prostate cancer (Gleason score >7) at any age with > 2 close blood relatives with breast and/ovarian cancer and /or pancreatic or aggressive prostate cancer (Gleason score >7) at any age

8. Family history only (Significant limitations of interpreting test results for an unaffected individual should be discussed)

- First or second-degree blood relatives meeting any of the above criteria
- Third degree blood relative with breast cancer and/or ovarian cancer with > 2 close blood relatives with breast cancer (at least one with breast cancer < 50y) and/or ovarian cancer
- Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.
- Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

* Close blood relatives include first-, second- and third degree relatives on same side of family. First-degree relatives include parents, siblings and children on both maternal and paternal sides. Second-degree relatives include grandparents, grandchildren, aunts and uncles, half-siblings, nieces and nephews on both maternal and paternal sides. Third-degree relatives are relatives with whom you share one-eighth of your genes, such as first cousins.

Table 8 | Health New England' Coverage of *BRCA1/2* Testing

Criteria for Approval:

Section A. For Medicare Advantage Members

1. Genetic tests for cancer are only a covered benefit for a beneficiary with a personal history of an illness, injury, or signs/symptoms thereof (i.e. clinically affected). A person with a personal history of a relevant cancer is a clinically affected person, even if the cancer is considered cured. Genetic testing is considered a non-covered screening test for patients unaffected by a relevant illness, injury, or signs/symptoms thereof.

2. Predictive or pre-symptomatic genetic tests and services, in the absence of past or present illness in the beneficiary, are not covered under national Medicare rules. For example, Medicare does not cover genetic tests based on family history alone.

3. A covered genetic test must be used to manage a patient. Medicare does not cover a genetic test for a clinically affected individual for purposes of family planning, disease risk assessment of other family members, when the treatment and surveillance of the beneficiary will not be affected, or in any other circumstance that does not directly affect the diagnosis or treatment of the beneficiary.

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4. The results of the genetic test must potentially affect at least one of the management options considered by the referring physician in accordance with accepted standards of medical care (e.g. surgery, the extent of surgery, a change in surveillance, hormonal manipulation, or a change from standard therapeutic or adjuvant chemotherapy).
 5. Pre-test genetic counseling must be provided by a qualified and appropriately trained practitioner.
 6. An informed consent form signed by the patient prior to testing which includes a statement that he/she agree to post-test counseling is required. This consent form must be available on request by Medicare.
 7. Genetic analysis must be provided through a laboratory which meets the American Society of Clinical Oncology (ASCO) recommended requirements:
 - The lab must meet appropriate Clinical Laboratory Improvement Amendment (CLIA) 1988 regulations;
 - Successful participation in the American College of Medical Genetics (ACMG)/College of American Pathologists (CAP) inspection and survey program;
 - appropriate state licensing; and
 - credentialing of laboratory directors and staff by the American Board of Medical Genetics (ABMG).
 8. In addition, criteria in section C must be met.

Section B. For Commercial and Medicaid Members

1. A covered genetic test must be used to manage a patient. HNE does not cover a genetic test for a clinically affected individual for purposes of family planning, disease risk assessment of other family members, when the treatment and surveillance of the beneficiary will not be affected, or in any other circumstance that does not directly affect the diagnosis or treatment of the beneficiary.
2. The results of the genetic test must potentially affect at least one of the management options considered by the referring physician in accordance with accepted standards of medical care (e.g., surgery, the extent of surgery, a change in surveillance, hormonal manipulation, or a change from standard therapeutic or adjuvant chemotherapy).
3. Pre-test genetic counseling must be provided by a qualified and appropriately trained practitioner.
4. An informed consent form signed by the patient prior to testing which includes a statement that he/she agrees to post-test counseling is required. This consent form must be available on request.
5. Genetic analysis must be provided through a laboratory which meets the American Society of Clinical Oncology (ASCO) recommended requirements:
 - a. The lab must meet appropriate Clinical Laboratory Improvement Amendment (CLIA) 1988 regulations;
 - b. Successful participation in the American College of Medical Genetics (ACMG)/College of American Pathologists (CAP) inspection and survey program;

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- c. Appropriate state licensing; and
 - d. Credentialing of laboratory directors and staff by the American Board of Medical Genetics (ABMG).

6. In addition, criteria in section C must be met.

Section C. Hereditary Breast and Ovarian Cancer Syndromes Criteria

1. BRCA1 and BRCA2 genetic testing is covered only for the following individuals: For the purpose of this policy, only genetic relations are relevant (i.e., "blood relatives"). Nongenetic relations, such as through marriage or adoption, are not relevant to coverage. A close relative means a first-degree (parents, full siblings, offspring) or second-degree (grandparents, grandchildren, aunts, uncles, nephews, nieces, half-siblings). Also, for this policy, invasive and ductal carcinoma in situ (DCIS) breast cancers should be included.

2. Individual from a family with a known deleterious BRCA1/BRCA2 mutation

3. Personal History of breast cancer plus one or more of the following:

- a. Diagnosed age < 45 years
- b. Diagnosed age < 50 years with > 1 first-, second-, or third-degree blood relative with breast cancer < 50 years and/or > 1 first-, second-, or third-degree blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
- c. Two breast primaries when first breast cancer diagnosis occurred prior to age 50 years
- d. Diagnosed < 60 years with a triple negative breast cancer
- e. Diagnosed < 50 years with a limited family history
- f. Diagnosed at any age with > first-, second-, or third-degree blood relatives with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer
- g. First-, second- or third-degree male blood relative with breast cancer
- h. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
- i. For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required.

4. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer

5. Personal history of male breast cancer

6. Personal history of breast and/or ovarian cancer at any age with >2 first-, second-, or third-degree blood relatives with breast and/or ovarian and/or pancreatic cancer at any Age

7. Family history only:

- a. First- or second-degree blood relative meeting any of the above criteria
- b. First- or second-degree blood relative with breast cancer and/or ovarian/fallopian tube/primary peritoneal cancer with > 2 first-, second-, or third-degree blood relatives with breast cancer (at least one breast cancer < 50 years) and/or ovarian cancer

Table 9 | Health Partners' Coverage of *BRCA1/2* Testing

BRCA genetic testing for breast/ovarian cancer predisposition is covered when ALL of the following criteria are met:

- I. Individual has not previously been tested for a BRCA genetic mutation
- II. Individual to be tested is at least 18 years old
- III. The member has received genetic counseling from one of the following independent, specialty-trained professionals who is not affiliated with the genetic testing lab:
 - a. board eligible or board certified genetic counselor
 - b. medical geneticist
 - c. other health professional with expertise and experience in cancer genetics (this list is not all-inclusive): oncologist, surgeon, oncology nurse, genetics clinical nurse, advanced practice nurse in genetics
- IV. The health professional recommends BRCA testing per National Comprehensive Cancer Network (NCCN) Guidelines based on the following:
 - a. review of the individual and family history
 - b. counseling of the individual about the potential benefits and harms of genetic testing
 - c. obtaining written, informed consent from the individual to be tested
- V. Summary notes from the ordering provider must be submitted

BRACAnalysis® Rearrangement Test (BART) is covered when ALL the following criteria are met:

- I. Individual meets all criteria in 2-5 listed above for BRCA testing; AND
- II. Previous Comprehensive BRACAnalysis® testing is negative (an exception may be made when surgical decisions are being based on concurrent results of BRCA1/2 and BART testing); AND
- III. Individual has not previously been tested using BART.

Table 10 | Humana's Coverage of *BRCA1/2* Testing**Known Familial Mutation**

- Individual with a close blood relative* with a known deleterious or suspected deleterious BRCA1 or BRCA2 mutation (Note: Test for known familial mutation);

Personal History of Cancer

- Breast cancer diagnosed at 45 years or younger; OR
- Two primary breast cancers, with the first breast cancer diagnosis occurring at or before age 50 years; OR
- Breast cancer diagnosed at 50 years or younger AND a limited family history, defined as fewer than two first or second degree female relatives or female relatives surviving beyond 45 years of age on either side of the family; OR
- Breast cancer diagnosed at 50 years or younger AND at least one close blood relative* diagnosed with breast cancer at any age; OR
- Triple negative breast cancer diagnosed at 60 years or younger; OR
- Breast cancer diagnosed at any age AND at least one close blood relative* diagnosed with breast cancer at 50 years or younger; OR
- Breast cancer diagnosed at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with breast cancer at any age; OR
- Breast cancer diagnosed at any age AND at least one close blood relative* diagnosed with epithelial ovarian cancer; OR
- Breast cancer diagnosed at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with pancreatic cancer at any age or aggressive prostate cancer (Gleason score at least seven) at any age; OR
- Breast cancer diagnosed at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with pancreatic cancer at any age or aggressive prostate cancer (Gleason score at least seven) at any age; OR
- Breast cancer diagnosed at any age AND a close male blood relative* diagnosed with breast cancer at any age; OR
- Breast cancer diagnosed at any age AND is of an ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish**); OR
- Epithelial ovarian, fallopian tube or primary peritoneal cancer diagnosed at any age; OR
- Male breast cancer diagnosed at any age; OR
- Pancreatic cancer diagnosed at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with breast and/or ovarian cancer at any age, and/or pancreatic or aggressive prostate cancer (Gleason score at least seven) at any age; OR
- Aggressive prostate cancer (Gleason score at least seven) diagnosed at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with breast and/or ovarian cancer at any age, and/or pancreatic or aggressive prostate cancer (Gleason score at least seven) at any age; OR

Family History Only

- First or second degree blood relative diagnosed with breast cancer at 45 years or younger; OR
- First or second degree blood relative diagnosed with two primary breast cancers, with the first breast cancer diagnosis occurring at or before age 50 years; OR
- First or second degree blood relative diagnosed with breast cancer at 50 years or younger AND a limited family history, defined as fewer than two first or second degree female relatives or female relatives surviving beyond 45 years of age on either side of the family; OR
- First or second degree blood relative diagnosed with breast cancer at 50 years or younger AND at least one additional close blood relative,* on the same side of the family, diagnosed with breast cancer at any age; OR
- First or second degree blood relative diagnosed with triple negative breast cancer at 60 years or younger; OR
- First or second degree blood relative diagnosed with breast cancer at any age AND at least one

close blood relative,* on the same side of the family, diagnosed with breast cancer at 50 years or younger; OR

- First or second degree blood relative diagnosed with breast cancer at any age AND at least two additional close blood relatives,* on the same side of the family, diagnosed with breast cancer at any age; OR
- First or second degree blood relative diagnosed with breast cancer at any age AND at least one close blood relative,* on the same side of the family, diagnosed with epithelial ovarian cancer; OR
- First or second degree blood relative diagnosed with breast cancer at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with pancreatic cancer at any age or aggressive prostate cancer (Gleason score at least seven) at any age; OR
- First or second degree blood relative diagnosed with breast cancer at any age AND a close male blood relative,* on the same side of the family, diagnosed with breast cancer at any age; OR
- First or second degree blood relative diagnosed with breast cancer at any age AND is of an ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish**); OR
- First or second degree blood relative diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer at any age; OR
- First or second degree blood relative diagnosed with male breast cancer at any age; OR
- First or second degree blood relative diagnosed with pancreatic cancer at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with breast and/or ovarian cancer at any age, and/or pancreatic or aggressive prostate cancer (Gleason score at least seven) at any age; OR
- First or second degree blood relative diagnosed with aggressive prostate cancer (Gleason score at least seven) at any age AND at least two close blood relatives,* on the same side of the family, diagnosed with breast and/or ovarian cancer at any age, and/or pancreatic or aggressive prostate cancer (Gleason score at least seven) at any age; OR
- Third degree relative with breast cancer and/or epithelial ovarian, fallopian tube or primary peritoneal cancer with at least two close blood relatives,* on the same side of the family, diagnosed with breast cancer (at least one with breast cancer diagnosed at 50 years or younger) and/or epithelial ovarian, fallopian tube or primary peritoneal cancer

Table 11 | Kaiser's Coverage of *BRCA1/2* Testing**Clinical Indications for Referral**

BRCA1 and BRCA2 testing is considered medically necessary when both pre and post test genetic counseling is provided by a qualified and appropriately trained practitioner, and one of the following criteria is met:

A. Persons with a family history but no personal history of breast and/or ovarian cancer in blood relatives from a single (same side) family linewith at least one of the following:

1. Breast cancer in at least:
 - a. two first or second degree relatives (mother, sister, daughter, grandmother, aunt, niece, or half sister) both diagnosed before age 50 and at least one of the relatives is first degree (mother, sister, or daughter) OR
 - b. three first or second degree relatives regardless of age OR
 - c. Two first degree relatives with breast cancer, one of whom was diagnosed at age 50 or younger
2. Ovarian cancer in at least two first or second degree relatives
3. Breast cancer in at least one first or second degree relative and ovarian cancer in at least one first or second degree relative
4. Women with one or more first or second degree relatives with multiple primary or bilateral breast cancer
5. A first or second degree relative with both breast and ovarian cancer
6. Women with increased risk for specific mutation due to ethnic background, (e.g. founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or others), and has any first degree or two second degree relatives on the same side of the family with breast cancer or ovarian cancer at any age.
7. History of breast cancer in male relatives

B. Persons with a personal history of breast and/or epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer but no family history, with at least one of the following:

1. Breast cancer diagnosed before age 45
2. Breast or epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer in women with increased risk for specific mutation due to ethnic background, (e.g. founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or others)
3. Personal history of breast and epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
4. Multiple primary or bilateral breast cancers when the first breast cancer diagnosis occurred before age 50.
5. Men with breast cancer

C. Persons with a personal and family history (in blood relatives from a single family line) of breast and/or ovarian cancer with at least one of the following:

1. Women with breast cancer:
2. See below
 - 2.1. diagnosed before age 50 and one or more first or second degree relatives with breast cancer diagnosed before age 50 and/or one or more first or second degree relatives with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
 - 2.2. diagnosed at any age and
 - 2.2.1. breast cancer in two or more first or second degree relatives at any age OR

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- 2.2.2. epithelial ovarian, fallopian tube cancer, or primary peritoneal cancer in one or more first or second degree relatives
 - 3. Women with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer and:
 - 3.1. Breast cancer in one or more first or second degree relatives OR
 - 3.2. Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer in one or more first or second degree relatives
 - 4. Women with breast or epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer at any age and
 - 4.1. Breast cancer in first or second degree male relative

D. Persons with a first or second degree blood relative who has previously been tested and found to have a clinically significant alteration in a BRCA1/2 gene. Note: “Clinically significant alteration” refers to an inherited alteration in a BRCA gene that is associated with an increased risk for the development of breast or ovarian cancer.

E. Persons with a lifetime risk of developing breast or ovarian cancer calculated at 10% or more using BRCAPRO software

Table 12 | Medicare: Coverage for *BRCA1/2* Testing

-
- 1. Personal history of breast cancer + one or more of the following:
 - Diagnosed age ≤ 45 y, with or without family history
 - Diagnosed age ≤ 50 y or two breast primaries, with ≥ 1 close blood relative(s) with breast cancer ≤ 50 y and/or ≥ 1 close blood relative(s) with epithelial ovarian/fallopian tube/primary peritoneal cancer
 - Two breast primaries when first breast cancer diagnosis occurred prior to age 50
 - Diagnosed age < 60 y with a triple negative breast cancer (ER-, PR-, HER2-)
 - Diagnosed age < 50 y with a limited family history, defined as fewer than 2 first- or second degree female relatives or female relatives surviving beyond 45 years in either lineage
 - Diagnosed at any age, with ≥ 2 close blood relatives with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer, at any age
 - Close male blood relative with breast cancer
 - Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
 - If of certain ethnicity associated with higher mutation frequency, (e.g., Ashkenazi Jewish) no additional family history required
 - A close relative with a known BRCA1 or BRCA2 gene mutation
 - 2. Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer.
 - 3. Personal history of male breast cancer.

Table 13 | Tufts Health Plan: Coverage for BRCA1/2 Testing

Tufts Health Plan may authorize coverage for BRCA1 & BRCA2, Multi-site BRCA3, or single-site BRCA1 or BRCA2 testing for Members at high risk for breast cancer. Tufts Health Plan defines high risk as a greater than ten percent risk for a positive test result based upon either the Myriad or BRCAPRO model. A letter of medical necessity from the Member's PCP or genetic specialist must be submitted to Tufts Health Plan which includes how the Member's high risk has been determined. Tufts Health Plan may authorize coverage of this testing when both A and B are met. In addition, the Member must meet one of the criteria listed under C, D, E, F or G.

A. The results of the genetic test will significantly alter the medical management of the Member (documentation required).

B. The recommendation for testing is based on a review of risk factors, clinical presentation and family history, and is supported by consultation with a licensed genetic counselor or a physician with expertise in genetic counseling (documentation required).

C. Tufts Health Plan may authorize the Multi-site BRCA3 test for female Members of Ashkenazi descent with ONE of the following risks:

1. Personal history of a primary breast cancer or ovarian cancer at any age.
2. No personal history of breast or ovarian cancer and one of the following:
 - a. Family history of breast or ovarian cancer, at any age, in any 1st degree relative.
 - b. Family history of breast or ovarian cancer, at any age, in at least two 2nd degree relatives.
 - c. A 1st degree relative with a known BRCA1 or BRCA2 mutation.

D. Tufts Health Plan may authorize the full panel BRCA 1& BRCA2 genetic tests for female Members who are NOT of Ashkenazi descent and have ONE of the following risks:

1. Personal history of primary breast cancer, diagnosed before age 50
2. Personal history of ovarian cancer at any age
3. Family history which includes one of the following:
 - a. Two 1st degree relatives with breast cancer, one of whom received the diagnosis at age 50 or younger.
 - b. A combination of three or more 1st or 2nd degree relatives with breast cancer regardless of age at diagnosis.
 - c. A combination of both breast and ovarian cancer among 1st or 2nd degree relatives.
 - d. A 1st degree relative with bilateral breast cancer.
 - e. A combination of two or more 1st or 2nd degree relatives with ovarian cancer regardless of age at diagnosis.
 - f. A 1st or 2nd degree relative with both breast and ovarian cancer at any age.
 - g. A history of breast cancer in a male relative.

4. A 1st degree relative with a known BRCA1 or BRCA2 mutation

E. Member is a male with ONE of the following:

1. Personal history of breast cancer at any age.
2. A 1st degree relative with a known BRCA1 or BRCA2 mutation.

F. The Member's requesting provider submits the results of BRCAPRO which shows that the calculated risk of the Member having the mutation is \geq (greater than or equal to) 10%.

G. The Member, of any age, has triple negative breast cancer. Breast cancer is defined as triple negative breast cancer when the tumor that does not have receptors for any of the following; estrogen, progesterone or human epidermal growth factor receptor 2 (HER2).

Note: For male Members, Multi-site BRCA3 test will be approved if Ashkenazic. If not Ashkenazic, a full panel BRCA1&2 will be approved. If there is a known mutation, single-site testing will be approved.

Tufts Health Plan may authorize single site analysis only for Members who have a 1st degree relative with a known BRCA 1 or 2 mutation, regardless of personal history or descent. For Members who are of a partial

Ashkenazic or non-Ashkenazic descent if the Member meets the Ashkenazic criteria above and the family history of breast and/or ovarian cancer occurred predominantly in non-Ashkenazic relatives, Tufts Health Plan may authorize full panel BRCA1 & BRCA2 genetic testing. For Members who are of Ashkenazic descent who meet the criteria for Multisite 3 testing and who have a negative multi-site 3 test, Tufts Health Plan may authorize full panel BRCA1 & BRCA2 genetic testing (reflex testing). All testing must be performed at a contracting laboratory facility when available.

COVERAGE GUIDELINES FOR BART TESTING

Large genomic rearrangements occur in a small percentage (<1%) of all patients tested for hereditary breast and ovarian cancer. In August 2002, Myriad launched an enhancement to the BRCAAnalysis test to detect five common large rearrangements. The BRCAAnalysis Rearrangement Test, or BART, launched in 2006, is designed to detect large rearrangements beyond these five.

Tufts Health Plan may authorize coverage of BART™ testing for Members who meet the clinical criteria outlined below. Please note: When using the chart below, the following conditions apply:

- Male breast cancer qualifies at any age
- At least one relative must be a first or second degree relative and qualifying cancers must be on the same side of the family
- Breast cancer includes ductal carcinoma in situ (DCIS) and invasive cancers

Member Affected With: Additional History Required

Breast Cancer before age 50 : 2 or more diagnoses of breast cancer before age 50 and/or ovarian cancer at any age

Ovarian cancer at any age : 2 or more diagnoses of breast cancer before age 50 and/or ovarian cancer at any age

Male breast cancer at any age : 2 or more diagnoses of breast cancer before age 50 and/or ovarian cancer at any age

Breast cancer at or after age 50 and ovarian cancer at any age : 1 or more diagnoses of breast cancer before age 50 and/or ovarian cancer at any age

Breast cancer before age 50 and ovarian cancer at any age: No additional relatives required

Table 14 | United Healthcare's Coverage of *BRCA1/2* Testing**BRCA Testing Criteria**

- I. BRCA1 and BRCA2 testing is proven for women with a personal history of breast cancer in the following situations:
 - A. Breast cancer diagnosed at age 45 or younger with or without family history; OR
 - B. Breast cancer diagnosed at age 50 or younger with:
 1. At least one close blood relative with breast cancer at any age; OR
 2. Limited family history (see Definitions section for further clarification)
 - C. Breast cancer diagnosed at any age with:
 1. Two breast primary cancers, when first breast cancer diagnosis occurred prior to age 50 OR
 2. Personal history of ovarian cancer; OR
 3. At least one close blood relative with breast cancer diagnosed at age 50 or younger; OR
 4. At least two close blood relatives on the same side of the family with breast cancer at any age; OR
 5. At least one close blood relative with ovarian cancer at any age; OR
 6. At least two close blood relatives on the same side of the family with pancreatic or aggressive prostate (Gleason score ≥ 7) cancer at any age; OR
 7. Close male blood relative with breast cancer; OR
 8. At least one close blood relative that has a BRCA1 or BRCA2 mutation; OR
 9. Ashkenazi Jewish or ethnic groups associated with founder mutations. Testing for Ashkenazi Jewish founder-specific mutations should be performed first.
 - D. Triple negative breast cancer diagnosed at age 60 or younger.
- II. BRCA1 and BRCA2 testing is proven for women with a personal history of ovarian cancer.
- III. BRCA1 and BRCA2 testing is proven for women and men with a personal history of pancreatic cancer at any age and at least two close blood relatives on the same side of the family with breast, ovarian, pancreatic and/or aggressive prostate (Gleason score ≥ 7) cancer at any age.
- IV. BRCA1 and BRCA2 testing is proven for men with a personal history of aggressive prostate (Gleason score ≥ 7) cancer at any age and at least two close blood relatives on the same side of the family with breast, ovarian, pancreatic and/or aggressive prostate (Gleason score ≥ 7) cancer at any age.
- V. BRCA1 and BRCA2 testing is proven for men with a personal history of breast cancer.
- VI. BRCA1 and BRCA2 screening tests are proven for men and women without a personal history of breast or ovarian cancer with at least one of the following familial risk factors:
 - A. At least one first- or second-degree blood relative meeting any of the above criteria (I-V); OR
 - B. At least one third-degree blood relative with breast cancer and/or ovarian cancer who has at least 2 close blood relatives with breast cancer (at least one with breast cancer at age 50 or younger) and/or ovarian cancer; OR
 - C. A known BRCA1/BRCA2 mutation in the family (defined as first-, second- or third degree relative)
- VII. BRCA1 and/or BRCA2 testing is unproven for all other indications including: 1) screening of breast or ovarian cancers for individuals not listed in the proven indications above or 2) for risk assessment of other cancers. Further evidence is needed to establish the clinical

utility of testing in other populations.

Large Genomic Rearrangement Testing

Certain large genomic rearrangements are not detectable by primary sequencing assay, thereby necessitating supplementary testing, in some cases. In these circumstances, NCCN guidelines emphasize the need for comprehensive testing, which encompasses full BRCA1/2 sequencing and detection of large gene rearrangements.

- I. Detection of large genomic rearrangements (e.g., BRACAnalysis® Large Rearrangement Test (BART)) is proven for individuals who meet the testing criteria for BRCA1/BRCA2 and have no known familial BRCA1/BRCA2 mutations*. Detection of large genomic rearrangements (e.g., BRACAnalysis® Large Rearrangement Test (BART)) is medically necessary when the following criteria are met:
 - A. Individual meets the testing criteria for BRCA1/BRCA2 and has no known familial BRCA1/BRCA2 mutations*
 - B. Testing is conducted on an affected family member. If an affected family member is unavailable, testing is conducted on the unaffected family member with the highest likelihood of a BRCA1/BRCA2 mutation (NCCN, 2013)
- II. Detection of large genomic rearrangements (e.g., BRACAnalysis® Large Rearrangement Test (BART)) is unproven for the purpose of screening in the general population. There is inadequate clinical evidence that such screening reduces mortality from breast cancer in a normal risk population.

NOTE: National Comprehensive Cancer Network (NCCN) guidelines state that significant limitations of interpreting test results for an unaffected individual should be discussed. Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing. Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation (NCCN, 2013).

Appendix 4

Screening Tools

Note to Reader: The following tools are those recognized by the U.S. Preventive Services Task Force (USPSTF) as being “clinically useful predictors of which women should be referred for genetic counseling due to increased risk for potentially harmful BRCA mutations.”^{256,257} Many other risk tools exist. Each of the following tools has its “limitations” and the USPSTF has “found insufficient comparative evidence to recommend one tool over another.” The tables presented in this Appendix were taken directly from the USPSTF’s report.²⁵⁸ Some tables are simply summaries, so readers should access the original risk tools for the most accurate representation. The original journal articles are cited below.

Contents:

Table 1.	Ontario Family History Assessment Tool (FHAT) ²⁵⁹
Table 2.	Manchester Scoring System ²⁶⁰
Table 3.	Referral Screening Tool ²⁶¹
Table 4.	Pedigree Assessment Tool ²⁶²
Table 5.	FHS-7 ²⁶³

²⁵⁶ "Final Recommendation Statement - Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women," U.S. Preventive Services Task Force (USPSTF). <http://www.uspreventiveservicestaskforce.org/uspstf12/brcatest/brcatestfinalrs.htm>. December 2013. Accessed February 2, 2013.

²⁵⁷ Moyer, V.A. (2014) Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer in Women: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine* 160, no. 4: 271-281.

²⁵⁸ Moyer, *Annals of Internal Medicine*.

²⁵⁹ Gilpin, C. A., Carson, N., & Hunter, A. G. W. (2000). A preliminary validation of a family history assessment form to select women at risk for breast or ovarian cancer for referral to a genetics center. *Clinical Genetics* 58(4), 299-308.

²⁶⁰ Oros, K. K., Ghadirian, P., Maugard, C. M., Perret, C., Paredes, Y., Mes-Masson, A. M., ... & Tonin, P. N. (2006). Application of BRCA1 and BRCA2 mutation carrier prediction models in breast and/or ovarian cancer families of French Canadian descent. *Clinical Genetics* 70(4), 320-329.

²⁶¹ "Breast Cancer Genetics: Referral Screening Tool (B-RST)," Georgia Breast Cancer Genomic Consortium: Education Surveillance and Policy. Peachtree Solutions, LLC. <https://www.breastcancergenescreen.org/default.aspx>. Accessed February 2, 2014.

²⁶² Hoskins, K. F., Zwaagstra, A., & Ranz, M. (2006). Validation of a tool for identifying women at high risk for hereditary breast cancer in population-based screening. *Cancer* 107(8), 1769-1776.

²⁶³ Ashton-Prolla, P., Giacomazzi, J., Schmidt, A. V., Roth, F. L., Palmero, E. I., Kalakun, L., ... & Camey, S. A. (2009). Development and validation of a simple questionnaire for the identification of hereditary breast cancer in primary care. *BMC Cancer* 9(1), 283.

Table 1. Ontario Family History Assessment Tool*

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7
Second-/third-degree relative	5
Breast cancer relative	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset at age 20–29 y	6
Onset at age 30–39 y	4
Onset at age 40–49 y	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relative	
Mother	7
Sibling	4
Second-/third-degree relative	3
Age at ovarian cancer onset	
<40 y	6
40–60 y	4
>60 y	2
Age at prostate cancer onset	
<50 y	1
Age at colon cancer onset	
<50 y	1
Family total	
Referral†	≥10

* From reference 19.

† Referral with a score of ≥10 corresponds to doubling of lifetime risk for breast cancer (22%).

Table 2. Manchester Scoring System*

Risk Factor	<i>BRCA1</i> Score	<i>BRCA2</i> Score
Age at onset of female breast cancer†		
<30 y	6	5
30–39 y	4	4
40–49 y	3	3
50–59 y	2	2
≥60 y	1	1
Age at onset of male breast cancer†		
<60 y	5‡	8§
≥60 y	5‡	5§
Age at onset of ovarian cancer†		
<60 y	8	5
≥60 y	5	5
Pancreatic cancer	0	1
Age at onset of prostate cancer†		
<60 y	0	2
≥60 y	0	1

* From reference 13. Developed so that a score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation.

† For relatives in direct lineage.

‡ If *BRCA2* tested.

§ If *BRCA1* tested.

*Table 3. Referral Screening Tool**

Risk Factor	Breast Cancer at Age ≤ 50 y	Ovarian Cancer at Any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥ 2 cases of breast cancer after age 50 y		
on the same side of the family		
Male breast cancer at any age in any		
relative		
Jewish ancestry		

* From reference 16. A patient completes the checklist if she has a family history of breast or ovarian cancer and receives a referral if she checks ≥ 2 items.

Table 4. Pedigree Assessment Tool*

Risk Factor	Score†
Breast cancer at age ≥ 50 y	3
Breast cancer at age < 50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4

* From reference 17. A score of ≥ 8 is the optimum referral threshold.

† For every family member with a breast or ovarian cancer diagnosis, including second- or third-degree relatives.

Table 5. FHS-7*

- Did any of your first-degree relatives have breast or ovarian cancer?
- Did any of your relatives have bilateral breast cancer?
- Did any man in your family have breast cancer?
- Did any woman in your family have breast and ovarian cancer?
- Did any woman in your family have breast cancer before age 50 y?
- Do you have 2 or more relatives with breast and/or ovarian cancer?
- Do you have 2 or more relatives with breast and/or bowel cancer?

* From reference 18. One positive response initiates referral.

Appendix 5

Genes and Conditions

Note to Reader: The following table lists the genes referenced in Appendix 2, as well as the condition with which these genes are associated.

Gene	Condition
APC	Familial adenomatous polyposis
ATM	Moderate-risk breast cancer susceptibility
BLM	Bloom Syndrome
BMPR1A	Juvenile Polyposis Syndrome
BRCA1	Hereditary breast and ovarian cancer syndrome
BRCA2	Hereditary breast and ovarian cancer syndrome
BRIP1	Moderate-risk breast cancer susceptibility
CDC73	Hyperparathyroidism-Jaw Tumor Syndrome
CDH1	Hereditary diffuse gastric cancer
CDKN2A/p16	Familial Cutaneous Malignant Melanoma; Moderate-risk breast cancer susceptibility
CDK4	Familial Cutaneous Malignant Melanoma
CHEK2	Breast cancer and Li-Fraumeni syndro
EPCAM	Lynch syndrome
FLCN	Birt-Hogg-Dube Syndrome
FH	Hereditary Leiomyomatosis and Renal Cell Cancer
MEN1	Multiple Endocrine Neoplasia, Type 1
MET	Hereditary papillary renal cell carcinoma

MLH1	Lynch syndrome
MUTYH	MYH-associated polyposis syndrome
MSH2	Lynch syndrome
MSH6	Lynch syndrome
NBN	Moderate-risk breast cancer susceptibility
PALB2	Moderate-risk breast cancer susceptibility
PALLD	Familial pancreatic adenocarcinoma
PMS2	Lynch syndrome
PRKAR1A	Carney Complex
PTCH1	Gorlin Syndrome; Basal cell nevus syndrome
PTEN	PTEN Hamartoma Tumor Syndrome
RAD51C	Moderate-risk breast cancer susceptibility
RET	Multiple Endocrine Neoplasia, Type 2A and 2B
SMAD4	Juvenile Polyposis Syndrome
STK11	Peutz-Jeghers Syndrome
TP53	Li-Fraumeni Syndrome
VHL	Von Hippel-Lindau Syndrome

Appendix 6

CPT® codes²⁶⁴

Note to Reader: The following table lists the CPT codes for the *BRCA1/2* tests detailed in Chapter 3: A Changing Genetic Landscape, and then described again in Appendix 2.

CPT code	Code Description
81211	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81214	BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
81215	BRCA1 (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant Large genomic rearrangements (e.g., BART)
81213	BRCA1, BRCA2 (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants

²⁶⁴ "CPT Coding, Medical Billing and Insurance," American Medical Association. <http://www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance.page?>. Accessed February 22, 2014.