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Myriad Genetics and the Debate Over Genetic Testing for Breast Cancer Susceptibility

Since their discovery and patent of the two primary breast cancer-linked genes, BRCA1 and BRCA2, in 1990 and 1996, Myriad Genetics has led the way in providing comprehensive genetic testing for breast cancer susceptibility. Through genetic testing, scientists can check for the presence of genes as indicators of people's biological programming. Based on their findings, scientists evaluate a person's chance for acquiring a specific kind of cancer before the cancer even appears and make suggestions for early detection and preventative care. Today Myriad provides the first and only available commercial testing for breast cancer. However, policy and ethics groups, such as Stanford University Medical Center's Program in Genomics, Ethics, and Society, have brought to light many underlying concerns for genetic testing, indicating that the use of genetic testing also comes with many limitations and dangers. With the power to peek into people's genomes comes a duty to do so appropriately, properly, responsibly. Groups conducting genetic testing must ensure the best interests of the patients, research, and the company. Among other standards, they must obtain informed consent, provide pre- and post-test genetic counseling, train counselors in genetics and social issues, mandate a follow-up, and conduct research.¹ I will argue that Myriad Genetics succeeds in providing efficient genetic sequencing and analysis for breast cancer susceptibility, but it is severely lacking in many other crucial aspects of patient care.

Two genes, BRCA1 and BRCA2, are associated with some cases of breast cancer. Under normal circumstances, these genes are tumor suppressor genes; that is, they encode proteins that restrain uncontrolled cell growth and prevent the growth of malignant cells

in breast tissue. Any number of over 100 known mutations in BRCA1 and BRCA2ⁱⁱ can lead to inactivation or loss of function, thereby suppressing that gene's ability to control abnormal cell growth.ⁱⁱⁱ However, tumor suppressor genes come in pairs—one gene inherited maternally and the other gene inherited paternally. Inactivation of one copy of BRCA1 or BRCA2 would not prevent normal cell growth because the other copy would still function normally. Mutations are a normal part of growth, and through the life cycle of the cell, additional mutations can take place. Under normal circumstances, a cell has the ability to prevent malignancy through its tumor suppressor genes. If a child receives a mutated copy of BRCA1 or BRCA2 from either parent, that child will lack the “back-up” copy of the gene and therefore, theoretically, be more susceptible for hereditary breast cancer, especially if another mutation inactivates the remaining tumor suppressor gene.

Myriad Genetics, through testing known as BRACAnalysis, has the ability to test for the presence of a mutated BRCA1 and BRCA2 and thereby suggest susceptibility to breast cancer. BRCA1 and BRCA2 are responsible for 90% of hereditary breast cancer.^{iv} By comparing a person's DNA sequence with that of all known breast cancer-causing mutations, Myriad can evaluate a person's risk for breast cancer. BRACAnalysis is the only clinically available total gene sequencing for BRCA1 and BRCA2, and with one's family history and needs, patients can be tested with Comprehensive Sequencing (full gene), Single Site Sequencing (one specific mutation), or Multisite Sequencing (three common mutations).^v

Breast cancer is unlike Huntington's Disease or other 100% penetrance diseases. These other diseases offer patients no hope, no prevention, no treatments. On the other hand, breast cancer is treatable. In fact, early detection of breast cancer can mean early intervention, proper medical care, and, in most cases, a cure. Late detection, in its worst case, can ultimately lead to the spread of the malignant tumor to other parts of the body and possible death. Companies like Myriad Genetics advocate genetic testing for breast

cancer because of the possible treatment. BRACAnalysis is highly accurate, sensitive, and specific.^{vi} After giving a blood sample to the laboratory, patients can expect results within 2-3 weeks. Positive test results from BRACAnalysis can benefit people by raising awareness for taking preventative measures against breast cancer, increasing surveillance, facilitating its earlier detection, and thereby increasing patients' chance of survival if they do indeed develop cancer. And furthermore, positive or negative results can also reduce people's anxiety of their risk and their children's risk, give them certainty and peace of mind, and allow them to plan their lives.^{vii}

Genetic testing is only conducted for people with a high risk for breast cancer. Myriad determines risk based on four main factors: family history (two or more relatives with breast cancer), diagnosis of breast cancer, diagnosis of ovarian cancer, and a relative with a known BRCA1 or BRCA2 mutation.^{viii} In other words, susceptibility testing is available to the people who would benefit most from the test results. A guide provided by Myriad, *Clinical Research for Health Care Professionals*, outlines how physicians should determine their patient's risk, and a questionnaire (*The Family History Questionnaire for Breast and Ovarian Cancer*, available on-line) provides patients with points of consideration when deciding whether genetic testing is appropriate.^{ix}

Myriad provides information for pre- and post-test genetic education and counseling to doctors and patients to promote proper use of its services and proper interpretation of the test results. For all stages of the genetic testing process, Myriad provides the patient with a handbook with a list of genetic counselors and health professionals who can help with counseling and support. Post-test resources include booklets to provide information and facilitate better understanding for positive or negative results.

However, this isn't the full story. Genetic testing for breast cancer raises ethical issues because often the costs and risks outweigh the benefits. When there are potential

significant, negative effects for the patient and the patient's family, one must consider what is the best option? Only the patient can weigh all sides of the equation and decide. Moreover, it is the duty of the company conducting the test to actively ensure that the patient makes an educated, well-informed decision.

The company should inform the patient about all aspects of the test. Genetic testing is not explicitly beneficial for all patients, as it may seem at first. A positive test result may have implications on family members who may also need to be tested for susceptibility. If the company conducts a linkage study, it will require blood samples from relatives, both those that are affected and those that are not. In short, the genetic test extends beyond the individual. Likewise, a negative test result does not necessarily mean relief, lowered anxiety, or better life planning. A negative test is often accompanied by unforeseen psychological stress, including intense feelings of guilt toward relatives who tested positive, or stress due to concern of children who may now also be at risk. Furthermore, while positive or negative test results may seem to offer a sense of certainty, many people are left with only "inconclusive" results. Thus, these people may suffer all of the psychological consequences of the test—increased anxiety, even greater uncertainty about their lives, and problems finding insurance and employment.

Genetic tests also offer a false sense of certainty in that the results are not always reliable. There are no reliable early detection methods, and correlations between genes and breast cancer are hazy at best. Precise knowledge of the underlying genetic processes is not known. Studies have found a correlation between breast cancer and mutations on BRCA1 and BRCA2, but there are other confounding genes as well, with BRCA1 and BRCA2 only making up 90% of inherited breast cancer. Genetic determinism can be dangerous. A positive result on a genetic test does not necessarily mean the patient will develop cancer, and a negative result does not necessarily mean the patient won't develop cancer. In fact, scientists are uncertain as to what BRCA mutations

make a person susceptible breast cancer, and to what extent each mutation influences susceptibility. Only 5-10% of women with a genetic mutation develop breast cancer, and the penetrance rate of the breast cancer genes is 10% for the general population and 50-85% for people with BRCA1 mutations.^x Thus, many people with the mutation never develop breast cancer. In fact, no single mutation can account for a large percentage of breast cancers. More than one gene can be involved in susceptibility, as well as countless environmental factors that are as of yet unknown. Patients who test negative for a BRCA1 or BRCA2 mutations still have the same chance of developing breast cancer as the general population. Companies must ensure that patients take the proper preventative measures regardless of the presence of the mutation. If genetic testing companies do not take the necessary precautions, a patient may feel she is immune to breast cancer, stop going to regular mammograms, and stop conducting regular self-breast exams. Results could prove disastrous.

Myriad seems to downplay the potential insurance and employment problems that many patients of genetic testing face. Often employers refuse to hire a person with record of a genetic test, or the patient is limited in employment opportunities because prospective jobs may not provide the kind of insurance that the patient needs. A focus group at Duke University, consisting of women with breast cancer or relatives who had it, noted that one of the major concerns for testing was the loss of insurance.^{xi} Many insurance companies are unwilling to insure a patient whose record indicates a past genetic test, regardless of the test results. While some companies cover part of the cost of the genetic test for high risk patients, they usually do not insure the patient for costs beyond the initial testing, such as costs for pre- and post-test counselors, education, and follow-up exams. Given the importance of these factors to work in conjunction with the genetic test, results could be dangerous for a patient who does not receive adequate counseling because the patient could not afford it.

We also need to reconsider “high risk” as a criterion for genetic testing. Myriad Genetics formed an agreement with Aetna U.S. Healthcare to provide medical coverage for BRCA testing for high risk patients. But what defines high risk? If a patient has two relatives with breast cancer, Myriad considers that patient to have a family history of breast cancer and, therefore, to be a candidate for genetic testing. However, breast cancer is a very common disease, affecting one out of nine women, and it is not uncommon for two breast cancer cases to randomly occur in the same family, completely unconnected to an inherited mutation.^{xii}

Genetic testing is very costly, and most health insurance companies do not provide for it. Testing for just one common mutation in BRCA1 or BRCA2 runs at \$395.^{xiii} However, because of multiple possible mutation causes, genetic testing requires sequencing the entire gene. Thus, most people obtain a total sequencing of BRCA1 and BRCA2 (comprehensive BRACAnalysis) for \$2,400.^{xiv} Multisite BRACAnalysis, which tests the patient for common mutations, would cost \$2,050.^{xv} Compounded with emotional and psychological costs on the individual and family, genetic testing is expensive.

Myriad’s genetic education and counseling also seems inadequate in that the company does not actively strive to ensure patient education. While Myriad advertises access to professional consultations and information, patients receive handbooks and lists on finding their own counselor. Myriad leaves it up to the patients and their physicians to carry out the genetic analysis, education, and counseling. While Myriad encourages it, Myriad does not see that these steps are carried out, neither by conducting counseling themselves nor through follow-up examinations.

Furthermore, under Myriad’s standard procedures, the responsibility for obtaining informed consent falls on the patient’s doctor. While perhaps the doctor is in the best position to discuss matters with the patient, Myriad should modify its procedures to

ensure greater involvement. There is no procedure to make sure that every patient upon whom Myriad conducts a genetic susceptibility test was actually informed about the procedure, issues, costs, and benefits of the test. Aetna U.S. Healthcare, under an agreement with Myriad Genetics, uses consent forms to release test information and obtain informed consent. However, informed consent means little unless accompanied by appropriate counseling, which Aetna does not cover and Myriad does not provide. This is a critical aspect of genetic testing, and the leading company providing the test should take better precautions against uninformed consent. Again, patients are provided with a handbook of factors to consider for evaluating their own risk for breast cancer, but no genetic counseling is available through Myriad to help them make this decision.

Breast cancer has a wide variety of causes, none of which are known for certain, no known methods of prevention, and limited treatment options. Some risk factors include women, increased age, a family history, early menstruation, and bearing no children or a child after age 30. About 51-73% of women with mutations in BRCA1 or BRCA2 will develop breast cancer by age 50, and 82-87% will develop cancer by age 70.^{xvi} While some genetic correlations can be made, over 70% of women with breast cancer have no known risk factors.^{xvii} Effective medical treatment and a cure are still a long way off. Current treatment options include traditional prophylactic mastectomy, a surgery to remove part or all of a cancerous breast, but even this method does not guarantee the person will not get the disease. The best known method to deal with breast cancer is early detection through regular mammograms and monthly self-breast examinations.

There are many recommendations in regard to genetic testing for breast cancer susceptibility that one could make to Myriad. Their responsibility goes beyond merely providing written information to the patients. For example, Myriad should attempt a multidisciplinary approach—that is, it could integrate its genetic expertise with

knowledge of social and psychological issues. They may accomplish this through expanding its areas of service, such as by hiring its own counselors or training its genetic experts in the social implications and counseling of its services. Myriad could also offer prospective patients better access to formerly tested individuals, so they could learn more about life after the genetic test and discuss their concerns.

It is the duty of Myriad Genetics, as sole providers of this genetic test and arguably the most informed and up-to-date experts in the field, to take care of their patients. Given that they will continue to conduct the genetic test for breast cancer susceptibility, they must do so ethically—that is, they must inform, educate, and counsel their patients on the full extent of the many issues, costs, and benefits of the test. Genetic testing in itself can be extremely valuable, but when dealing with such a cancer with far-reaching effects in people's lives, we must be careful to use it wisely. We must remember that the test offers only limited information, and nothing is definite. Genetic testing can have far more harmful effects and problems than good, and until research is done, we should operate with cautious steps.

ⁱ Koenig B, et al. "Genetic Testing for BRCA1 and BRCA2: Recommendations of the Stanford Program in Genomics, Ethics, and Society," *Journal of Women's Health* 1998; 7:5.

ⁱⁱ Greely HT. "Genetic Testing for Cancer Susceptibility: Challenges for Creators of Practice Guidelines," *Oncology* Nov 1997; 11:11A.

ⁱⁱⁱ Alberts B, et al. *Essential Cell Biology: An Introduction to the Molecular Biology of the Cell*. Garland Publishing, Inc.: New York. 1998; p.588

^{iv} Myriad Genetics. Genetic Testing Information for Health Care Professionals. Mar 2, 1999. <<http://www.myriad.com/0health/hlthff.html>>.

^v *ibid*

^{vi} Myriad Genetics. Myriad Genetic Laboratories, Inc. Research. Mar 7, 1999. <<http://www.myriad.com>>.

^{vii} Greely HT. "Genetic Testing for Cancer Susceptibility: Challenges for Creators of Practice Guidelines," *Oncology* Nov 1997; 11:11A.

^{viii} Myriad Genetics. Identifying Patients at Risk of Hereditary Breast and Ovarian Cancer. Mar 2, 1999. <<http://www.myriad.com/0health/hlthff.html>>.

^{ix} *ibid*

^x Greely HT. "Genetic Testing for Cancer Susceptibility: Challenges for Creators of Practice Guidelines," *Oncology* Nov 1997; 11:11A.

^{xi} Tessaro I. "Genetic testing for susceptibility to breast cancer: findings from women's focus groups." *Journal of Women's Health* 1997 Jun; 6(3):317-27.

^{xii} Memorial Sloan-Kettering Cancer Center. Cancer and Treatment Information: What Is Breast Cancer? Mar 7, 1999. <<http://www.mskcc.org/document/wicbrst2.htm>>

^{xiii} Myriad Genetics. Terms of Payment and Reimbursement. Mar 4, 1999. <<http://www.myriad.com/0health/hlthff.html>>.

^{xiv} *ibid*

^{xv} *ibid*

^{xvi} Memorial Sloan-Kettering Cancer Center. Cancer and Treatment Information: What Is Breast Cancer? Mar 7, 1999. <<http://www.mskcc.org/document/wicbrst2.htm>>

^{xvii} *ibid*