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Genomic Testing and the Ethical Implications of BRCA 1/2 Testing

BRCA1/2 and the Development of Hereditary Breast and Ovarian Cancer

Identifying common genetic variants in association with common cancers allows for the production of effective target screening and treatments for these specific cancers. An impressive example of this target screening process is represented by BRCA mutation testing for breast and ovarian cancer susceptibility. Genetic tests screen for BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 1, early onset) mutations in people with a family history of cancer which suggest the possible presence of harmful mutations in one of these genes. This paper will focus on the ethical dynamic between cancer-driven genomics medicine and the indication of a hereditary predisposition for breast and ovarian cancer. Breast cancer gene testing and its medical consequences may considerably affect one's quality of life. As beneficial as this technology is in terms of its predictive value, it creates the possibility for harmful psychosocial consequences. Therefore, I will explore the extent to which individuals benefit from this genetic knowledge and the ethical concerns associated with it.

When considered together, inherited BRCA1 and BRCA2 mutations increase the risk of both breast and ovarian cancers. The proteins made by BRCA1/2 play a critical role in enabling DNA repair in damaged cells[1]. Therefore, these mutations produce cancer by disrupting DNA repair that results in the accumulation of harmful mutations. In addition, they have been associated with increased risks for other types of cancer[2]. They account for about 20 to 25

[1] "BRCA1 AND BRCA2." Ambry Genetics. Web. 03 Dec. 2014. <http://www.ambrygen.com/tests/brca1-and-brca2>.
[2] "BRCA1 & BRCA2: Cancer Risk & Genetic Testing." *National Cancer Institute*. National Institutes of Health. Web. 03 Dec. 2014. <http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA>.

percent of hereditary breast cancers and 5 to 10 percent of all breast cancers as well as 15 percent of ovarian cancers[2]. Breast cancers associated with BRCA1/2 tend to develop at younger ages than sporadic breast cancers[2]. Both abnormalities translate to higher than average cancer risk and can be inherited by men or women from either parent. According to recent estimates, 55 to 65 percent of women who inherit a BRCA1 mutation and 45 percent of women who inherit a BRCA2 mutation will develop breast cancer by 70 years of age[2]. In general, these mutations confer about a 50 to 80 percent increased lifetime risk for developing breast cancer[3]. Demand for genetic testing for BRCA1/2 mutations are expected to be high among first-degree relatives of breast cancer patients as well as amongst the general population[4].

Benefits and Risks Associated with BRCA1/2 Genetic Testing

The discovery of gene mutations directly involved in breast cancer susceptibility allowed for the identification of these mutations in women that were at very high risk. Several options are available for managing cancer risk in individuals who are known to have a harmful BRCA1 or BRCA2 mutations. They are given options of early and intensive surveillance, prophylactic surgery, and chemoprevention. A positive test indicates an increased need for surveillance through regular mammographies and clinical breast examinations. In addition, some experts recommend that men who are known to carry a harmful mutation undergo regular mammography as well as testing for prostate cancer, which may also be a cancer associated with these mutations[2]. Another option available for these individuals relies on prophylactic surgery. This specific type of surgery involved removing as much of "at-risk" breast tissue as possible. Removing a woman's ovaries and fallopian tubes (bilateral prophylactic salpingo-oophorectomy)

[3] Surbone, Antonella. "Ethical Implications of Genetic Testing for Breast Cancer Susceptibility." Critical Reviews in Oncology/Hematology 40.2 (2001): 149-57. Web. 5 Dec. 2014. <http://www.ncbi.nlm.nih.gov/pubmed/11682322>.
[4] Brédart, A., P. Autier, R. A. Audisio, and J. Geragthy. "Psycho-social Aspects of Breast Cancer Susceptibility Testing: A Literature Review." *European Journal of Cancer Care* 7.3 (1998): 174-80. Web. 5 Dec. 2014. <http://www.ncbi.nlm.nih.gov/pubmed/9793009>.

also has the potential of reducing her risk for ovarian cancer or breast cancer depending on the nature of the mutation[2]. The mortality reduction associated with this surgery is substantial, High-risk women who undergo a prophylactic bilateral mastectomy have an 85 to 100 percent reduction in risk[5]. Yet, prophylactic surgery does not completely guarantee that cancer will not develop because not all at-risk tissue can be removed by this procedure. Additionally, if an individual is found to have a BRCA1 mutation, the breast cancer is less likely to be estrogen-receptor positive[2]. Therefore, the individual is not an ideal candidate for traditional hormone therapy. On the other hand, if an individual is found to have a BRCA2 mutation, they are more likely to be a candidate for hormone therapy[2]. Overall, these available risk reduction strategies due to genetic screening have significantly lowered the change that high-risk woken develop breast and ovarian cancer over the past 15 years[6].

Since the initial first applications of BRCA testing, scientists, physicians, and bioethicists have cautioned the general public about the limited predictive power of genetic testing, especially outside of families with high-risk for breast and ovarian cancers[6]. Mainly, the weakness in this methods lack of predictive power lies in relatively low gene penetrance, the possibility of new mutations with different significance that are not yet identified, and the role of environmental factors in cancerogenesis and tumor development[6]. With regards to gene penetrance, the impact of allele-specific has not been extensively looked into. In general, both preventive and interventional methods are still being developed and genetic testing may potentially have negative psychsocial repercussions for both carriers and their families. The reliability of BRCA genetic testing relies on "prior probability of the condition, sensitivity and

[5] Wolff, Tracy A., and Jane E. Wilson. "Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility." *American Family Physician* 74.10 (2006): 1759-760. Web. 5 Dec. 2014. <http://www.aafp.org/afp/2006/1115/p1759.html>.
[6] Surbone, Antonella. "Social and Ethical Implications of BRCA Testing." *Annals of Oncology* 22.Supplement 1 (2011): I60-66. Web. 5 Dec. 2014. <http://annonc.oxfordjournals.org/content/22/suppl_1/i60.abstract>.

specificity, screening techniques, and number of mutations"[3]. According to the United States Preventive Services Task Force (USPSTF), BRCA1/2 testing clearly has important psychological, ethical, legal, and social implications[5]. Potential harms of intensive screening amongst high-risk groups include overdiagnosis and overtreatment. Therefore, the predictive value of a positive result can vary greatly.

Weighing the Risks of Genetic Testing

Overall knowledge about the ethical implications of genetic testing is becoming essential knowledge for oncologists who guide their patients through the necessary treatments in response to a positive test. The frequency of BRCA mutations is low and in the general population, the BRCA1 gene frequency has been estimated to be at about 0.0006 percent[4]. Therefore, in many of the cases, not all individuals carrying these mutations will develop cancer. This has interesting repercussions on the way treatment is designed for women who are at high-risk. Since not all female BRCA carriers will develop cancer, the psychological and physical consequences of preventative treatment seem to be compounded. In many cases, acceptance of the breast cancer genetic test is associated with the belief that mammography effectively detects early breast cancer, that early breast cancer is curable, and that regular mammograms give a feeling of control over one's health. As mentioned above, demand is high when it comes to BRCA1/2 genetic testing. Yet, it's not clear whether this demand is due to complete information about the potential as well as the consequences of this medical option. Therefore, most individuals who consider participating in genetic testing have skewed perspectives on the benefits of the predictive value of the results.

Genetic Testing and the Ethics of Psychosocial Effects

Many of the prominent psychosocial issues that affect BRCA1/2 testing are related to a patient's confidentiality and autonomy in genetic testing. One paper presented the results of a survey that assessed the attitudes of 238 first-degree relatives of women with breast or ovarian cancer regarding the ethical issues related to BRCA1/2 testing[7]. The goal was to assess baseline knowledge about BRCA1/2 testing and psychosocial characteristics of these women were examined to determine the associated attitudes. The majority of these women, 86 to 87 percent of them, felt that healthcare providers should not disclose the results of genetic tests for hereditary breast-ovarian cancer to insurance companies or employers without consent[7]. Yet, only 57 percent felt that written consent should be required for a spouse or immediate family member to receive this information. Overall, 98 percent of the surveyed women agreed that genetic testing for breast-ovarian cancer should be voluntary with 95 percent agreeing that a person should be able to have genetic testing against a doctor's recommendation[7]. Mainly, most women surveyed felt that the results of genetic testing should be kept confidential. Yet, women were more lenient about the release of these test results to their family members than to other parties such as health insurance. This type of information creates tension between respecting the privacy of the individual and the responsibility to warn other family members for the potential of genetic risks[7].

The direct psychological consequences of these results, whether positive or negative, are also potent. Mainly, anecdotal reports and studies on anticipated reactions indicate that anxiety will be a predominant feature of emotional responses to genetic risk[4]. There is a significant burden of ambiguity on both carriers and non-carriers of the gene mutation as to whether or

[7] Benkendorf, Judith L., Jeri E. Reutenauer, Chanita A. Hughes, Nadine Eads, Jan Willison, Madison Powers, and Caryn Lerman. "Patients' Attitudes about Autonomy and Confidentiality in Genetic Testing for Breast-ovarian Cancer Susceptibility." *American Journal of Medical Genetics* 73.3 (1997): 296-303. Web. 5 Dec. 2014. <http://www.ncbi.nlm.nih.gov/pubmed/9415688>.

when cancer will develop[4]. Individuals who carry the deleterious gene may experience feelings of anger and guilt in relation to the possibility of passing the gene on to one's offspring. Gene carriers who fear the development of cancer also have the possibility of experiencing "the same emotional spectrum" as cancer survivors. For example, they may experience a sense of personal vulnerability as well as tenuous longevity. Additionally, further anticipated reactions to a positive test in first-degree relatives of ovarian cancer patients included increased levels of anxiety (77 percent), depression (80 percent), and impaired quality of life (32 percent)[4]. Yet it's important to keep in consideration that those who have requested the test shouldn't be generalized. Individuals who are members of high-risk families may have, by definition, lived with the knowledge of their higher risk for cancer for quite some time. Therefore, they could be better informed and prepared for the outcome of a possible positive result. As a result, less well-informed individuals who undergo BRCA1/2 genetic testing has a higher chance of encountering these psychosocial problems.

Psychology of Genetic Knowledge and Risk Perception

With regards to BRCA1/2 testing, it's important to distinguish the weight of genetic information from general medical information. Genetic information refers to any manifestation of a disease or disorder in a family member, and to the participation of a person or family member in research that involves genetic testing, counseling or education[6]. Genetic knowledge differs because of its individual, predictive, and probabilistic nature[3]. Therefore, genetic information carries value as well as danger to the individuals tested as well as individuals other than the person tested. Experts have expressed different views on the value of BRCA testing, ranging from stressing the importance of genetic knowledge for high-risk women as a means to control their own lives to being uneasy about the potential negative repercussions[6]. Therefore,

the psychological impact of BRCA testing is important to consider when evaluating its ethical impact. Presenting these individuals with the different dimensions of BRCA1/2 genetic testing is necessary in order to have them make informed decisions about this subject. It is important for healthcare professionals to present "tailored and personalized" risk communication to their patients in order to increase lay knowledge and modify the risk perceptions of these individuals[8]. Properly adjusting these individuals risk perceptions about the genetic testing must be balanced and heavily considered alongside the incorporation of genetic testing into oncology practices. Identification of women for whom testing is necessary and management of their risk for breast and ovarian cancer after testing are important fundamentals that oncologists and geneticists have to consider.

Individuals who choose to proceed with prophylactic surgery represent critical examples of the ethical considerations that have been presented thus far. The issue of prophylactic mastectomy for women with a germline mutation of BRCA genes has been often called "the price of fear"[9]. For many experts, the ethical issue stems from the fact that the benefits of risk-reduction surgery will never be visible at the individual level. The Cochrane Collaboration published a review of the topic, stating that prophylactic mastectomy was an extreme intervention that a single recommendation for practice was not appropriate[10]. For every preventative action, the success of the operation can only be evaluated at the population level[10]. Since the penetrance of BRCA is not 100 percent, there is the possibility that all cancer-free women who have had preventive breast mastectomies may have had the same outcome without

[8] Chowdhury, Susmita, Tom Dent, Nora Pashayan, Alison Hall, Georgios Lyratzopoulos, Nina Hallowell, Per Hall, Paul Pharoah, and Hilary Burton. "Incorporating Genomics into Breast and Prostate Cancer Screening: Assessing the Implications." *Genetics in Medicine* 15.6 (2013): 423-32. Web. 5 Dec. 2014. <http://www.nature.com/gim/journal/v15/n6/full/gim2012167a.html>.

[9] Eisen, Andrea, and Barbara L. Weber. "Prophylactic Mastectomy — The Price of Fear." New England Journal of Medicine 340.2 (1999): 137-38. Web. 6 Dec. 2014. <http://www.ncbi.nlm.nih.gov/pubmed/9887166>.

[10] Eisinger, Francois. "Prophylactic Mastectomy: Ethical Issues." *British Medical Bulletin* 81-82.1 (2007): 7-19. Web. 5 Dec. 2014. <http://bmb.oxfordjournals.org/content/81-82/1/7.full>.

resorting to surgery. It's important to stress that prevention does not improve well-being, but rather reduces the risk of becoming affected[10]. It's difficult to communicate these specific issues to high-risk individuals that believe prophylactic surgery is their best option. The efficacy of risk-reduction surgery is fairly high, if not completely absolute in comparison to other risk-reduction strategies. Overall, it's a difficult issue to consider from an ethical standpoint because of the efficacy of the procedure. The benefits of complete and effective communication of the necessary information pertaining to the risk-reduction benefits of the procedure are critical.

Alongside these factors, the emotional ramifications of genetic testing not only affect these individuals' quality of life but their medical management as well. Psychological distress in response to the process and the results of BRCA1/2 genetic testing showed has been shown to interfere with comprehension of risk information. One study presented information that risk perception improvement after genetic counseling was limited to those who had initially overestimated their risk[4]. The resulting psychological distress can be a barrier to adherence to cancer screening guidelines among high-risk women. For example, many individuals who find themselves to be at a high predisposition to breast-ovarian cancer may attempt to lessen their concerns by "avoiding cancer-related" experiences such as frequent screening and mammograms[4]. On the other hand, individuals with a negative test result may develop a sense of false reassurance. Therefore, they may be less heedful about cancer surveillance and not realize that they are still prone to the same breast-ovarian cancer risk present in the general population. Although these reactions are generalized, they do indicate the tenuousness of the responses to sensitivity of this information. The ethical dilemma lies in the fact that genetic information must be presented to patients in a way that lessens the effects of these negative psychological responses.

Fundamental Issues of BRCA1/2 Genetic Testing

There are fundamental issues of justice and ethics that can be, more or less, applicable to genetic testing for most diseases. Yet, the distinctiveness of BRCA testing lies in the fact that BRCA 1/2 differ from genes that have higher penetrance. In the cases of genes with higher penetrance, ethical issues relate more so to certainties rather than to risks[3]. Since genetic information heavily relies on probabilities and risk assumption, which emphasizes the importance of informed consent. Additionally, the sensitivity of the information brings up issues in relation to a person's autonomy and the right to self-determination. There are opposing dynamics in play when considering a patient's "right not to know" as well as the very concept of self-determination itself[3]. Some experts argue that At this point, BRCA testing is not indicated for mass screening and is only restricted to high-risk groups. Therefore, some may say that a right to undergo genetic testing is not being strictly observed in this case. The ethical dilemmas here mostly focus on the individuals who are outside of these high-risk groups. There are also socioeconomic imbalances to consider. For example, rates of test use may be higher in persons of a higher socioeconomic status. Therefore, genetic testing would only benefit those who individuals of a higher socioeconomic status, which presents itself as another ethical dilemma. Although many of these ethical considerations are not readily resolved, many of them could be addressed with the appropriate presentation of information to individuals who are considering genetic testing. An overarching ethical constraint related to BRCA1/2 testing is the risk of patients taking decisions based on a false or incomplete comprehension of information.

Improving Genetic Counseling and Moving Forward

Centrally important to the decision-making process of BRCA1/2 is the genetic counseling process. The underlying assumptions behind genetic counseling attempt to address the ethical implications that arise due to the nature of genetic information. Genetic counseling for hereditary breast cancer includes the provision of medical information and probabilities of the positive and negative aspects of genetic testing[11]. Normally, genetic counseling does not include a direct effort to help patients clarify their preferences. The assumption is that if patients have the necessary information, they will be able to appropriately weight the risks and benefits of each option related to genetic testing[11]. Therefore, they will be able to make a decision that is consistent with their own values and preferences. Yet, there has been discussion about the need to move beyond the "normative assumption" that defines informed decision making in the BRCA1/2 context. A newer model may define an informed decision that leads focuses instead on positive long-term outcomes rather than one that matches the patient's preferences[11]. There is no data at this point that can support which model is the more appropriate one. Yet, a model that focuses on positive long-term outcomes may lessen the degree to which a patient receives incomplete information. Additional research is needed to clarify how patients and medial practitioners can use the complex information of genetic testing to effectively guide medical decisions.

Overall, genetic information has enormous potential to inform and transform cancer risk identification, risk reduction, and treatment practices. Individuals who elect to receive their test results should be extensively counseled about the consequences of their results as well as about the limitations and risks of available treatment options. As a result, proper informed consent and

[11] Schwartz, Marc D., Beth N. Peshkin, Kenneth P. Tercyak, Kathryn L. Taylor, and Heiddis Valdimarsdottir. "Decision Making and Decision Support for Hereditary Breast-Ovarian Cancer Susceptibility." *Health Psychology* 24.Supplement 4 (2005): S78-84. Web. 5 Dec. 2014. <http://www.ncbi.nlm.nih.gov/pubmed/16045423>.

counseling is absolutely essential in order to combat any ethical constraints and optimize patient decisions about BRCA1/2 testing. The goal of the proper communication of information for both high-risk individuals and the general population is to maximize the potential benefits and minimize the risks of this technology[12]. Minimization of the psychological consequences of the weight of genetic knowledge must also be taken into consideration when designing models that address counseling and presentation of information to patients. One study concluded that for some high-risk individuals who receive test results in a setting that includes counseling, there may be even be psychological benefits[12]. Healthcare professionals will require additional training and support in discussing genetic risks with their patients and the importance of sharing results at-risk family members. In this regard, the importance that BRCA1/2 genetic testing has on the psychological and functional health of both high-risk and low-risk individuals must be seriously taken into account.

[12] Lerman, Caryn, Steven Narod, Kevin Schulman, Chanita Hughes, Andres Gomez-Caminero, George Bonney, Karen Gold, Bruce Trock, David Main, Jane Lynch, Cecil Fulmore, Carrie Snyder, Stephen J. Lemon, Patricia Tonin, Gilbert Lenoir, and Henry Lynch. "BRCA1 Testing in Families with Hereditary Breast-ovarian Cancer. A Prospective Study of Patient Decision Making and Outcomes." *JAMA: The Journal of the American Medical Association* 275.24 (1996): 1885-892. Web. 5 Dec. 2014. <http://jama.jamanetwork.com/article.aspx?articleid=404205>.