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Bridging the Gap Between Doctor and Patient Utilization and Understanding of *BRCA1/2* Mutation Testing

I. Introduction

With the early detection of deadly diseases in mind, genetic testing is growing more and more important in the practice of medicine. Genetic testing has evolved greatly since its rise in utility over the past two decades. As in all forms of medical screening, however, doctors must carefully weigh the benefits and risks in referring patients for genetic testing. In 2005, the US Preventive Services Task Force (USPSTF) issued a recommendation against routine *BRCA* genetic testing for breast and ovarian cancer on the basis that only a small population of women are actually genetically predisposed to the harmful genetic mutations associated with these types of cancer.¹ According to the USPSTF, risks such as false-positive and false-negative results and other psychological and behavioral outcomes greatly outweigh any potential benefit to routine screening for women without specific family history patterns.² Despite the USPSTF recommendation, 89% of primary care physicians have indicated needs for more clinical guidelines for genetic testing for cancer susceptibility.³ One problem seems to be that, although doctors recognize the growing importance of genetics regardless of their field of medicine, many feel they have inadequate resources to meet the demands of their practice. Another problem is that patients may be exacerbating the issue by overestimating their risks for *BRCA* mutations and needlessly requesting testing themselves.

This paper will explore the issues related to doctor and patient utilization and understanding of clinical guidelines to genetic predisposition testing using the case study of the

¹ U.S. Preventive Servs. Task Force, *Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement*, 143 ANNALS INTERNAL MED. 355 (2005), <http://www.uspreventiveservicestaskforce.org/uspstf05/brcagen/brcagenrs.pdf> [hereinafter USPSTF].

² *Id.*

³ See Robert Klitzman, *Attitudes and Practices Among Internists Concerning Genetic Testing*, 22 J. GENETIC COUNSELING 90, 91 (2013).

USPSTF recommendations for *BRCA* mutation testing. Part II will discuss the *BRCA1/2* genes and mutations, the various risk assessment tools and methods that are used as screening devices, and the DNA sequencing test. Part III will discuss the report used by the USPSTF in making its recommendation. Part IV will discuss the issues related to physician and patient use and understanding of genetic screening for cancer susceptibility. Finally, Part V will contain my recommendations for how to address the issues raised in Part IV.

II. The *BRCA 1/2* Genes, Mutations, and Tests

A. The *BRCA1/2* Genes and Mutations

Doctors and geneticists have identified two genes related to breast and ovarian cancer in women: *BRCA1* and *BRCA2*. The names *BRCA1* and *BRCA2*, respectively, stand for breast cancer susceptibility gene 1 and breast cancer susceptibility gene 2.⁴ Although the functions of *BRCA1* and *BRCA2* are interrelated, their structures are quite different.

BRCA1 is a tumor-suppressor gene that is important in regulating the growth of breast epithelial cells.⁵ As a tumor-suppressor gene, the *BRCA1* gene produces a protein that helps prevent cells from growing and dividing too rapidly or in an uncontrolled way.⁶ The human *BRCA1* gene is located on the long (q) arm of chromosome 17 at region 2 band 1, from base pair 41,196,312 to base pair 41,277,500.⁷ The *BRCA1* gene was first identified by the King Laboratory at UC Berkeley in 1990.⁸ Later, scientists at the University of Utah, National Institute of Environmental Health Sciences (NIEHS), and Myriad Genetics cloned the gene for the first

⁴ See Nat'l Cancer Inst., *BRCA1 & BRCA2: Cancer Risk and Genetic Testing*, <http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA> (reviewed May 29, 2009).

⁵ See J. Fergus Couch ET AL., *BRCA1 Mutations in Women Attending Clinics That Evaluate the Risk of Breast Cancer*, 336 NEW ENG. J. MED. 1409, 1409 (1997).

⁶ See Genetics Home Reference, *BRCA1*, <http://ghr.nlm.nih.gov/gene/BRCA1> (reviewed Aug. 2007) [hereinafter Genetics Home Reference, *BRCA1*].

⁷ See J.A. Duncan ET AL., *BRCA1 & BRCA2 Proteins: Roles in Health and Disease*. UNIV. DEP'T SURGERY, GLASGOW ROYAL INFIRMARY (1998).

⁸ See JM Hall ET AL., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 SCIENCE (1990).

time in 1994.⁹ It is critical for the repair of double-strand DNA breaks (DSBs) and interstrand crosslinks (ICLs) by homologous recombination (HR).¹⁰ These breaks can be caused by natural and medical radiation or other environmental exposures, and also occur when chromosome exchange genetic material in preparation for cell division.¹¹ Researchers believe that the *BRCA1* protein also regulates the activity of other genes and plays a critical role in embryonic development.¹²

There are more than 1,000 mutations in the *BRCA1* gene.¹³ The majority of these mutations lead to the production of an abnormally short version of the *BRCA1* protein, or prevent any protein from being made from one copy of the gene.¹⁴ The most common mutations are a deletion of adenine and guanine (185delAG) and an insertion of cytosine (5382insC).¹⁵ A defective or missing *BRCA1* protein is unable to help repair damaged DNA or fix mutations that occur in other genes. When these defects accumulate, the uncontrolled growth and division of cells can form a tumor.¹⁶ *BRCA1* mutations account for 45 percent of hereditary cases of breast cancer and 80 to 90 percent of hereditary cases of combined breast and ovarian cancer.¹⁷ Harmful *BRCA1* mutations may also increase a woman's risk of cervical, uterine, pancreatic, and colon cancer.¹⁸

⁹ See Hall, *supra* note 8.

¹⁰ See Shane R. Stecklein ET AL., *BRCA1 and HSP90 Cooperate in Homologous and Non-Homologous DNA Double-Strand-Break Repair and G2/M Checkpoint Activation*, 109 PROC. NAT'L ACAD. SCI. 13650, 13651 (2012).

¹¹ See Genetics Home Reference, *BRCA1*, *supra* note 6.

¹² *Id.*

¹³ *Id.*

¹⁴ *Id.*

¹⁵ See Couch, *supra* note 5 at 1409.

¹⁶ See Genetics Home Reference, *BRCA1*, *supra* note 6.

¹⁷ See Couch, *supra* note 5 at 1409.

¹⁸ See Nat'l Cancer Inst., *supra* note 4.

The *BRCA2* gene also belongs to the tumor-suppressor gene family.¹⁹ Like the *BRCA1*, it is similarly important for the regulation of cell growth and division.²⁰ It is located on the long (q) arm of chromosome 13 at position region 12 band 3 from base pair 32,889,616 to 32,973,808.²¹ The *BRCA2* gene was first cloned by scientists at Myriad Genetics, Endo Recherche, Inc., HSC Research and Development Limited Partnership, and University of Pennsylvania.²² Research shows that the *BRCA2* protein may also help regulate cytokinesis, which is the step in cell division when the cytoplasm divides to form two separate cells.²³ There are approximately 800 different mutations associated with the *BRCA2* gene.²⁴ Many of the mutations disrupt protein production from one copy of the gene in each cell, resulting in an abnormally small, nonfunctional version of the *BRCA2* protein.²⁵ Harmful *BRCA2* mutations may additionally increase the risk of pancreatic cancer, stomach cancer, gallbladder and bile duct cancer, and melanoma.²⁶

The next two sections will explain how patients are tested for *BRCA1/2* mutation susceptibility. There are two methods: risk assessment testing and DNA sequencing. Risk assessment testing is typically completed first to determine whether DNA sequencing is warranted.

B. Risk Assessment Testing for *BRCA1/2* Mutation Among Women

There are two important types of testing related to breast and ovarian cancer susceptibility: risk assessment testing and DNA sequencing. Risk assessment is important

¹⁹ See Genetics Home Reference, *BRCA2*, <http://ghr.nlm.nih.gov/gene/BRCA2> (reviewed Aug. 2007) [hereinafter Genetics Home Reference, *BRCA2*].

²⁰ *Id.*

²¹ See Duncan, *supra* note 7.

²² *Id.*

²³ See Nat'l Cancer Inst., *supra* note 4.

²⁴ *Id.*

²⁵ *Id.*

²⁶ *Id.*

because guidelines recommend testing for mutations only when an individual has personal or family history features suggestive of inherited cancer susceptibility.²⁷ Although the *BRCA1/2* mutations can occur in anyone, certain specific family history patterns are associated with an increased risk for mutation. For example, specific *BRCA* mutations are clustered among certain ethnic groups, such as Ashkenazi Jews, and among families in the Netherlands, Iceland and Sweden.²⁸ For non-Ashkenazi Jewish women, patterns associated with an increased risk for *BRCA1/2* mutation include two first-degree relatives with breast cancer, one of whom received the diagnosis at age 50 years or younger; a combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; a combination of two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative.²⁹ About two percent of adult women in the general population have an increased-risk family history as defined above.³⁰ Those women that do not fall into any of the increased family history patterns have a low probability of having a deleterious mutation in *BRCA1* or *BRCA2* genes.³¹ It is important to remember that developing breast or ovarian cancer does not necessarily automatically follow from a *BRCA* mutation. The probability of developing breast or ovarian cancer by age 70 years in a woman

²⁷ See HD Nelson ET AL., *Genetic Risk Assessment and BRCA Mutation Testing for Breast and Ovarian Cancer Susceptibility: Systematic Evidence Review for the U.S. Preventive Services Task Force*, ANNALS INTERNAL MED. (2005), <http://www.ncbi.nlm.nih.gov/books/NBK43308>.

²⁸ See USPSTF, *supra* note 1.

²⁹ *Id.*

³⁰ *Id.*

³¹ *Id.*

who has a clinically important *BRCA* mutation, is estimated to be 35 percent to 84 percent for breast cancer and 10 to 50 percent for ovarian cancer.³²

There are several different risk tools for predicting risk for deleterious *BRCA1/2* mutations. The four most widely used risk tools include the Myriad Genetic Laboratories model, the Couch model, *BRCAPRO*, and the Tyrer model.³³ Unfortunately, no studies of their effectiveness in a primary care screening population are available, as much of the data from these models are from women with existing cancer, and their applicability to asymptomatic, cancer-free women in the general population is unknown.³⁴

There are two Myriad Genetic Laboratories models. The first model is used exclusively to predict risk for *BRCA1* mutation and is based on a population of women with either early-onset breast cancer or ovarian cancer, or with a family history of breast or ovarian cancer.³⁵ This logistic regression model also takes into account bilateral breast cancer, age of diagnosis, and Ashkenazi Jewish ancestry, and is not dependent on affected relatives.³⁶ The second model predicts risk for both *BRCA1* and *BRCA2* mutations and is based on a population of women with breast cancer under age 50 or ovarian cancer who have at least one first- or second-degree relative with early breast and ovarian cancer.³⁷ This model considers bilateral breast cancer, concurrent breast and ovarian cancer, and breast cancer under age 40.³⁸

The second risk assessment tool is the Couch Model. This model is based on logistic regression of data from a population of women with breast cancer and a family history of breast

³² See USPSTF, *supra* note 1.

³³ See Nelson, *supra* note 27.

³⁴ See USPSTF, *supra* note 1.

³⁵ See D Shattuck-Eidens ET AL., *BRCA1 Sequence Analysis in Women at High Risk for Susceptibility Mutations. Risk Factor Analysis and Implications for Genetic Testing*, 278 J. AM. MED. ASS'N 1242, 1245 (1997).

³⁶ *Id.*

³⁷ *Id.*

³⁸ *Id.*

and/or ovarian cancer, and predicts risk for *BRCA1* mutation.³⁹ The original model determined mutations by conformation sensitive gel electrophoresis (CSGE) rather than DNA full sequencing, which potentially underestimated mutation prevalence.⁴⁰ The refined model includes both *BRCA1* and *BRCA2* mutations using DNA full sequencing.⁴¹ This model does not require the individual to have breast or ovarian cancer, however the family must have more than two cases of breast cancer.⁴² Some of the predictors used in the Couch model include the number of women diagnosed with breast cancer under age 50, concurrent breast and ovarian cancer, ovarian cancer, male breast cancer, and Ashkenazi Jewish ancestry.⁴³

The third risk assessment tool is the *BRCAPRO* model. The *BRCAPRO* model is a Bayesian model that provides estimates of risk for *BRCA1* and *BRCA2* mutations.⁴⁴ It has been validated in populations of women with increased prevalence of specific mutations.⁴⁵ In *BRCAPRO*, the individual may or may not have breast or ovarian cancer.⁴⁶ It considers factors such as current age, age at diagnosis, bilateral breast cancer, concurrent breast and ovarian cancer, all first- and second-degree relatives with and without cancer, males with breast cancer, and Ashkenazi Jewish ancestry.⁴⁷ It includes information on both affected and unaffected relatives.⁴⁸

³⁹ See Couch, *supra* note 5 at 1411.

⁴⁰ See Nelson, *supra* note 27.

⁴¹ See MA Blackwood ET AL., *Predicted Probability of Breast Cancer Susceptibility Gene Mutations*. 69 BREAST CANCER RESEARCH AND TREATMENT (2001).

⁴² See Nelson, *supra* note 27.

⁴³ *Id.*

⁴⁴ See DA Berry ET AL., *Probability of Carrying a Mutation of Breast-Ovarian Cancer Gene BRCA1 Based on Family History*, 89 J. NAT'L CANCER INST. 227, 229 (1997) [hereinafter Berry, *Probability*].

⁴⁵ See DA Berry DA ET AL., *BRCAPRO Validation, Sensitivity of Genetic Testing of BRCA1/BRCA2, and Prevalence of Other Breast Cancer Susceptibility Genes*, 20 J. CLINICAL ONCOLOGY 2701, 2702 (2002) [hereinafter Berry, *BRCAPRO*].

⁴⁶ See Nelson, *supra* note 27.

⁴⁷ *Id.*

⁴⁸ *Id.*

The fourth model is the Tyrer model. This model provides a comprehensive risk estimate using personal risk factors in combination with a genetic analysis.⁴⁹ Similar to the Couch model and *BRCAPRO*, the individual is not required to have breast or ovarian cancer.⁵⁰ The model includes personal risk factors such as current age, age at menarche, parity, age at first childbirth, age at menopause, atypical hyperplasia, lobular carcinoma in situ, height, and body mass index (BMI).⁵¹ As part of the genetic analysis, the model incorporates the high-risk, high-penetrance *BRCA1* and *BRCA2* germline mutations with the addition of a low-penetrance gene.⁵² The low-penetrance gene is included as a stand-in to account for the effect of all other unidentified genes.⁵³ The Tyrer Model is run through a computer program that is still not yet widely distributed.⁵⁴ The program uses segregation analysis techniques based on Bayes' theorem to determine the risk of *BRCA1/2* mutations.⁵⁵

As mentioned *supra*, the effectiveness of risk assessment tools such as the Myriad Genetic Laboratories model, Couch model, *BRCAPRO*, and Tyrer model is unknown in a primary care setting. Primary care physicians do, however, have access to three other risk assessment tools for potential *BRCA1/2* mutations. These tools are the Family History Risk Assessment Tool (FHAT), the Manchester scoring system, and the Risk Assessment in Genetics (RAGs) tool.⁵⁶ Using these risk tools, primary care physicians can manage recommendations of

⁴⁹ See J Tyrer ET AL., *A Breast Cancer Prediction Model Incorporating Familial and Personal Risk Factors*, 23 STATISTICS IN MEDICINE 1111, 1112 (2004).

⁵⁰ See Nelson, *supra* note 27.

⁵¹ *Id.*

⁵² *Id.*

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ See CA Gilpin ET AL., *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*, 58 CLINICAL GENETICS 2999, 3002 (2000).

reassurance, referral to a breast clinic, or referral to a geneticist on the basis of the patient's respective risk categories.⁵⁷

The FHAT helps clinicians select patients for referral to genetic counseling.⁵⁸ This tool uses a point system based on the number of relatives, third-degree or closer, diagnosed with breast, ovarian, colon, or prostate cancer, and the relationship to the individual being evaluated, age at diagnosis, and type and number of primary cancers.⁵⁹ If a patient receives a score of 10 points or higher, then the doctor should refer her for genetic counseling.⁶⁰ The sensitivity and specificity of FHAT for a clinically significant *BRCA1* or *BRCA2* mutation were 94% and 51%, respectively.⁶¹

The Manchester scoring system is a risk assessment tool developed in the U.K. to predict deleterious *BRCA1/2* mutations at the 10% likelihood level.⁶² Similar to the FHAT, the Manchester scoring system assigns points depending on the type of cancer (breast, ovarian, pancreatic, or prostate) affected family members, and age at diagnosis and provide scores for *BRCA1* and *BRCA2* mutations separately.⁶³ The Manchester model had 87% sensitivity and 66% specificity for combined *BRCA1* and *BRCA2* mutations, which compared well with other models tested.⁶⁴

The Risk Assessment in Genetics (RAGs) tool is a computer program used to assess and manage family breast and ovarian cancer in primary care settings.⁶⁵ Using information about the patient and relatives, including family history and the age of the presenting patient, RAGs

⁵⁷ See USPSTF, *supra* note 1.

⁵⁸ See Gilpin, *supra* note 56.

⁵⁹ See Nelson, *supra* note 27.

⁶⁰ *Id.*

⁶¹ *Id.*

⁶² See DG Evans ET AL., *A New Scoring System for the Chances of Identifying a BRCA 1/2 Mutation Outperforms Existing Models Including BRCA PRO*, 41 J. MED. GENETICS 474 (2004).

⁶³ See Nelson, *supra* note 27.

⁶⁴ *Id.*

⁶⁵ *Id.*

generates categories of risk for breast and ovarian cancer, referral guidelines, and suggests appropriate management. This tool assigns one of three risk levels: low (<10% risk of having a clinically significant *BRCA1/2* mutation), in which the patient is reassured and managed in primary care; moderate (10-25% risk), in which the patient is referred to a breast clinic; and high (>25% risk, in which the patient is referred to a clinical geneticist.⁶⁶ Tested against other primary care risk assessment tools, RAGs resulted in significantly more appropriate management decisions and more accurate pedigrees, and was the preferred approach.⁶⁷ Moreover, RAGs took on average 178 seconds to administer.⁶⁸

In sum, primary care physicians have numerous risk assessment tools at their disposal in order to determine a patient's risk for a genetic predisposition to a *BRCA1/2* mutation. Using these tools, a physician will classify women according to the risk group that they fall in. In the case of a patient falling into a low or moderate-risk group, a doctor will recommend against further testing. Alternatively, if the patient falls into a high-risk category, further testing should be recommended. Women who are classified as being at high-risk for a *BRCA1/2* mutation go on to DNA sequencing testing, which is described in the next section.

C. DNA Sequencing Tests for the *BRCA1/2* Mutations

The second type of testing for susceptibility to breast and ovarian cancer is DNA sequencing for clinically significant *BRCA1/2* mutations. Guidelines for testing recommend DNA sequencing only for women in the high-risk category as defined above.⁶⁹ Nevertheless, any woman could request testing on her own regardless of her personal risk factor. Several clinical laboratories in the United States test for specific mutations or sequence-specific exons.

⁶⁶ See Nelson, *supra* note 27.

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ *Id.*

Individuals without linkages to others with known mutations undergo direct DNA sequencing. In these cases, guidelines recommend that testing begin with a relative who has known breast or ovarian cancer to determine whether a clinically significant mutation is segregating in the family.⁷⁰ Myriad Genetic Laboratories provides direct DNA sequencing in the United States and reports analytic sensitivity and specificity exceeding 99 percent.^{71 72} Test results include not only positive (denoting a deleterious mutation) and negative (no mutation found) interpretations, but also variants of uncertain clinical significance.⁷³ Approximately 13 percent of all those tested will have results with uncertain clinical significance.⁷⁴ For testing, a small sample of blood must be drawn or an oral rinse sample taken.⁷⁵ DNA sequencing can take up to two weeks for results.⁷⁶ DNA sequencing tests can cost several hundred dollars, although some insurance companies will cover the cost.⁷⁷

This section discussed the *BRCA1/2* genes and mutations and also the two methods for screening for the mutations. Now, it is time to turn to the USPSTF recommendations and the study that provided the foundation for those recommendations. The study relied on the answers to five key questions to issue its conclusions for the USPSTF to review. Those key questions are answers are discussed in the next section.

III. Analysis of the Nelson Study, 2005 US Preventive Services Task Force

Recommendation, and Recommendations of Other Professional Medical Groups

⁷⁰ See Nelson, *supra* note 27.

⁷¹ *Id.*

⁷² Analytic sensitivity refers to the proportion of actual positives results that are correctly identified. This is sometimes called the true positive value. For example, sensitivity refers to the percentage of sick people who are correctly identified as having the condition. Specificity, however, measures the proportion of negative that are correctly identified. For example, the specificity of a study would show the percentage of healthy people who are correctly identified as not having the condition. This is sometimes called the true negative value.

⁷³ See Nelson, *supra* note 27.

⁷⁴ *Id.*

⁷⁵ See Myriad Genetics, *Genetic Testing Process*, <http://www.myriad.com/physicians/genetic-testing/genetic-testing-process-2/> (last visited May 5, 2103).

⁷⁶ *Id.*

⁷⁷ See Nelson, *supra* note 27.

A. Discussion of the Nelson Study, Five Key Questions, and USPSTF Recommendations

Concerned with the growing public interest in *BRCA* testing, despite the rarity of mutations in the general population, the USPSTF commissioned a research group to determine the benefits and harms of screening for inherited breast and ovarian cancer susceptibility in the general population of women without cancer presenting for primary health care in the United States.⁷⁸ The study was published in 2005 in the *ANNALS OF INTERNAL MEDICINE*. The research was funded by the Centers for Disease Control and Prevention under a contract with the Agency for Healthcare Research and Quality.⁷⁹ The ultimate recommendations issued by the USPSTF were based on the responses to five key questions investigated in the Nelson study.

The first key question is whether risk assessment and *BRCA* mutation testing leads to a reduction in the in the incidence of breast and ovarian cancer and cause-specific or all-cause mortality. The research group found that no studies demonstrate that a screening approach consisting of risk assessment in a primary care setting followed by *BRCA* mutation testing and preventive interventions for appropriate candidates ultimately reduces the incidence of breast and ovarian cancer and cause-specific or all-cause mortality.⁸⁰

The second key question investigates how well clinicians in a primary care setting select candidates *BRCA* mutation testing using risk assessment. The Nelson study began by identifying three methods used by primary care physicians to complete risk assessment for cancer susceptibility. The most important method is a determination of family history. Decisions about referral, testing, and prevention interventions are often based on self-reports of family histories that include types of cancers, relationships within the family, and ages of onset. Appropriate

⁷⁸ See Nelson, *supra* note 27. The research was conducted by Heidi D. Nelson, MD, MPH; Laurie Hoyt Huffman, MS; Rongwei Fu, PhD; and Emily L. Harris, PhD, MPH. The report published by Nelson, Huffman, Fu, and Harris will hereinafter be referred to as the Nelson study.

⁷⁹ See Nelson, *supra* note 27.

⁸⁰ *Id.*

decisions rely on family histories that are accurately reported by women and correctly obtained by clinicians.⁸¹ One study determined the sensitivity and specificity of a family history of breast or ovarian cancer in first-degree relatives reported by individuals without cancer to be more reliable with respect to breast cancer than ovarian cancer. Specifically, the study found a sensitivity of 82 percent and specificity of 91 percent with respect to breast cancer, but 50 percent and 99 percent, respectively, for ovarian cancer.⁸²

Risk assessment tools are the second method utilized to determine how well primary care physicians select candidates for *BRCA* mutation testing. As discussed above, there are several different tools and methods available to primary care physicians such as the Myriad Genetics model, the Couch model, BRCAPRO, the Tyrer model, and others. Their effectiveness in screening the general population is unknown.

Finally, the third method is referral guidelines. In order to help primary care physicians identify women at potentially increased risk for *BRCA* mutations, health maintenance organizations, professional organizations, cancer programs, state and national health programs, and investigators develop referral guidelines. Most include questions about personal and family history of *BRCA* mutations, breast and ovarian cancer, age of diagnosis, bilateral breast cancer, and Ashkenazi Jewish heritage.⁸³ Moreover, most guidelines are not intended to lead directly to testing, but instead lead to a referral for more extensive genetic evaluation and counseling.⁸⁴ The effectiveness of referral guidelines is still unknown as no studies have been conducted to measure the efficacy of the guidelines.⁸⁵

⁸¹ See Nelson, *supra* note 27.

⁸² RA Kerber & ML Slattery, *Comparison of Self-Reported and Database-Linked Family History of Cancer Data in a Case-Control Study*, 146 AM. J. EPIDEMIOLOGY 244, 245 (1997).

⁸³ See Nelson, *supra* note 27.

⁸⁴ *Id.*

⁸⁵ *Id.*

Thus, the Nelson study determined that primary care physicians use three different methods in selecting candidates for *BRCA* mutation testing: family history, risk assessment tools, and referral guidelines. Despite the fact that primary care physicians have a multitude of different resources at their fingertips, it is generally unknown how effective these methods are in the general population among asymptomatic women. Moreover, the use of these methods will increase the amount of time doctors will have to spend with each patient, something doctors may be unwilling to do if they must see a high volume of patients each day. Still, risk assessment, particularly through a collection of family history information, may be a cheap and effective way to conduct risk assessment because many primary care physicians collect family history information as part of their routine exam. Overall, more research needs to be done on the effectiveness of these three methods in the general population among asymptomatic women.

The third key question explores the benefits of genetic counseling before testing. On the one hand, there are no studies that determine the physical benefits of genetic counseling before testing. That is to say that no studies describe cancer or mortality outcomes related to genetic counseling.⁸⁶ On the other hand, there are ten studies that measure the psychological and behavioral outcomes associated with genetic counseling before testing.⁸⁷ These studies specifically looked to measure the impact of genetic counseling on breast cancer worry, anxiety,

⁸⁶ See Nelson, *supra* note 27.

⁸⁷ See DJ Bowen, *Breast Cancer Risk Counseling Improves Women's Functioning*, 53 PATIENT EDUC. COUNSELING 79, 81 (2004); DJ Bowen, *Effects of Risk Counseling on Interest in Breast Cancer Genetic Testing for Lower Risk Women*, 4 GENETICS MED. 359, 362 (2002); W Burke, *Genetic Counseling for Women with an Intermediate Family History of Breast Cancer*, 90 AM. J. MED. GENETICS 361, 363 (2000); A Cull, *The Use of Videotaped Information in Cancer Genetic Counseling*, 77 BRIT. J. CANCER 830, 831 (2000); C Lerman, *Racial Differences in Testing Motivation and Psychological Distress Following Pretest Education for BRCA1 Gene Testing*, 8 CANCER EPIDEMIOLOGY BIOMARKERS PREV. 361, 362 (1999); C Lerman, *A Randomized Trial of Breast Cancer Risk Counseling*, 15 HEALTH PSYCHOL. 75, 75 (1996); C Lerman, *Effects of Individualized Breast Cancer Risk Counseling*, 87 J. NAT'L CANCER INST. 286, 288 (1995); E Lobb, *The Use of Audiotapes in Consultations with Women from High Risk Breast Cancer Families*, 39 J. MED. GENETICS 697, 698 (2002); M Watson, *Family History of Breast Cancer*, 35 J. MED. GENETICS 731, 732 (1998); MJ Green, *Effect of a Computer-Based Decision Aid on Knowledge, Perceptions, and Intentions About Genetic Testing for Breast Cancer Susceptibility*, 292 J. AM. MED. ASS'N 442, 444 (2004).

depression, perception of cancer risk, and intent to participate in genetic testing. Nine of the ten studies reported a decrease in psychological distress or no effect after counseling.⁸⁸ Five trials showed increased accuracy of perception of cancer risk among women who received genetic counseling.⁸⁹ One study showed less accurate risk perception after genetic counseling and one had mixed results.⁹⁰ In conclusion, there is no data that suggests genetic counseling before testing has any physical benefit; however, a majority of studies report either a positive psychological impact or no impact at all.

The fourth key question measures how well *BRCA* mutation testing predicts risk for breast or ovarian cancer among women with family histories predicting an average, moderate, or high risk for a deleterious mutation. This key question incorporates two issues. First, it is important to define which women qualify as either possessing an average, moderate or high risk for a deleterious mutation. A woman with an average risk has no first-degree relatives and no more than one second-degree relative on each side of the family with breast or ovarian cancer.⁹¹ A woman has a moderate risk if she has one first-degree relative or two second-degree relatives on the same side of the family with breast or ovarian cancer.⁹² Lastly, a woman has a high risk if she has at least two first-degree relatives with breast or ovarian cancer.⁹³

The second issue is addressing how to measure the efficacy of *BRCA* mutation testing in identifying risk for breast and ovarian cancer. One method is to look at the prevalence of *BRCA1/2* mutations in women. Nelson's study estimated the prevalence of *BRCA1* and *BRCA2* mutations in women at average risk could be as high as .24%, moderate risk to be .24% to 3.4%, and high risk to

⁸⁸ See Nelson, *supra* note 27.

⁸⁹ *Id.*

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² *Id.*

⁹³ *Id.*

be 8.7% and above.⁹⁴ Other models estimate the prevalence of deleterious mutation in the non-Jewish US population to be about 1 in 300 to 500 persons.⁹⁵ Still another model estimates the prevalence among women with a strong family history of cancer to be 8.7%.⁹⁶ These numbers are remarkable in that they show just how rarely *BRCA1/2* mutations occur in average or moderate risk groups.

The second method for determining how well *BRCA* mutation testing predicts risk for breast and ovarian cancer is to look at the penetrance. Penetrance is the probability of developing breast or ovarian cancer among women who have a clinically significant *BRCA1* or *BRCA2* mutation.⁹⁷ For breast cancer, Nelson's study estimates *BRCA1* penetrance to age 75 years are 68.8% in average-risk groups; 49.9% in moderate-risk groups, and 60.5% in high-risk groups.⁹⁸ *BRCA2* penetrance estimates are only available for the high-risk group: 53.0%.⁹⁹ For ovarian cancer, *BRCA1* penetrance estimates to age 75 years are 29.2% in average-risk groups, 55.1% in moderate-risk groups, and 26.1% in high-risk groups. *BRCA2* penetrance estimates for ovarian cancer are 34.2%, 27.0%, and 6.4%.¹⁰⁰ These numbers show that a woman with a deleterious mutation does not automatically develop breast or ovarian cancer. In addition, there does not seem to be an obvious correlation between either a *BRCA1* or *BRCA2* mutation and breast or ovarian cancer across women in different risk groups.

The fifth key question explores the adverse effects of risk assessment, genetic counseling, and testing. This is an important step in order to weigh both the benefits and Two important

⁹⁴ *Id.*

⁹⁵ Anglian Breast Cancer Study Group, *Prevalence and Penetrance of BRCA1 and BRCA2 Mutations in a Population-Based Series of Breast Cancer Cases*, 83 BRIT. J. CANCER 1301, 1302 (2000).

⁹⁶ TS Frank, *Clinical Characteristics of Individuals with Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals*, 20 J. CLINICAL ONCOLOGY 1480, 1483 (2000).

⁹⁷ See Nelson, *supra* note 27.

⁹⁸ *Id.*

⁹⁹ *Id.*

¹⁰⁰ *Id.*

adverse effects of risk assessment, genetic counseling, and testing are false-positive and false-negative results that could occur at each step of screening for a *BRCA1/2* mutation. False-positive and false-negative results are especially troublesome because that can lead to inappropriate reassurance or intervention.¹⁰¹ An obvious example would be a woman that unnecessarily undergoes chemoprevention as a result of a false-positive result of the DNA sequencing screening. False-positive and false-negative results are not exclusive to *BRCA1/2* mutation screening. But, considering the serious and often drastic preventive measures that may follow from a false-positive result, the harm in subjecting oneself to a questionably beneficial test seems to substantially any benefit. Unfortunately, no studies directly address these issues.¹⁰²

Another potential adverse effect is emotional distress. Nelson's study focused on nine studies that assessed breast cancer risk assessment, genetic testing, and genetic counseling their subsequent impact on distress measured as breast cancer worry, anxiety, or depression.¹⁰³ According to Nelson, more studies showed decreased cancer worry or anxiety after risk assessment and testing.¹⁰⁴ There were mixed results as to depression.¹⁰⁵ Distress varied according to whether

¹⁰¹ See Nelson, *supra* note 27.

¹⁰² *Id.*

¹⁰³ See A Bish ET AL., *No News Is (Not Necessarily) Good News: Impact Of Preliminary Results For BRCA1 Mutation Searches*, 4 GENETIC MED. 353, 354 (2002); K Brain ET AL., *A Randomized Trial of Specialist Genetic Assessment: Psychological Impact on Women at Different Levels of Familial Breast Cancer Risk*, 86 BRIT. J. CANCER 233, 234 (2002); LC Friedman ET AL., *Psychological Impact of Receiving Negative BRCA1 Mutation Test Results in Ashkenazim*, 1 Genetic Med. 74, 76 (1999); P Hopwood ET AL., *Psychological Support Needs for Women at High Genetic Risk of Breast Cancer: Some Preliminary Indicators*, 7 PSYCHO-ONCOLOGY 402, 403 (1998); C Lerman ET AL., *What You Don't Know Can Hurt You: Adverse Psychologic Effects in Members of BRCA1-Linked and BRCA2-Linked Families Who Decline Genetic Testing*, 16 J. CLINICAL ONCOLOGY 1650, 1651 (1998); EA Lobb ET AL., *Communication and Information-Giving in High-Risk Breast Cancer Consultations: Influence on Patient Outcomes*, 90 BRIT. J. CANCER 321, 322 (2004); B Meiser ET AL., *Psychological Impact of Genetic Testing in Women from High-Risk Breast Cancer Families*, 38 EUR. J. CANCER 2025, 2027 (2002); KR Smith ET AL., *Familial Context of Genetic Testing for Cancer Susceptibility: Moderating Effect of Siblings' Test Results on Psychological Distress One to Two Weeks After BRCA1 Mutation Testing*, 8 CANCER EPIDEMIOLOGY BIOMARKERS PREV. 385, 386 (1999); M Watson ET AL., *The Impact of Genetic Counseling on Risk Perception and Mental Health in Women with a Family History of Breast Cancer*, 79 BRIT. J. CANCER 868, 867 (1999).

¹⁰⁴ See Nelson, *supra* note 27.

¹⁰⁵ *Id.*

studies evaluated risk assessment, genetic testing, or both.¹⁰⁶ In four studies that evaluated risk assessment, most measures of breast cancer worry, anxiety, and depression decreased, and only 1 measure of breast cancer worry increased.¹⁰⁷ When genetic testing was evaluated, breast cancer worry and anxiety increased, and results for depression were mixed.¹⁰⁸

Lastly, there are several adverse effects associated with interventions for women identified as high risk by history, positive genetic test results, or both.¹⁰⁹ Women with known mutations typically undergo one to three annual breast cancer screen examinations. The four most popular, intensive cancer screening methods are magnetic resonance imaging (MRI), mammography, ultrasonography, and clinical breast examinations. Use of MRI, ultrasonography, and mammography together had a sensitivity of 95%.¹¹⁰ Nelson did not identify any studies describing the adverse effects of intensive cancer screening for breast or ovarian cancer. However, her study did mention potential adverse effects such as inconvenience of frequent examinations and procedures, exposure to ionizing radiation that could increase risk for breast cancer, cost, harms resulting from false-positive finding and subsequent testing and biopsies, and false reassurance for women who may have increased risks for developing cancer between periodic cancer screening tests.¹¹¹ Other serious adverse effects are associated with chemoprevention and prophylactic surgery (mastectomy and oophorectomy), both of which may follow as interventions for women identified as high risk by history, positive genetic test results, or both.¹¹²

¹⁰⁶ See Nelson, *supra* note 27.

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *Id.*

¹¹¹ *Id.*

¹¹² *Id.*

In conclusion, Nelson's study uncovered two important points. First, Nelson explained that more information is needed about the impact of screening in the general population in order to determine the appropriateness of risk assessment and testing for *BRCA* mutations in primary care.¹¹³ While primary care physicians have a number of risk assessment tools at their disposal, their effectiveness is not known among asymptomatic women in the general population. Secondly, Nelson concluded that there are significant potential harms related to *BRCA* mutation testing among women in the general population. Using these conclusions, the USPSTF issued its recommendation, which are discussed below.

In its recommendation statement, the USPSTF made two significant recommendations. First, the USPSTF recommended against routine referral for genetic counseling or routine *BRCA* testing for women whose family history is not associated with an increased risk for deleterious *BRCA1/2* mutations.¹¹⁴ Second, the USPSTF recommended that women whose family history is associated with an increased risk for deleterious mutations in *BRCA1/2* genes be referred for genetic counseling and evaluation for *BRCA* testing.¹¹⁵ In weighing the clinical utility of routine *BRCA1/2* mutation testing for women without certain specific family history patterns, the USPSTF found that any benefit to routine screening or routine referral for genetic counseling would be small or zero.¹¹⁶ As mentioned above, the prevalence of *BRCA1/2* mutations among average risk and moderate risk women is only .24% and .24% to 3.4%, respectively.¹¹⁷ These numbers are too low to warrant a recommendation for routine screening. Moreover, the USPSTF found substantial evidence regarding important adverse ethical, legal, and social consequences

¹¹³ See Nelson, *supra* note 27.

¹¹⁴ See USPSTF, *supra* note 1.

¹¹⁵ *Id.*

¹¹⁶ *Id.*

¹¹⁷ See Nelson, *supra* note 27.

that could result from routine referral and testing of these women.¹¹⁸ The USPSTF estimated that the magnitude of the potential harms associated with interventions such as prophylactic surgery, chemoprevention, or intensive screening is small or greater.¹¹⁹ Thus, the USPSTF concluded that the potential harms of routine referral for genetic counseling or *BRCA* testing in these women outweigh the benefits.¹²⁰ As to the second recommendation, the USPSTF found that women with certain specific family history patterns would benefit from genetic counseling. The task force believes that counseling will give these women an opportunity to make informed decisions about testing and further prophylactic treatment.

B. Recommendations of Other Professional Medical Groups

Four other organizations have made recommendations on genetic susceptibility testing. The American College of Medical Genetics (ACMG) recommends risk assessment and genetic counseling before testing for *BRCA1/2* mutations in individuals at increased risk, based on a personal or family history of breast cancer, ovarian cancer, or both.¹²¹ The National Comprehensive Cancer Network recommends offering genetic susceptibility testing to individuals who meet the criteria for hereditary breast or ovarian cancer or both.¹²² The American Society of Clinical Oncology recommends that genetic testing be offered when: 1) an individual has a personal or family history that suggests a genetic cancer susceptibility; 2) the test can be adequately interpreted and its results will influence diagnosis or management of the patient or family members at risk for hereditary cancer.¹²³ The American College of Obstetrician and

¹¹⁸ See USPSTF, *supra* note 1.

¹¹⁹ *Id.*

¹²⁰ *Id.*

¹²¹ See American College of Medical Genetics, *Statement on Population Screening for BRCA1 Mutation in Ashkenazi Jewish Women*, <http://www.acmg.net/resources/policies/pol-002.asp> (1996).

¹²² See National Comprehensive Cancer Network, *Genetic/Familial High Risk Assessment: Breast and Ovarian Cancer*, http://www.nccn.org/professionals/physicians_gls/PDF/genetics_screening.pdf (2005).

¹²³ See American Society of Clinical Oncology *Policy Statement Update: Genetic Testing for Cancer Susceptibility*, www.asco.org/asco/downloads/GeneticTesting.pdf (2003).

Gynecologists Committee Opinion (ACOG) on breast and ovarian cancer screening, written in 2000, recommends offering BRCA mutation testing to families in which multiple family members have had breast or ovarian cancer or in which a *BRCA* mutation has been found.¹²⁴ The recommendations of each of these groups are analogous to the USPSTF recommendations in that they only recommend *BRCA* testing when the patient falls into a high-risk category.

In sum, there are five different professional medical organizations that recommend *BRCA* testing only when a woman falls into a high-risk category. Despite this apparent plethora of information for doctors and patients, these groups seem disconnected from the overall message. The following section discusses issues related to doctor and patient use and understanding of clinical guidelines for genetic predisposition screening.

IV. Problems Related to Physician and Patient Use and Understanding of Genetic Screening for Cancer Susceptibility

A. Primary Care Physicians

The purpose of the USPSTF's recommendations is to improve care by providing national guidelines for doctors. It is often difficult for doctors to keep up with the most recent literature, especially in areas beyond their specific area of concentration. Thus, the recommendations and guidelines released by the USPSTF are important to catch doctors up on the latest procedures and practices to promote more efficient and effective care. For example, when it comes to susceptibility testing for diseases such as breast and ovarian cancer, interpretations of genetic tests require sophisticated knowledge that many primary care providers may lack. In fact, physician knowledge of genetics has been low in self-reported surveys and in direct

¹²⁴ American College of Obstetricians and Gynecologists, *Breast-Ovarian Cancer Screening*. 75 INT'L J. GYNAECOLOGY OBSTRETRICS 339, 340 (2000).

assessment.¹²⁵ Only 37% regularly read articles on genetic testing.¹²⁶ Interestingly, despite the USPSTF recommendation discussed above, 89% of physicians have indicated needs for clinical guidelines for genetic testing for cancer susceptibility.¹²⁷ Physicians also expressed concern for insurance discrimination, confidentiality.¹²⁸ Finally, most physicians believe that their responsibilities include counseling patients about genetic testing, but only 51% have time to do so.¹²⁹ These numbers show not only that doctors recognize the importance of genetics regardless of their field of medicine, but also that doctors feel they have inadequate resources to meet the demands of their practice.

Although doctors seem to have serious concerns with respect to genetic testing, doctors continue to order genetic tests and refer patients for testing. One study has suggested that 60% of primary care physicians have ordered genetic test, and 74% have referred a patient for testing.¹³⁰ There seems to be a serious disconnect between what doctors feel and do with respect to genetic testing. Many factors are involved in whether physicians order tests, including patient inquiry about testing, provider assessment of the probability of a patient's carrying a mutation, and practice environment.¹³¹ Referral for cancer susceptibility tests has been associated with patient request and physicians receiving genetic test advertising.¹³²

Understanding the issues related to physicians and their attitudes and practices concerning genetic testing is important in the discussion of the USPSTF recommendations. Klitzman says clinical guidelines for utilization of genetic testing are increasingly being developed, but it is unclear how many physicians are aware of these guidelines, or in what specific areas they see

¹²⁵ See Klitzman, *supra* note 3 at 91.

¹²⁶ *Id.*

¹²⁷ *Id.*

¹²⁸ *Id.*

¹²⁹ *Id.*

¹³⁰ *Id.*

¹³¹ *Id.*

¹³² *Id.*

themselves as needing training.¹³³ The USPSTF, ACMG, and others cannot achieve their goal of educating doctors and promoting efficient and effective health care if doctors are not even aware of the guidelines or how to apply them. It is important that doctors are driven to ordering tests for the right clinical reasons, and not by other uninformed motivations.

B. Patients

Recent developments in science and technology have captured the public consciousness. With news coverage of advances in genetics, and direct-to-consumer (DTC) marketing of tests, patients' interest in testing will no doubt continue to grow.¹³⁴ Despite a growing interest in testing, patients still have serious misconceptions about testing and their risk for cancer susceptibility. Women often overestimate their risks for breast cancer or *BRCA* mutations and most women responding to surveys, including women at average and moderate risk, report a strong desire for genetic testing even though only those at high risk would potentially benefit.¹³⁵ Ultimately, the USPSTF hopes that its guidelines lead to better care for patients. But, as doctors, rather than patients, are the targeted audience for its recommendation, it is unclear if patients have any knowledge of the USPSTF guidelines. Perhaps the USPSTF needs to do more to promote its recommendations and expand its targeted audience. Whether patients would heed the advice of the USPSTF or even understand the guidelines and the technical reasoning behind the recommendation is unclear.

V. Author's Recommendation

In order to meet the growing demand of information regarding genetic testing for cancer susceptibility, certain programs and initiatives need to be developed to educate doctors and patients. Within the medical profession, organizations, such as the USPSTF, American College

¹³³ Klitzman, *supra* note 3 at 92.

¹³⁴ *Id.* at 91.

¹³⁵ *See* Nelson, *supra* note 27.

of Medical Genetics, and others, need to create educational programs for doctors, especially primary care physicians who are often on the frontline in assessing risk for cancer susceptibility among patients. For example, one recommendation is that practicing physicians should be required to attend continuing education seminars on advancements in genetics once every five years. Additionally, current medical students could be required to take multiple genetics classes so they are prepared to meet the demand for information regarding cancer susceptibility once they begin practicing medicine.

On the other side of the issue, in order to better educate patients, the USPSTF could push for publication of its clinical guidelines for genetic predisposition testing in more widely circulated streams of media and social media. Furthermore, it can be expected that information passed on doctors will eventually trickle down to patients.

Conclusion

Practice and procedural guidelines provide an invaluable resource to physicians. In the field of genetics, the recommendations of the USPSTF are especially important in guiding how physicians tackle the issue of genetic testing cancer susceptibility. Armed with these recommendations and the scientific data to support them, doctors can provide better care to their patients. Studies have shown that the clinical utility of *BRCA1/2* mutation testing is greatly outweighed by the adverse effects of testing among women that do not belong to specific high-risk groups. Nevertheless, there is a gap between the recommendations and the actions of physicians and patients. Hopefully, with the use of greater educational programs and resources for physicians and greater outreach by the medical community to the general public, practices can be improved to fall in line with the recommendations of the USPSTF.