

# GENETICS: HEREDITARY BREAST AND OVARIAN CANCER SYNDROME: GENETIC TESTING AND COUNSELING

## **Goal:**

The goal of this module is to improve recognition of hereditary breast and ovarian cancer syndromes so that appropriate patient management strategies can be implemented.

## **After completing this activity participants will be able to:**

- Recognize individuals at increased risk for hereditary breast and ovarian cancer syndrome
- Describe healthcare options for individuals at increased risk for a BRCA mutation
- Locate cancer and BRCA mutation risk assessment tools
- Explain the process of genetic counseling for hereditary cancer risk
- Discuss benefits and limitations of BRCA testing
- Interpret BRCA genetic test results
- Locate genetics and cancer resources for medical staff and patients

## **Professional Practice Gaps**

In an effort to define what healthcare providers need to know about medical genetics, several organizations developed core competencies (NCHPEG, 2000; ASHG, 2001). However, because clinical genetics is a relatively young and evolving field of medicine, many practitioners received insufficient formal genetics education. As a result, they express a lack of confidence in their clinical genetics knowledge and a lack of confidence in their ability to provide genetic counseling.

## WILL I REALLY ENCOUNTER REQUESTS FOR BREAST CANCER GENE TESTING?

### **Many primary care physicians, obstetricians/gynecologists, and cancer specialists field questions about BRCA testing.**

Multiple genes are known to be associated with breast and/or ovarian cancer. Among them are BRCA1 (breast cancer 1 gene) and BRCA2 (breast cancer 2 gene). Genetic testing for both BRCA1 and BRCA2 is commercially available. The availability of these tests has been advertised directly to the consumer in targeted areas of the United States. In addition, the genetic tests for BRCA mutations have also received a fair amount of media coverage.

The combination of direct-to-consumer marketing and media coverage has increased consumer awareness of the existence of a breast cancer gene test. Given that many women have a personal or family history of breast cancer, a considerable number of women likely will continue to inquire about genetic testing.

# TEST YOUR KNOWLEDGE 1

What is the average American woman's lifetime risk of developing breast cancer?

Choose one:

1. 1 in 4

- Feedback:

Incorrect. Try again. The answer '1 in 4' (or 25%) overestimates an American woman's risk for breast cancer.

2. 1 in 8

- Feedback:

Correct. Good job! You are correct. One in 8 (or 12.5%) American women develop breast cancer.

3. 1 in 36

- Feedback:

Incorrect. Try again. The answer '1 in 36' (or 25%) underestimates an American woman's risk for breast cancer.

4. 1 in 60

- Feedback:

Incorrect. Try again. The answer '1 in 60' (or 25%) underestimates an American woman's risk for breast cancer.

## SHOULD I ORDER THE TEST FOR EVERYONE REQUESTING IT?

**No!**

Only a small percentage of individuals with breast and/or ovarian cancer will have either a BRCA1 or BRCA2 mutation. About 20% to 25% of heritable breast cancers and about 5% to 10% of all breast cancers are caused by BRCA1 or BRCA2, and about 15% of ovarian cancer is attributed to BRCA1 or BRCA2 (Chen & Parmigiani 2007; Campeau, Foulkes, & Tischkowitz 2008; U.S. National Library of Medicine 2007; National Cancer Institute 2014).

At present, genetic testing for BRCA1 and BRCA2 is expensive, time-consuming, full of caveats, and does not have a 100% detection rate. In addition, interpretation of results is rarely straightforward.



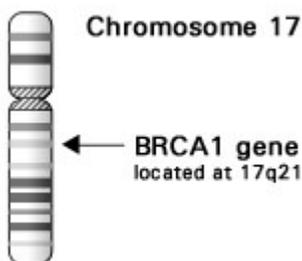
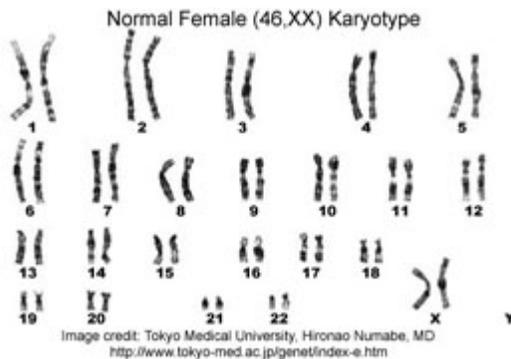
Because relatively few breast and ovarian cancers are BRCA related and because of the intricacies of the test, only the minority of women in the general population are appropriate candidates for BRCA testing. The process of assessing an individual woman for BRCA testing is complex and will be explored in the coming pages.

## WHAT IS BRCA1, ANYWAY?

### General information about BRCA1

BRCA1 is located on the long arm of chromosome 17 (Miki et al. 1994). People are normally born with 2 functioning copies of the BRCA1 gene. All people have the BRCA 1 gene, including men. The presence of these genes does not cause an increased risk for cancer. In fact, one function of BRCA1 is to act as a tumor suppressor. It is only when mutations disrupting the normal function of the BRCA1 gene occur that an increased cancer risk is associated with BRCA1.

The image on the left, below, is a normal karyotype from a female. On the right is an ideogram of a single copy of chromosome 17 specifically, showing the location of the BRCA1 gene.



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### Cancer risks associated with BRCA1

People who are born with a mutation in one of the 2 copies of BRCA1 are at increased risk for breast cancer, ovarian cancer, and prostate cancer. However, not all individuals with BRCA1 mutations will develop cancer. Of women with BRCA1, 55% to 65% will develop breast cancer and 39% will develop ovarian cancer by age 70 (National Cancer Institute 2014; U.S. National Library of Medicine 2007).

Men with BRCA1 mutations may also be at increased risk for breast cancer, and their risk for prostate cancer is approximately 8% to 16% (Ford et al. 1994; Struewing et al. 1997). Although some data suggest that the risk of colon cancer may be fourfold higher, with an estimated cumulative risk of 6%

by age 70 years [Ford et al 1994], more recent data question the association of colon cancer with *BRCA1* and *BRCA2* gene mutations [Niell et al 2004].

### How is *BRCA1* inherited?

Mutations in the *BRCA* genes are inherited in autosomal dominant fashion. The term **autosomal** means that *BRCA1* is not linked to a sex chromosome (the X and Y chromosomes). The term **dominant** indicates that if a person inherits a *BRCA1* mutation, the abnormal gene will be expressed. A person who has a *BRCA1* mutation has a 50% chance of passing the gene onto each of his or her children.

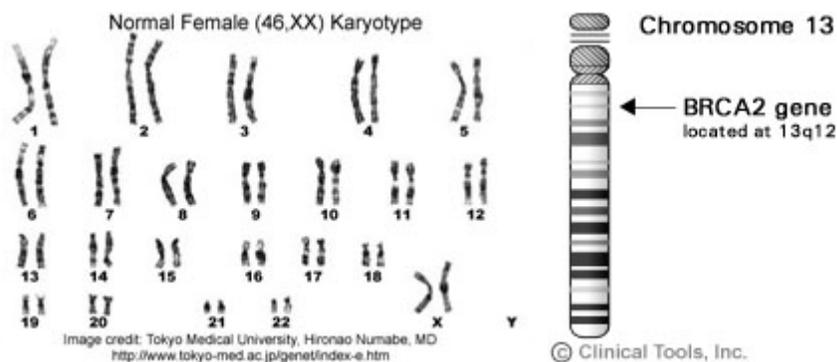
## WHAT IS *BRCA2*, ANYWAY?

### General information about *BRCA2*

Shortly after *BRCA1* was identified, *BRCA2* was discovered. *BRCA2* is located on the long arm of chromosome 13 (Wooster et al., 1995). As with *BRCA1*, most people, including men, are born with 2 functioning copies of the *BRCA2* gene, which normally function as tumor suppressors. Only when mutations disrupting the normal function of the *BRCA2* gene occur is an increased cancer risk is associated with *BRCA2*.

### Illustrations

The image to the left, below, is a normal karyotype from a female. To the right is an ideogram of a single copy of chromosome 13 specifically, showing the location of the *BRCA2* gene.



### Cancer risks associated with *BRCA2*

People with a mutation in *BRCA2* are at increased risk for breast cancer and ovarian cancer. An increased risk of prostate cancer and pancreatic cancer may also occur in individuals with *BRCA2* cancer-predisposing mutations (Berman et al. 1996, Easton et al. 1997, Gayther et al. 1997, Naderi & Couch 2002, Hahn et al. 2003). Similar to those with a *BRCA1* mutation, not all people with a *BRCA2* mutation will develop cancer. Women with *BRCA2* mutations have approximately a 45% chance of developing breast cancer and a 11% to 17% chance of developing ovarian cancer by age 70 (National Cancer Institute 2014; U.S. National Library of Medicine 2007).

Men with a *BRCA2* mutation also have a 6% to 16% increased risk of for prostate cancer, similar to men with *BRCA1* mutations (Easton et al. 1997; Struwing et al. 1997). In addition, men with a *BRCA2* mutation have a 6% chance to develop breast cancer (Easton et al. 1997, Friedman et al.

1997). In addition, for men with a *BRCA2* mutation, the risk of breast cancer by age 80 years has been estimated at 6.9% (Thompson & Easton 2001).

### How is BRCA2 inherited?

Mutations in *BRCA2* are inherited in an autosomal dominant fashion. The term **autosomal** means that *BRCA2* is not linked to a sex chromosome (the X and Y chromosomes). The term **dominant** indicates that if a person inherits a *BRCA1* mutation, the abnormal gene will be expressed. A person who has a *BRCA1* mutation has a 50% chance of passing the gene onto each of his or her children.

## COMPARISON OF CANCER RISKS

Below is a table comparing specific cancer risks of the general population to the cancer risks of people with a *BRCA* mutation.

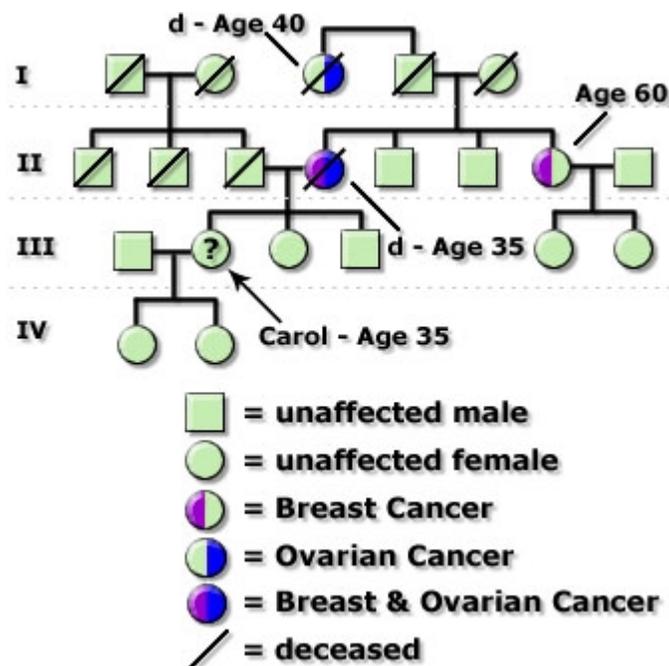
### Estimated Risks of Developing Cancer by Age 70 Based on *BRCA* Mutation Status

<b>BRCA1 Mutation</b>	<b>BRCA2 Mutation</b>	<b>No Mutation</b>	
<b>Breast Cancer</b>	55%-65% (female)	45% (female)	12% (female)
	1.2% (male)	6.8% (male)	0.1% (male)
<b>Ovarian Cancer</b>	39%	11%-17%	1.42%
<b>Prostate Cancer</b>	8%-16%	6%-16%	3.8%

(Tai et al. 2007; National Cancer Institute 2014)

## CONSTRUCTING A PEDIGREE

The first step in deciding who is an appropriate candidate for *BRCA* testing is to construct a pedigree, or medical family history. Several organizations and cancer specialists have published guidelines for a constructing a pedigree when focusing on cancer history (Eisinger et al. 1998; Fries et al. 2002; Schneider 1994; Karp 2000; American College of Medical Genetics Foundation 1999). These guidelines recommend taking a 3-generation family history that includes both maternal and paternal family members. The history of cancer for each family member is especially important to collect and should include cancer diagnoses, age at



diagnosis, whether the cancer affected one side (unilateral) or both sides (bilateral) of the body, and any genetic test results.

Carol is a 35-year-old Caucasian woman concerned about her risk to develop breast cancer. She reports that her mother died at age 35. She believes that her mother had both breast and ovarian cancer. Carol also reports that her aunt, Matilda, was diagnosed with unilateral breast cancer at age 60. Finally, Carol explains that her great-aunt, Alice, died at age 40 from ovarian cancer. No other cancers are reported. Carol explains that she recently had her annual gynecologic examination and that her breast exam and Pap smear were normal.

Paternal Ethnicity: Irish    Maternal Ethnicity: English

(No Ashkenazi Jewish ancestry)

## CHARACTERISTICS OF A BRCA PEDIGREE

Pedigrees of families that possess a BRCA gene mutation often, **but not always**, reflect the autosomal dominant pattern of inheritance. Other characteristics of pedigrees from families with a BRCA mutation include the following:

- Another family member with a known BRCA mutation
- Breast or ovarian cancer in multiple family members
- Cancer diagnosis at a young age (younger than 45 years or premenopausal)
- Bilateral cancers (in paired organs)
- Breast cancer in a male family member
- Ashkenazi Jewish ancestry
- Multiple primary breast or breast and other BRCA-associated cancer diagnoses in the same patient (Shih et al. 2002)



Because of the possibility that patient-reported family medical histories are inaccurate or incomplete, practitioners should review all relevant available family medical records to confirm diagnoses (Fries et al. 2002; Karp 2000; American College of Medical Genetics Foundation 1999). It is important to note that not all families or individuals with a BRCA mutation demonstrate a family history that is considered "classic." Because of this fact, it is not sufficient to base a testing decision on pedigree analysis alone. Statistical models designed specifically to generate a patient risk estimate for either breast cancer or for having a BRCA mutation are also used.



Clinical management of BRCA1- and BRCA2-associated breast cancer. *Semin Surg Oncol.* 2000; 18: 296-304.

Guidelines for evaluation of patients at risk for inherited breast and ovarian cancer: recommendations of the Department of Defense Familial Breast/Ovarian Cancer Research Project. *Mil Med.* 2002; 167: 93-98.

## ESTIMATING PATIENT RISK

Statistical tools commonly used to generate a woman's risk to develop breast cancer are the Claus and Gail models (Claus et al. 1991; Gail et al. 1989). Statistical tools that calculate a patient's likelihood of having a BRCA mutation, not a risk for breast cancer, include the BRCAPRO (from Duke University) and Myriad II models (Berry et al. 1997; Frank et al. 2002; Parmigiani et al. 1998).

Often, healthcare professionals will use multiple models to generate several different risk estimates for each patient. No one model works best in every clinical situation, so familiarity with the strengths and weaknesses of each statistical tool is helpful. One statistical package, Cancergene, is available online at no cost to healthcare providers. Cancergene simultaneously calculates risk using several different models and risk tables. Additional information about those risk models is included in pop-ups below.

### **Breast Cancer Risk Models**

#### **Claus model**

The Claus model (Claus et al., 1994) generates an estimate for a person to develop breast cancer. The model adjusts an individual's breast cancer risk based on the following:

- The woman's current age
- The presence of breast cancer in first- and second-degree relatives
- Age of cancer diagnosis

The Claus model does not take into account the following:

- Presence of Ashkenazi Jewish ancestry
- Hormonal history factors
- BRCA status of patient or family members
- Any history of ovarian cancer
- Information from more than 2 first- and/or second-degree relatives with breast cancer

The model may be useful for patients at moderate risk with paternal family history and in assessing risk of breast cancer in women with several close relatives with breast cancer. The model is less useful for women with 3 or more first- or second-degree relatives with breast cancer.

#### **Gail model**

The Gail model (Gail et al., 1989) generates an estimate for a person to develop breast cancer. The model adjusts an individual's breast cancer risk based on the following:

- Ethnicity
- Patient age
- Age of menarche

- Age of first childbirth
- Number of breast biopsies
- Number of first-degree maternal relatives with breast cancer

The Gail model does not take into consideration the following:

- Paternal family history of breast cancer
- Family history of breast cancer in second-degree relatives
- Age of onset of breast cancer in family members
- BRCA status of patient or family members
- Any history of ovarian cancer
- Presence of Ashkenazi Jewish ancestry

This model may be useful for assessing breast cancer risk for a woman at moderate risk but without an extensive or paternal family history of breast cancer.

## **BRCA Mutation Risk Models**

### **BRCAPRO (Duke University) model**

The BRCAPRO model (Berry et al., 1997; Parmigiani et al., 1998) generates an estimate for a person to have a BRCA1 and/or BRCA2 mutation. It can also generate a risk for the individual to develop breast or ovarian cancer. The model adjusts an individual's mutation risk based on the following:

- Whether or not the patient is of Ashkenazi Jewish descent
- The patient's breast and ovarian cancer status
- Breast and ovarian cancer status in first- and second-degree relatives
- Sex of the patient and each first- and second-degree relative
- Exact relationship of each first- and second-degree relative to the patient
- Age of each person at breast or ovarian cancer diagnosis

This model is useful for assessing an individual's risk to have a BRCA mutation when a significant family history of breast and/or ovarian cancer exists.

(BRCA1 and/or BRCA2 estimates)

### **Myriad II (Myriad.com) model**

The Myriad II model (Frank et al., 2002.) generates an estimate for a person to have either a BRCA1 or BRCA2 mutation. The model adjusts an individual's mutation risk based on the following:

- Presence of breast cancer in family members before age 50
- Presence of ovarian cancer in family member(s) of any age
- Whether the proband had breast cancer before or after age 50
- Presence of male breast cancer in a proband
- Whether the proband had ovarian cancer
- Whether the proband is of Ashkenazi Jewish ancestry

This model is appropriate for patients at significant risk with multiple family members diagnosed with cancer.

(BRCA1 or BRCA2 estimate)

Once patient-specific risk estimates have been generated, the individual will either have a risk estimate great enough to proceed to pretest counseling or have a low risk estimate that does not warrant the time and expense of testing. Most guidelines for BRCA testing recommend a generated risk of 10% or greater to proceed with genetic testing (American Society of Clinical Oncology 1996; Karp 2000).

## NOW DO I ORDER THE TEST?

My patient's calculated risk was 20% to 30% using several models. Now do I order the test?

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**Believe it or not, not just yet.**

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So far, you have spent quite a bit time creating a pedigree, examining medical records, and calculating patient-specific risk estimates. For patients with significant risk estimates, there is a recommended protocol to follow for BRCA testing.



## OVERVIEW OF THE TESTING PROCESS

Multiple professional societies and cancer specialists have published guidelines for the BRCA genetic testing process (American College of Medical Genetics Foundation 1999; Eisinger et al. 1998; Fries et al. 2002; McKinnon et al. 1997). Most guidelines recommend that a testing protocol include the following:

- An initial risk assessment
- Pretest counseling and psychological assessment
- Blood draw for testing
- Face-to-face result disclosure
- Post-test counseling

Given the complexity of genetic testing for BRCA and the time commitment involved, each healthcare professional must decide how feasible it is to provide either a portion of the testing process or the entire service.

## PRETEST COUNSELING

Many people requesting the "gene test for breast cancer" do so because they know genetic testing exists and are worried about their own cancer risk. Few people are aware that the test is only appropriate for a minority of individuals or that the test has limitations. Pretest counseling provides an opportunity for patients to learn about HBOC syndrome and the genetic test for BRCA and to explore potential consequences of testing (Lancaster et al. 2007; Thull & Vogel 2004; Arver 2004).

Pretest counseling for BRCA testing should include discussions of the following:

- Basic genetics, including information about BRCA1 and BRCA2
- The patient's actual risks to inherit a BRCA mutation and the chance that the patient will develop cancer
- The potential psychological impact of test results
- The potential impact of test results on relationships
- The potential impact of test results on health and/or life insurance
- Benefits and technical limitations of testing
- Healthcare options available to the patient

(American College of Medical Genetics Foundation 1999; Eisinger et al. 1998; Fries et al. 2002; Karp 2000)

## A VERY PERSONAL DECISION

After learning about the genetic test for BRCA, not all people requesting testing will decide to proceed. Each person at increased risk for cancer will have a unique set of concerns and personal reasons for choosing or not choosing genetic testing. Some people will simply decide that they do not want to know their genetic status, while others feel an overwhelming need to know.



### Common Reasons People Decide to Proceed With Testing

- Defining genetic status to help make personal healthcare decisions
- Defining genetic status to help make reproductive decisions
- Resolving genetic status for the sake of children and other relatives
- Defining genetic status to help financial planning
- Learning genetic status to reduce uncertainty

(Miller et al. 2007; American College of Medical Genetics Foundation 1999; Jacobsen et al. 1997)

## THINGS TO CONSIDER

### Personal Psychological Impact

For people who decide to proceed with BRCA testing, some time should be spent with them exploring potential psychological consequences. Several well-respected BRCA testing experts report that patients who spend time thinking about possible test results during counseling generally handle test results relatively well (Croyle et al. 1997; Lerman et al. 1996; Marteau and Croyle 1998; Meiser et al. 2002).

### Individuals Can Prepare for Test Results by Doing the Following:

- Anticipating their feelings such as anger, sorrow, anxiety, or relief at having an answer
- Thinking about how a positive test result might alter marriage and/or reproductive decisions

- Thinking about whether or not he or she might feel guilt from potentially passing a cancer-predisposing gene onto children
- Thinking about reactions to a result that is uninformative, e.g., if a gene change of unknown significance is found

## Family Impact

Explore the potential impact on the family as a unit, or on individual members:

- **Potential impact on family dynamics**

Genetic testing impacts not only the person undergoing testing but family members as well (American College of Medical Genetics Foundation 1999; National Cancer Institute 2004; Geller et al. 1997; Nicoletto et al. 2001; Braithwaite et al. 2008; Trepanier et al. 2004).



**Example 1:**

A woman with early-onset breast and ovarian cancer suspected she was at an increased risk to have a BRCA mutation her entire life but elected not proceed with testing once it became available. Her daughter, however, felt differently and pursued genetic testing. The daughter's positive mutation result increases the chance that the mother is also mutation positive and may upset the mother, who did not want to know her genetic status.

**Example 2:**

For members of a family used to facing the threat of cancer as a unit, redefining individual members' risk(s) through gene testing can be upsetting. Prior to genetic testing, no one family member is known to be at a greater or lesser risk than another. After genetic testing, however, the family can potentially be subdivided into groups by test result. Perhaps some individuals who test positive for a cancer gene mutation did not previously have a close personal relationship, but post-testing revealed they have something in common on which to build a relationship. Alternatively, some family members may find that a close relationship existent prior to testing becomes strained after the individuals receive disparate test results.

- **Testing minors**

Parents who test positive for a BRCA mutation are understandably concerned for the welfare of their children. Parents may feel guilt or anxiety over the "not knowing." Well-meaning parents may request testing of their children to help ease parental concern but may neglect to consider that parenting and parent-child relationships could be impacted by test results.

**Example:**

A parent may subconsciously be more lenient toward a child known to carry a BRCA mutation, or a parent may more easily identify with a child who has the same BRCA status as the parent.

Knowledge of a child's BRCA status may also negatively impact a child's self-esteem and perspective on life. Because of the potential damage to a child's psyche and because no

preventive measures for BRCA-related cancers are suggested in childhood, it has been recommended by several organizations that minors not be tested for BRCA (American College of Medical Genetics Foundation, 1999; ASHG Board of Directors and ACMG Board of Directors, 1995; Eisinger et al., 1998).

- **Prenatal testing**

It is technically possible to test a pregnancy to determine the BRCA status of the fetus. However, prenatal diagnosis of fetal BRCA status raises many complex ethical issues (Lancaster et al. 1996; Lodder et al. 2000; Wagner & Ahner 1998). Several groups either advise against or recommend extreme caution in proceeding with prenatal diagnosis for BRCA (Petrucci et al. 2004; Karp 2000; National Society of Genetic Counselors 1995).

Some reasons that prenatal diagnosis for BRCA is cautioned against are listed below:

- Testing a pregnancy for BRCA carries with it an increased risk of miscarriage.
- Having the BRCA mutation does not guarantee that the fetus will develop cancer.
- BRCA mutations do not cause cancer until an individual reaches adulthood, and it is possible that better treatment/management options will exist in the future.
- Testing a fetus for BRCA status and carrying the pregnancy to term eliminates that individual's choice of whether or not to pursue genetic testing as an adult.

## GENERAL INFORMATION ABOUT BRCA TESTING

### General Information About BRCA Testing

Genetic tests, unlike some clinical tests that are fairly straightforward, are limited by current technologies and may have results that are difficult to interpret. Those electing to pursue testing for BRCA need to learn about these limitations so that they will better understand their results.

- Test methodology for most ethnicitiesThe analysis technique used for the majority of people undergoing genetic testing for BRCA is called sequencing. Sequence analysis allows laboratories to review a person's genetic information at the most basic level, nucleotide by nucleotide. (Myriad Genetics Laboratories, 2005). However, sequencing cannot detect all genomic rearrangements, some RNA transcript processing errors, and may not detect mutations in regions studied due to rare technical limitations (such as polymorphisms underlying primer sites). These types of potentially undetectable mutations are estimated to account for about 10% of all clinically significant BRCA mutations (Myriad Genetics Laboratories, 2005). Thus, the detection rate for BRCA mutations is 90% (Myriad Genetics Laboratories, 2005; Michelle Martin, Myriad Genetics, personal correspondence, December 21, 2005). This means that there are families with cancer-causing BRCA mutations that will not be detected by current technologies. close
- Test methodology for individuals of Ashkenazi Jewish descent

People of Ashkenazi Jewish descent (Jewish families from Eastern or Central Europe) are at a higher risk to have BRCA mutations than non-Ashkenazi Jewish people. Individuals of Ashkenazi Jewish ancestry have a 1 in 40 chance to have a BRCA mutation (Oddoux et al.,

1996; Roa et al., 1996; Struwing et al., 1995), while the general population has a 1 in 500 to 1 in 800 chance (Ford et al., 1995; Szabo and King, 1997).

Unlike the general population, which harbors hundreds of different types of gene changes, there are 3 specific mutations commonly found in Ashkenazi Jewish individuals (185delAG, 5382insC, and 6174delT). It is estimated that in the Ashkenazi Jewish population, 20% to 35% of women with early-onset breast cancer and approximately 60% of women with ovarian cancer have either a 185delAG or 6174delT mutation (FitzGerald et al., 1996; Abeliovich et al., 1997; King et al., 2003). These 3 mutations can be easily tested for without sequencing the BRCA genes in entirety. Multiple laboratories in the United States offer this 3-mutation panel, and cost generally is under \$500. If such an analysis is performed and is negative (no mutation detected), it may be appropriate to proceed to full sequencing in a patient with a significant family history of breast and/or ovarian cancer.

- Cost and reimbursement for testing - Myriad Genetics, Inc. created a special division to help patients and doctors obtain insurance coverage for genetic testing, the Myriad Reimbursement Assistance Program. The company reports that 60% of all patients requesting insurance coverage receive 100% coverage (Heather Shappell, Myriad Genetics, personal correspondence, August 2004). Another 20% to 30% of patients receive some insurance benefit (Heather Shappell, Myriad Genetics, personal correspondence, August 2004). Testing coverage depends on the insurance company and the indication for testing. Even when insurance companies agree to cover the majority of testing expenses, patients will still be required to pay an average of several hundred dollars out of pocket. For those choosing not to file an insurance claim, out-of-pocket expenses can be as high as \$3,000.00. close

### Points of significance

- There is only 1 commercial laboratory offering full sequencing for BRCA in the United States, Myriad Genetic Laboratories
- Full sequencing is very expensive (~\$3,000.00) and does not have a 100% detection rate (may be as high as 90%).
- Results usually are not available for several weeks.



## POSSIBLE RESULTS

BRCA test results must be interpreted within the context of each patient's personal and family medical history. The absence of a mutation does not necessarily mean that an individual is not at increased risk for cancer. The presence of a mutation does not necessarily mean that a person is at increased cancer risk. Mutations that do not cause disease are called polymorphisms.

Myriad Genetics, Inc. reports BRCA results as follows:

<b>Result</b>	<b>Interpretation</b>	<b>Clinical Significance</b>
Positive for a deleterious mutation	Predicted to be clinically significant	Patient at increased risk for breast/ovarian and associated cancers
Genetic variant, suspected deleterious	Suspected to be clinically significant	Patient thought to be at increased risk for breast/ovarian and associated cancers
Genetic variant, favor polymorphism	Not suspected to be clinically significant	Patient not thought to be at increased risk for breast/ovarian and associated cancers
Genetic variant of uncertain significance	Not known if clinically significant	Not known if patient is at increased risk for breast/ovarian and associated cancers
No deleterious mutation detected	Patient negative for genetic changes screened for	Result does not eliminate possibility that patient has an uncommon gene change in BRCA1/2 <b>or</b> a mutation in another cancer-causing gene
Specific variant/mutation not identified	Patient negative for a genetic changes found in a previous family member	Clinical impact dependent upon family history

## POTENTIAL BENEFITS OF TESTING

Although genetic testing is full of caveats given today's technological limits, for many patients the availability of an imperfect test is preferable to not having a genetic test for BRCA at all.

Potential benefits of genetic testing for BRCA mutations include defining a person's genetic status, providing additional information from which to make healthcare decisions, and reducing anxiety over the uncertainty of one's cancer risk(s) (U.S. National Library of Medicine 2014).



U.S. National Library of Medicine. What are the benefits of genetic testing?. *Genetics Home Reference Handbook*. 2014. Available at: <http://ghr.nlm.nih.gov/handbook/testing/benefits> Accessed on: 2014-09-10.

# POTENTIAL LIMITATIONS AND DRAWBACKS OF GENETIC TESTING

In addition to benefits associated with BRCA testing, potential limitations are also notable with BRCA testing. For example, some people will receive uninformative results or will be found to carry a genetic change of uncertain clinical significance. These types of results occur more often in the first person in the family to be tested and are often highly frustrating (American College of Medical Genetics Foundation 1999).



Some patients may experience a negative psychological impact. For patients who receive test results indicating an increased cancer risk, both self-esteem and outlook on life may be negatively influenced (Robson & Offit 2007; Kenen et al. 2007; Halbert et al. 2004, Palma et al. 2006). For patients receiving test results indicating no increased cancer risk, a percentage will experience "survivor guilt" (Geller et al. 1997). In other words, the patient feels guilty at not having a familial cancer-causing BRCA mutation when other family members test positive for it.

## DISCLOSING TEST RESULTS

Professional consensus is that result disclosure is best done face to face, given the anxiety surrounding BRCA test results and the potential for a lengthy discussion of them. As with pretest counseling, healthcare providers should be prepared to discuss the psychological impact of the results and all possible healthcare options (Braithwaite D et al. 2006; American Society of Human Genetics 2005; Dorval et al. 2008; Riley et al. 2011).



It is also important to discuss any increased cancer risks for family members. Any at-risk family members will need to be informed of their increased risk (Karp 2000). Notification allows family members to seek out additional information if desired and take potentially risk-reducing measures. Healthy family relationships make it easier for patients to discuss the increased cancer risk. Patients with strained or severed family relationships may prefer to either draft an informative letter to family members or have a healthcare provider draft a letter.

## TEST YOUR KNOWLEDGE 2

You are seeing a new patient, Kathy, on a very busy day in the clinic. Your nurse hands you the chart moments before you walk into the room. The patient has brought with her a few medical records, including a report for full BRCA sequence analysis. This report catches your attention, and you pause to look at it. According to the report, Kathy does not have a detectable BRCA mutation.

How do you interpret her results?

Choose one:

1. Kathy does not have a mutation and therefore is not at increased risk for cancers associated with the presence of a BRCA mutation.

- Feedback:

Incorrect. Try again. To accurately interpret her BRCA analysis result, you will need additional information from Kathy. You will need information about her family history, her personal medical history, and any BRCA analysis results from previously tested family members. Examples of how this information impacts result interpretation are provided on the following pages.

2. Kathy does not have a mutation but remains at increased risk for cancers associated with the presence of a BRCA mutation.

- Feedback:

Incorrect. Try again. To accurately interpret her BRCA analysis result, you will need additional information from Kathy. You will need information about her family history, her personal medical history, and any BRCA analysis results from previously tested family members. Examples of how this information impacts result interpretation are provided on the following pages.

3. Kathy's cancer risks cannot be determined by the negative test result without additional information about her personal or family history.

- Feedback:

Correct. Good job! You answered correctly. Examples of how Kathy's family history, her personal medical history, and any BRCA analysis results from previously tested family members impacts result interpretation are provided on the following pages.

## PATIENT-SPECIFIC RESULT INTERPRETATION

Below are 2 examples of women who receive a BRCA-negative test result; however, the interpretation is very different for each woman.



### **Example 1:**

Amy's sister is diagnosed with breast cancer at age 43 and elects to have genetic testing. The sister tests positive for a mutation in BRCA1. Amy is now concerned that she may also have a BRCA1 mutation and requests testing. Amy's test result is negative. This means that she does not have the cancer-causing gene change her sister does and is not at increased risk to develop breast or ovarian cancer. Amy's cancer risks return to the same risk as the general population (approximately 1 in 8).

### Example 2:

Monica's sister was diagnosed with breast cancer at age 43 and chose not to pursue testing. Monica is concerned with her personal risk to develop breast cancer and requests testing. Monica's test result is negative – she does not have a recognized mutation in BRCA1 or BRCA2 – but there are several possible interpretations.

- Her result is negative because her sister simply had a sporadic form of breast cancer, one not related to BRCA.
- Her result is negative because she did not inherit the cancer-causing gene change her sister did.
- Her result is negative because, although both she and her sister have a cancer-causing gene change in BRCA1, the gene change was not one detectable by the test.
- Her result is negative because the family does, in fact, have a hereditary form of breast and ovarian cancer. However, the gene change is in an as-yet-undescribed gene.



## PATIENT-SPECIFIC RESULT INTERPRETATION (CONTINUED)

Below are 2 examples of women who receive BRCA test results indicating that a gene change is identified. As with the examples on the previous page, the interpretation is different for each woman.

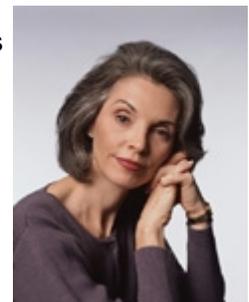


### Example 3:

Anita has several relatives with early-onset breast and ovarian cancer. No one in her family has undergone BRCA analysis. Anita is 36 years old and wonders if there is a hereditary component to the cancers in her family. She requests genetic testing. Her result is positive for a known cancer-causing BRCA2 mutation. This means that Anita is at increased risk for BRCA2-associated cancers. It also means that Anita's family members are at risk to have the same mutation. Each at-risk relative should be notified so he or she may seek appropriate healthcare options.

### Example 4:

Faye has a significant family history of BRCA-associated cancers and a personal history of unilateral breast cancer diagnosed at age 39 years. Her family members have not yet undergone genetic testing. Faye elects to proceed with BRCA analysis. She receives a result reported as "genetic variant of uncertain significance." In other words, Faye does have a mutation; however, it is not a mutation that has been studied well enough to determine its clinical impact. To help resolve the significance of the mutation, additional family members could undergo testing. Should the same mutation be located in relatives with cancer but absent in relatives without cancer, the mutation becomes a more likely cause of Faye's cancer.



# HEALTHCARE OPTIONS

Management guidelines have been published for people at increased breast and ovarian cancer risk or who test positive for a BRCA mutation. These guidelines collectively include the following:

- Increased surveillance
- Preventive drug therapies
- Prophylactic surgery
- Diet and/or lifestyle changes
- Psychosocial support

Different patients will choose different combinations of options, depending on their greatest concerns and perceived benefits of the management option. Healthcare options are summarized below:

## Healthcare Options for Cancer-Free Women With a BRCA Mutation

Increased Surveillance*	
<b>Breast Cancer</b>	Monthly breast self-exams, beginning age 18-21 Annual or semi-annual clinical breast exams, beginning age 18-25 Annual mammography and breast MRI, beginning age 25-35
<b>Ovarian Cancer**</b>	Annual or semi-annual transvaginal ultrasound, beginning age 25-35 Annual or semi-annual serum CA-125 levels
Preventive Drug Therapies	
<b>Tamoxifen</b>  (selective estrogen-receptor modulator)	May reduce breast cancer risk by 50%
<b>Oral Contraceptives</b>	May reduce ovarian cancer risk 60% May <b>increase</b> breast cancer risk
Prophylactic Surgery	
<b>Prophylactic Mastectomy</b>	May reduce breast cancer risk 90%+
<b>Prophylactic Oophorectomy</b>	May reduce ovarian cancer risk 96% (age 35 or after childbearing) May simultaneously reduce breast cancer risk by 53% in BRCA mutation-positive women

## Healthcare Options for Cancer-Free Men With BRCA Mutations

Increased Surveillance*	
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<b>Breast Cancer</b>	Monthly breast self-exams, beginning age 18-21 years Annual or semi-annual clinical breast exams, beginning age 18-25 Consideration of mammography based on exam findings
<b>Prostate Cancer</b>	Annual prostate exam Annual prostate-specific antigen levels, age 40

\*Screening should be individualized based on the earliest age of onset in the family.

\*\*The ovarian cancer screening measures available have limited sensitivity and specificity and have not been shown to reduce ovarian cancer mortality. However, these methods are still recommended in the absence of more effective means of screening.

## HEALTHCARE OPTIONS 2

Because the genes for BRCA were identified in the mid-1990s, the medical community is still gathering information about the reduction in cancer risk associated with each healthcare option. Studies have documented a 95% risk reduction in women who elected prophylactic surgery (National Cancer Institute 2013; Rebbeck et al. 2004). However, not all women desire preventive surgery because it carries with it a set of potential complications and drawbacks. For many women, the greatest drawback is the psychological impact of losing their breast tissue. Preventive drug therapy also reduces cancer risk in women. Tamoxifen conveys a 47% to 50% risk reduction in breast cancer (Gronwald et al. 2005; Metcalfe et al. 2004). Oral contraceptives may increase the risk for breast cancer (Grabrick et al., 2000; Narod et al., 2002) but may also reduce ovarian cancer risk up to 60% (Whittemore et al. 2004; Milne et al. 2005).



There are no clear data on the reduction in risk from increased surveillance or diet/lifestyle changes. Perhaps one advantage to the latter 2 approaches is that a patient may feel as if he or she is taking an active role in preventing cancer.

### Diet and/or Lifestyle Changes for Men and Women

Change	Risk Reduction
<b>Fat Intake Reduction</b>	Risk reduction unknown in BRCA mutation-positive patients
<b>Reduced Alcohol Consumption</b>	Risk reduction unknown
<b>Increased Physical Activity</b>	May reduce risk of some types of cancers, including breast cancer and colon cancer
<b>Increased Antioxidant Vitamin Intake</b>	Risk reduction unknown
<b>Decreasing Radiation Exposure</b>	Risk reduction unknown

<b>Psychosocial Support for Men and Women</b>	May reduce anxiety and negative impact of living at increased cancer risk May help women electing prophylactic surgery to adjust
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(References: National Cancer Institute 2013; Daly et al., 2003)

Each patient will select a slightly different approach in reducing his or her risk for cancer. Patients will make choices based on their personal level of comfort with cancer risks, the perceived potential benefit each option offers, and the perceived potential drawback(s) of each option. Although patients cannot control or change the risk for cancer they were born with, they may feel somewhat empowered with knowledge of their cancer risks and by tailoring their own healthcare plan.



## SUMMARY AND KEY POINTS

- **BRCA and breast and ovarian cancer risks:**

Only 5% to 10% of breast and ovarian cancer cases are considered hereditary. Researchers have identified mutations in 2 genes, BRCA1 and BRCA2, which convey an increased risk of breast and ovarian cancer.

- **Identifying candidates for genetic testing:**

Genetic testing for BRCA, as currently available, is not appropriate for everyone. Characteristics of a family history that should elevate suspicion of the presence of a BRCA mutation include the following:

- Previous family member with a known BRCA mutation
- Cancer in multiple family members
- Cancer diagnosis at a young age (younger than 45 years or premenopausal)
- Cancers on both sides of the body (in paired organ systems)
- Breast cancer in a male family member
- Ashkenazi Jewish ancestry
- Multiple cancer diagnoses in the same patient

- **Counseling and education:**

Adequate pretest counseling includes discussions of basic genetics, estimated risk, potential psychosocial impact of results, and available healthcare options. Individuals pursuing testing should be advised of the test limitations and benefits. Result disclosure should be done in person and include time for counseling. Healthcare options for individuals with an identified mutation include increased surveillance, preventive drug therapies, prophylactic surgery, and lifestyle and diet changes.

## RESOURCES AVAILABLE THROUGH THIS MODULE:

- [BRCAAnalysis Technical Specifications](#)  
This article includes information on the four different clinically available BRCA tests for the testing of hereditary breast cancer syndrome: comprehensive full-gene sequence analysis including five specific rearrangements, single site testing for known familial mutations, multisite test, and the rearrangement test. It also includes information on the performance characteristics and interpretive criteria of the tests.
- [BRCA1 and BRCA2 Hereditary Breast/Ovarian Cancer](#)  
This article provides comprehensive information on the BRCA1 and BRCA2 and Hereditary Breast/Ovarian Cancer. It includes information on prevalence, screening, diagnosis, counseling and management, as well as extensive information on genetic testing and the genes themselves.
- [Fact Sheet on Genetic Testing for Breast and Ovarian Cancer Susceptibility](#)  
This article discusses how Genomics and Health are tied with Breast and Ovarian Cancer and Family Health History.
- [Final Recommendation Statement BRCA-related Cancer](#)
- [Genetic Testing for BRCA1 and BRCA2: It's Your Choice](#)  
Information Resource for Genetic Testing for BRCA1 and BRCA2
- [NCI Genetics of Breast and Ovarian Cancer \(PDQ\)](#)  
This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the genetics of breast and ovarian cancer.
- [Online Mendelian Inheritance In Man \(OMIM\)](#)  
OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources. OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions (From their Website).

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