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Genetic tests to identify risk for breast cancer

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Abstract

Objectives—To describe the currently available genetic tests that identify hereditary risk for breast cancer.

Data sources—Systematic review of scientific literature, clinical practice guidelines, and data published by test manufacturers.

Conclusion—Changes in gene patent laws and advances in sequencing technologies have resulted in rapid expansion of genetic testing. While *BRCA1/2* are the most recognized genes linked to breast cancer, several laboratories now offer multi-gene panels to detect many risk-related mutations.

Implication for Nursing Practice—Genetic testing will be increasingly important in the prevention, diagnosis, and treatment of breast cancer. Oncology and advanced practice nurses need to understand risk factors, significance of various genetic tests, and patient counseling.

Keywords

Breast genetic testing; BRCA; genetic risk; hereditary risk; multigene panels

Genetic testing has an important role in hereditary risk assessment for breast cancer. There has been rapid expansion of genetic testing as a result of changes in gene patent laws and improvements in gene sequencing technologies. Oncology nurses and advanced practice nurses (APNs) are often asked to educate patients about genetic tests, or may need to assess

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a patient's family history to determine whether the patient should be referred for genetic counseling. This article provides oncology nurses and APNs with an overview of genetic tests for hereditary mutations that may increase a patient's personal risk of breast cancer.

Diagnostic Testing

When reviewing genetic diagnostic testing, it is important to understand the differences between genetic versus genomic testing and germline versus somatic mutations. Generally, a *genetic* test identifies heritable mutations in specific genes, whereas the term *genomic* test usually refers to the analysis of the sequence and/or expression of groups of genes, large fragments of the genome or even the entire genome. Similarly, the difference between germline and somatic mutations is that a germline mutation is present from the time of conception and therefore is carried in all cells of the body and can be passed on to the next generation. An example of a germline mutation is the inherited mutation in the *BRCA1* or *BRCA2* gene. Somatic mutations are acquired during an individual's lifetime through exposure to environmental factors and are usually only present in the tumor. Somatic cancer tests usually require analysis of tumor tissue whereas germline genetic tests usually analyze a blood sample or a cheek swab.

Mutations that Increase Breast Cancer Risk

The majority of breast cancer patients are the only member of their family with breast cancer and most cases are attributed to environmental or lifestyle factors. Fewer than 15% of women with breast cancer have a first-degree relative with this disease,[1] and only a small fraction of the population carries inherited germline mutations that increase their lifetime cancer risk. Several genes associated with an increased risk of breast cancer have been identified. The level of increased risk and type of cancers that occur in a family will vary with the particular gene involved. Mutations in each gene are rare, however collectively these mutations account for a significant amount of hereditary cancer susceptibility in the population.

The penetrance of a disease-causing mutation is the likelihood that an individual with the mutation will exhibit clinical symptoms. Mutations in two high penetrance genes, *BRCA1* and *BRCA2*, account for the majority of hereditary breast cancers and about 5%–10% of all breast cancers.[2, 3] Men and women with harmful *BRCA1*/*2* mutations are at increased risk of breast cancer development. In addition, *BRCA1*/*2* mutations account for approximately 15% of ovarian cancers[4] and these mutations increase the risk of fallopian tube and prostate cancers. Collectively, the inherited tendency to develop cancers associated with *BRCA1*/*2* mutations is known as hereditary breast-ovarian cancer (HBOC) syndrome. In addition to these germline mutations, somatic *BRCA1/2* mutations have also been described in ovarian cancer.[5] Mutations in a number of other genes, including *PTEN*, *TP53, STK11, CDH1* and *PALB2*, have been found to increase the risk of developing breast cancer, although to a lesser extent than *BRCA1/2*.[2, 6]

Genetic Testing

Several genetic tests that detect the presence of these cancer-predisposing mutations are commercially available. This type of test involves a blood sample (or a sample of a person's tissue, such as saliva or cheek swab) with DNA analysis for known mutations. Until recently, individual genes were tested separately and sequentially by traditional Sanger sequencing methods. However, decreasing costs and improved efficiencies in high throughput sequencing technology (next-generation sequencing) have made full gene sequencing and multi-gene panels more cost-effective.

The molecular testing landscape is currently in a state of flux. From the late 1990s until 2013, BRCA testing was offered exclusively by Myriad Genetics, a company that patented the *BRCA1* and *BRCA2* genes.[7, 8] In June 2013, the U.S. Supreme Court voided Myriad's patents and shortly thereafter, several academic and commercial reference laboratories began offering BRCA testing. Examples of academic laboratories that offer BRCA testing include: Baylor College of Medicine, City of Hope, Emory University, Washington University School of Medicine, Memorial Sloan Kettering, and University of Washington Medical Center. Examples of commercial laboratories that offer BRCA testing include: Ambry Genetics, GeneDx, Invitae Corporation, Laboratory Corporation of America, Myriad Genetics, Quest Diagnostics, and Pathway Genomics. These laboratories differentiate their services by bundling cancer predisposition gene tests and offering different turn-around times and costs.

Tests for mutations in other genes known to predispose individuals to breast cancer are also being offered. The National Comprehensive Cancer Network (NCCN) 2014 guidelines on genetic/familial high-risk assessment in breast and ovarian cancer outline the criteria for multi-gene testing in breast cancer, specifically pointing to the clinical relevance of the *TP53, PTEN, ATM*, and *PALB2* genes in addition to *BRCA1* and *BRCA2*.[9]

Genetic tests currently on the market are detailed in Table 1[2, 6, 10–28] with their corresponding trade names. These tests screen for known point mutations, small deletions and large chromosomal rearrangements. For patients with identified family members carrying a specific mutation, customized analyses detecting the same mutation can be offered. The first company to allow providers to custom order analyses of specific genes was Invitae Corporation (San Francisco, CA). As laboratory costs decrease and the technology expands to next generation sequencing, the amount of information available from a single test order will increase. As additional data about the implications of various mutations increases and bioinformatics algorithms are computerized, the interpretation of these data will also improve.

Multi-gene panels can evaluate the presence of several breast cancer-related mutations at once. However, genetic testing is expensive and the process can increase anxiety in patients. A complete evaluation of personal and family history prior to testing may decrease patient anxiety and save significant dollars. *BRCA1* and *BRCA2* are the most established breast cancer susceptibility genes. However, limiting testing to those two genes may miss a more

appropriate test. Table 2 lists some of the inherited syndromes that involve breast cancer as well as other selected malignancies.[3, 29, 30]

Genetic Counseling and Testing

Guidelines about genetic counseling and testing have been published by the American College of Medical Genetics[31] and the U.S. Preventive Services Task Force (USPSTF).[32] Conducting a comprehensive assessment of family history and obtaining informed consent for the right set of genetic tests takes expertise and time. A cursory family history can help define which patients should be referred for a genetic consultation prior to definitive genetic testing.

Genetic Counseling

Genetic counseling is a vital part of the genetic testing process for a number of reasons: to obtain a comprehensive family history, to select the most appropriate test(s), to obtain informed consent, to explain results to the patient and family, and to help the patient deal with the emotional and medical implications of learning their genetic results.[33, 34] Many specialty and primary care providers refer patients for a formal genetic evaluation. However, laboratories are making it possible for physicians to collect the biospecimen from the patient and order tests directly in the office setting. The practice results in tests being ordered without prior genetic counseling. When this occurs, primary care and oncology nurses must provide genetic information to patients if no certified genetic counselor is available. When genetic tests are ordered without the patient undergoing genetic counseling, there is a risk that reimbursement for the test is declined by the patient's insurer.

Personal and Family History

Collecting a personal and family history involves open-ended and targeted questions about personal health and each family member, with consideration of affected and unaffected individuals of paternal and maternal lineage for three generations. Information should include type of cancer, approximate age at diagnosis, current age of the person, or age and year at death. It is useful to obtain information about type(s) of treatment, any germline genetic testing, and any environmental exposures that may have caused the cancer. Professional clinical judgment is often necessary to assess the validity of family health history that is self-reported by a patient or other family member. In some cases, a genetic counselor may try to obtain records or pathology results to corroborate the family history prior to ordering tests.

In addition to collecting a comprehensive family history, the counseling session includes a genetic risk assessment and determination of any appropriate genetic tests. The informed consent discussion includes implications for cancers in other organs as well as the impact on extended family members, regardless of the result. When the primary care team is not comfortable or skilled with this level of detail, a genetic counseling referral will allow for comprehensive care of the patient.

Criteria for *BRCA* Testing

The current USPSTF guidelines state that the target population for BRCA testing includes "high risk individuals who have a personal or family history of breast or ovarian cancers at a young age (under 50 years), that suggests inherited cancer susceptibility, when an individual has access to a health professional who is trained to provide genetic counseling and interpret test results, and when test results will aid in decision making".[32] Recommendations vary, but the following criteria are generally considered when evaluating patients for genetic testing: 1) breast, colorectal, or endometrial cancer diagnosed before age 50, 2) bilateral breast cancer, 3) two primary breast cancers or clustering of breast and ovarian cancer, 4) multiple cancers at a young age, 5) rare cancer(s) presentation at any age, 6) two or more primary types of BRCA1- or BRCA2-related cancers in a single family member, or 7) family history of male breast cancer.

Ethnicity is also a factor, as the prevalence of BRCA1/2 mutations varies significantly across racial and ethnic groups.[35, 36] Persons of Ashkenazi Jewish ancestry have a ten-fold higher prevalence of deleterious BRCA1 and BRCA2 mutations than the general population. There are tests specifically designed to detect the three "founder" mutations characteristic of the Ashkenazi Jewish population. The 2012 update of the American Society of Clinical Oncology (ASCO) Breast Cancer Surveillance Guideline included Ashkenazi Jewish heritage in the list of the criteria for genetic counseling.[37] The 2014 NCCN guidelines specify that "for an ethnicity associated with higher mutation frequency (e.g. Ashkenazi Jewish), no additional family history may be required" for the HBOC syndrome testing.[9]

The USPSTF specifically recommends against routine genetic counseling or BRCA testing for women whose family history is not associated with an increased risk for BRCA1 or BRCA2 mutations. A recent editorial called for screening for cancer-causing genetic mutations in all American women 30 years of age or older, regardless of their race or ethnic background.[38] Many specialists in the field oppose this view, pointing to the complex relationship between the BRCA genes and cancer incidence, legal and privacy issues involved in creating a national database of mutations, and the cost and even potential harm of these tests, including psychological effects of a positive diagnosis with limited preventive options.

Risk Assessment and Preventive Strategies

Genetic testing is a component of risk assessment used to prevent breast cancer and to guide treatment decisions for newly diagnosed patients. A test result can be negative (no genetic abnormality detected), positive (a genetic abnormality was detected which is known to increase cancer risk), or a variant of uncertain significance (VUS). The latter means that a genetic change (variant) was identified, but it is unknown whether this variant may alter the individual's risk of cancer.

When BRCA testing is used for risk assessment in asymptomatic individuals, those who test positive for a risk-increasing mutation may consider several preventive strategies.[39] The most common strategy is increased surveillance, which includes breast MRI, annual

mammography and semiannual clinical breast exam. Other risk-reducing measures include chemoprevention with selective estrogen receptor modulators (SERMs) or aromatase inhibitors[40–42] and prophylactic breast and/or ovarian surgery. Preventive surgical interventions can reduce breast cancer incidence more effectively than chemoprevention or surveillance.[43] Surgical interventions include bilateral total mastectomy, which reduces the risk of breast cancer in high-risk women by 90%. Bilateral oophorectomy may also reduce the risk of breast cancer in *BRCA2* carriers by 72%.[44] Breast cancers in *BRCA2* carriers are more likely to be estrogen receptor positive and the surgery eliminates the body's main source of estrogen.

In newly diagnosed patients, BRCA testing is used to guide treatment decisions as breast cancers associated with BRCA mutations have poorer prognoses, increased incidence of recurrent disease, and *BRCA1* mutations are associated with a higher risk for triple negative breast cancer. BRCA carriers who have ovarian cancer may respond well to particular chemotherapies. If genetic testing is indicated, it should occur early in the cancer trajectory as patients who carry a mutation may receive more aggressive treatment.

Conclusion

Genetic testing will be increasingly important in the prevention, diagnosis, and treatment of breast cancer. The incorporation of multi-gene panels into clinical practice allows a growing number of genes to be routinely tested for cancer-related mutations. Oncology nurses will be expected to understand the risk factors, significance of various genetic tests, results, and related patient education. APNs need to know how to conduct a thorough family history to determine the appropriateness of a genetic counseling referral and, in some cases, may be required to explain and order genetic tests. Nurses and APNs in both primary care and oncology settings will be required to understand the impact of gene mutations on the cancer trajectory.

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Table 1

Selected genetic tests for germline mutations related to breast cancer

Target Population	Test/Company	Gene(s)/Mutations	Biological Material/Technology	Ref
High-risk individuals (family history suggestive of hereditary breast and ovarian cancer)	Comprehensive BRAC*Analysis* (Myriad Genetics)	*BRCA1* *BRCA2*	Blood or oral rinse DNA sequencing	10–14
	BRAC*Analysis* Large Rearrangement Test (BART) (Myriad Genetics)	Large genomic rearrangements in both *BRCA1* and *BRCA2*.	Blood or oral rinse DNA rearrangement by quantitative PCR	15–18
	myRisk (Myriad Genetics)	Multiple (25 genes, including *BRCA1, BRCA2, and PALB2)* Gene panel related to a broad number of hereditary cancer syndromes	Blood DNA sequencing	10, 12, 19
	BRCA1/2 (Ambry Genetics)	*BRCA1* *BRCA2*	Blood or saliva DNA Sequencing and deletion/duplication analysis	10
	BRCAplus (Ambry Genetics)	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53*	Blood or saliva DNA sequencing	2, 6, 10, 20
	BreastNext (Ambry Genetics)	Multiple (17 breast cancer-related genes, including *BRCA1* and *BRCA2*)	Blood or saliva Full gene sequencing and deletion/duplication analysis	21
	CancerNext (Ambry Genetics)	Multiple (28 cancer-related genes including *BRCA1* and *BRCA2*)	Blood or saliva Full gene sequencing and deletion/duplication analysis	21
	BRCA1 and BRCA2 Del/Dup (Gene Dx)	*BRCA1* *BRCA2*	Blood or oral rinse Exon Array CGH (screening for copy-number changes)	10–14
	BRCA1 and BRCA2 Sequencing (Gene Dx)	*BRCA1* *BRCA2*	Blood or oral rinse Next-generation sequencing	10–14
	OncoGeneDx Custom Panel (Gene Dx)	Multiple (28 cancer-related genes including *BRCA1* and *BRCA2*)	Blood or oral rinse Exon Array CGH and next-generation sequencing	21
	Breast/Ovarian Cancer Panel (Gene Dx)	Multiple (21 cancer-related genes including *BRCA1* and *BRCA2*)	Blood or oral rinse Exon Array CGH and next-generation sequencing	21
	BRCAvantage, Comprehensive (Quest Diagnostics)	*BRCA1* *BRCA2*	Blood NGS and MLPA	10–14
	BRCAvantage, Rearrangements (Quest Diagnostics)	Deletions and duplications in *BRCA1* and *BRCA2*	Blood MLPA	15–18
	BRCAvantage Plus (Quest Diagnostics)	*BRCA1* *BRCA2* *TP53* *PTEN* *CDH1* *STK11* *PALB2*	Blood NGS and MLPA	2, 6, 10, 20
Individuals at risk for hereditary pancreatic cancer	PANEXIA (Myriad Genetics)	*BRCA2* *PALB2*	Blood DNA sequencing	10, 12, 19

Target Population	Test/Company	Gene(s)/Mutations	Biological Material/Technology	Ref
(test also identifies breast cancer risk)				
High-risk individuals with breast cancer (family history suggestive of one of the hereditary cancer syndromes)	Breast Cancer High Risk Panel (Gene Dx)	*BRCA1* *BRCA2* *CDH1* *PTEN* *STK11* *TP53*	Blood or oral rinse Exon Array CGH and next-generation sequencing	2, 6, 10, 20
High-risk individuals (family history suggestive of one of the hereditary cancer syndromes)	OncoGeneDx High/Moderate Risk Panel (Gene Dx)	Multiple (20 cancer-related genes including *BRCA1* and *BRCA2*)	Blood or oral rinse Exon Array CGH and next-generation sequencing	21
	Comprehensive Cancer Panel (Gene Dx)	Multiple (29 cancer-related genes including *BRCA1* and *BRCA2*)		
Individuals with family members with an identified mutation in *BRCA1* or *BRCA2*	Single Site BRAC*Analysis* (Myriad Genetics)	*BRCA1* or *BRCA2* A single mutation previously identified in another family member	Blood or oral rinse DNA sequencing	10, 22
	BRCAvantage™, Single Site (Quest Diagnostics)		Blood NGS and MLPA	
Ashkenazi Jewish descent	Multisite 3 BRAC*Analysis* (Myriad Genetics)	187delAG *BRCA1* 5385insC *BRCA1* 6174delT *BRCA2*	Blood or oral rinse DNA sequencing	23–28
	BRCA Ashkenazi Jewish 3-site Mutation panel (Ambry Genetics)		Blood or saliva DNA Sequencing	
	BRCA1/2 Ashkenazi Founder Mutation Panel (Gene Dx)		Blood or oral rinse Capillary Sequencing	
	BRCAvantage, Ashkenazi Jewish Screen (Quest Diagnostics)		Blood Fluorescent PCR	

Manufacturers listed:

Myriad Genetics, Salt Lake City, UT

Ambry Genetics, Aliso Viejo, CA

Gene Dx, Gaithersburg, MD

Quest Diagnostics, Madison, NJ

Abbreviations: CGH, comparative genome hybridization; NGS, Next-generation sequencing; MLPA, Multiplex ligand-dependent probe amplification, PCR, Polymerase Chain Reaction

Table 2

Genetic disorders related to increased breast cancer risk

Syndrome	Gene(s)	Malignancies	Ref
HBOC	*BRCA1* *BRCA2*	Breast (female and male), fallopian tube, ovarian, peritoneal, prostate, pancreatic	3
Li Fraumeni syndrome	*TP53*	Adrenal, breast, colon, glioma, leukemia, lymphoma, neurofibrosarcoma, osteosarcoma	3
Cowden syndrome	*PTEN*	Breast, endometrial, non-medullary thyroid, kidney, colorectal	3
Ataxia telangiectasia	*ATM*	Breast, endometrium, gastric, glioma, skin	3
Peutz–Jeghers Syndrome	*STK11*	Colorectal, gastric, pancreatic, breast, ovarian	3
Neurofibromatosis 1	*NF1*	Peripheral nerve sheath tumor, astrocytoma (optic nerve), high-grade astrocytomas, glioma, pheochromocytoma, possibly breast	29
Bloom syndrome	*BLM*	Breast, colon, cervix, esophagus, larynx, lymphoma	30