The genesis and evolution of genetic testing technologies and their application in preventive medicine have changed the face of oncology. Despite the fact that only approximately 5 percent of all cancers are strongly hereditary, inherited cancer susceptibility can be significant to individual patients and their immediate families. While some degree of heredity may exist in the development of all types of cancer, breast cancer features a relatively pronounced element of inherited susceptibility for which genetic testing has been advanced in recent years. Specifically, inherited mutations in certain breast cancer susceptibility genes account for an estimated 5 to 10 percent of all female breast cancers and anywhere from 4 to 40 percent of all male breast cancers. As such, reputable cancer centers across the country have implemented genetic testing programs and even dedicated entire departments to the application of gene analysis in the discipline of oncology. The accuracy of the testing employed in these centers can be characterized via the concepts of analytical validity and clinical validity, which — when coupled with individual disease-specific scenarios — lend themselves to determining the clinical utility of genetic analyses for a particular patient. ManagedCare Oncology recently sat down with Nicoleta Voian, M.D., M.P.H., assistant professor of oncology and director, Clinical Genetics Service, Department of Medicine, Roswell Park Cancer Institute, to gain her insights on the application of genetic testing in managed care oncology and specifically in the early detection and treatment of breast cancer.

A Discussion with Nicoleta Voian, M.D., M.P.H.
Assistant professor of oncology and director, Clinical Genetics Service, Department of Medicine, Roswell Park Cancer Institute

MCO: Can you please describe the various roles of genetic testing in contemporary oncology practice?

Dr. Voian: Clinical cancer genetics is a critical component of modern oncology and preventive medicine. There are three distinct categories of molecular genetic testing in oncology: germline genetic testing, somatic genetic testing and pharmacogenetic testing. Germline genetic testing for cancer susceptibility assesses patients for an inherited gene mutation in order to determine the risk for cancer in an individual. Genetic counseling is strongly recommended before and after these tests, which are sent to specialized laboratories for analysis. The key goal of germline analyses is to offer appropriate genetic tests for appropriate patients in order to prevent and/or detect cancer early. The somatic genetic tests that oncologists use in collaboration with pathologists look for mutations in the cancer tumor that were acquired in order
to estimate an individual’s response to therapy as a prognostic measure. Pharmacogenetic testing, on germline as well as somatic mutations, enables oncologists to identify patients at risk for severe treatment toxicity or poor treatment response.

**MCO:** How does genetic testing impact the quality of care and the cost of managing the cancer patient?

**Dr. Voian:** Identifying individuals who carry a gene mutation that confers a significantly increased risk for cancer is important because preventive and/or early detection options can then be provided to these individuals, potentially helping them avoid costly treatment. Also, in families where there is a known familial gene mutation, other family members are at risk for carrying the same mutation and will benefit from the preventive/early detection measures. Conversely, identifying family members who do not carry that mutation will eliminate unnecessary costs associated with enhanced screening.

**MCO:** How does genetic testing fit into oncology care today?

**Dr. Voian:** Approximately 5 to 10 percent of all cancers occur due to an inherited susceptibility resulting directly from gene mutations. These mutations, usually inherited from a parent, confer a high risk of multiple primary cancers occurring at younger ages, and we typically see multiple family members who inherit the cancer-predisposing mutation. Early identification of hereditary cancer syndromes benefits patients through a growing number of preventive care options available to patients and blood relatives. The most common hereditary cancer syndromes known are in breast, ovarian and colorectal cancers.

Awareness regarding inherited susceptibility syndromes has been increasing over the past few years. Identifying and referring the appropriate patients diagnosed with breast cancer soon after their diagnosis for genetic counseling and testing is very important. If a patient is identified as having a gene mutation associated with an increased risk for a second breast cancer and/or other cancers, it will empower that individual with the information needed to make the appropriate treatment decisions, such as the type of breast and/or ovarian surgery necessary.

**MCO:** Can you describe the key opportunities and challenges in managing oncology genetic testing?

**Dr. Voian:** Genetic testing introduces the concept of personalized hereditary cancer risk assessment, which offers crucial information to help make medical management decisions to reduce cancer risk. This information is important to the patient and his or her family members and often reduces the anxiety and stress associated with hereditary cancer susceptibility — a negative result from testing is welcome news when there is a known mutation in the family. Conversely, testing may introduce anxiety in individuals identified as carrying a gene mutation. Also, the sensitivity of genetic testing is not 100 percent; therefore, some undetected mutations may exist, and testing does not detect all causes of hereditary cancer.

Furthermore, genetic testing for inherited cancer susceptibility syndromes is complex. There are different methods to assess for a gene mutation, including sequencing and looking for deletions or duplications. We need to carefully offer the most complete test available for a specific case. Because there are multiple cancer syndromes that increase the risk for cancer — such as hereditary cancer syndromes associated with an increased risk for breast cancer, ovarian cancer, colon cancer, etc. — it is important to establish which syndrome is the most robust in the differential. Sometimes we have several inherited cancer syndromes in the differential and we can use a next-generation sequencing panel that will assess for multiple genes in one test. In other cases, the most appropriate person to be tested first is...
family suggestive for an inherited cancer predisposition is not available for testing. In these situations, testing of at-risk, unaffected family members will encounter limitations. There is a need to very carefully assess the family pedigree on both sides, as there are cases, although rare, where individuals can inherit a gene mutation from each parent. We also encounter challenges when we need to recommend further medical management in individuals who tested negative for the genetic tests offered but still have an increased risk for cancer based on their family history or clinical findings.

**MCO:** Can you describe the key challenges and opportunities in managing oncology genetic testing specifically in the area of breast cancer?

**Dr. Voian:** As mentioned previously, there are situations when we have multiple inherited cancer syndromes associated with an increased risk for breast cancer in the differential. There are breast cancer panels that allow for testing of multiple genes in one sample. BRCA1 and BRCA2 were not historically included in those panels because one laboratory had the patent on those specific genes, but the Supreme Court ruled on June 13, 2013, that human genes cannot be patented.3 This recent development opens up the potential for more comprehensive and inclusive breast cancer panels and decreased costs for BRCA-related analyses. Still, for BRCA1 and BRCA2, there are different tests that are offered, and the most appropriate is selected on a case-by-case basis. This is often based on ethnicity, such as the Ashkenazi Jewish panel, or if there is a previously identified gene mutation or family history of breast cancer. The complete BRCA test includes full sequencing and testing for large genomic rearrangements in both BRCA1 and BRCA2 genes, which will likely now be available from a number of different laboratories after the Supreme Court’s ruling.

**MCO:** When is a patient referred for genetic testing? What is the process that you undertake to determine if a patient qualifies for genetic testing?

**Dr. Voian:** There are two types of patients that we see in the genetics clinic: affected patients and unaffected patients. Affected patients have cancer or a history of cancer, while unaffected patients have only a family history of cancer. For a patient who is affected with cancer, discussion with the breast surgeon, medical oncologist and/or radiation therapist will determine the impact of genetic testing on a patient’s medical care.

The National Comprehensive Cancer Network has established criteria for genetic testing eligibility for both groups, and several other professional organizations, such as the American Society of Breast Surgeons and the American Society of Clinical Oncology, also provide specific guidelines and recommendations to providers for identification of individuals at increased risk for hereditary cancer syndromes.4 Common characteristics of these patients include an early onset of cancer, a rare cancer such as male breast cancer or ovarian cancer, a known familial mutation, family members with multiple primary cancers, two or more relatives with the same type of cancer on the same side of the family, ethnicity, or pathologic findings for certain types of cancers, such as triple negative breast cancer before age 60.5 Ultimately, the most vital piece of information to help determine whether genetic testing is warranted is the potential clinical utility derived from testing and the benefits for family members with regard to their cancer risk.

**MCO:** What are the steps you have to consider when you see a patient who appears to qualify for genetic testing?

**Dr. Voian:** During genetic counseling, we perform a thorough evaluation. The individual’s personal and family medical histories are reviewed, with a focus on the cancer history and benign findings that can be associated with inherited cancer predisposition. We review the medical records of the patient and family members if possible, as well as the results of previous genetic tests when applicable. A physical evaluation may also be needed in some cases.

Based on the findings of this workup, we establish whether genetic testing is appropriate and what specific tests should be used in those patients deemed appropriate candidates. Before any genetic test is performed, the informed consent form needs to be signed by the patients to confirm that they acknowledge the test being performed in addition to the benefits, risks and limitations of the test. They’re also informed about state and federal genetic privacy laws that protect the majority of individuals from discrimination with regard to group health insurance and employment.

**MCO:** How do insurance regulations play into the process of genetic testing?

**Dr. Voian:** Although payors are generally cognizant of the validity of genetic consultation and testing and relatively liberal in their related coverage policies, these services may or may not be covered by insurance. By and large, the coverage is approached on an individual case-by-case basis, meaning that many health plans routinely cover genetic counseling and testing if the test is deemed appropriate. If the genetic test is not covered, patients often choose to forgo testing due to the high out-of-pocket costs.
MCO: Do you ever recommend testing as a private pay service to a patient if the test is not covered by insurance? If family history is not known, would you recommend testing?

Dr. Voian: The recommendation of a genetic test is based on its clinical utility and the impact on cancer risk assessment for family members, not on the reimbursement. If the testing is performed primarily for the medical management of other family members, the patient is informed about the out-of-pocket expense and given the option to pay if desired. If the family history is unknown, we base our risk assessment on personal history of cancer, such as the type of cancer and age at diagnosis.

MCO: Do you have to get the testing approved by the payor before administering the test?

Dr. Voian: Many genetic laboratories will hold the sample until insurance authorization is obtained and the patient agrees with any out-of-pocket expenses that may accompany the test, after which the analysis is initiated.

MCO: Are the analyses expensive?

Dr. Voian: Genetic testing is often considered expensive, with costs ranging anywhere from a few hundred to a few thousand dollars, depending on the genes tested and the method of analysis. A patient's characteristics may warrant only a single site test for a familial mutation or a full genetic panel.

MCO: What are the specific types of genetic testing for breast cancer? Ovarian cancer?

Dr. Voian: The most common gene mutations associated with breast cancer are BRCA1 and BRCA2, which are associated with hereditary breast-ovarian cancer (HBOC) syndrome. Rarer gene mutations include TP53 associated with Li–Fraumeni syndrome, PTEN associated with Cowden syndrome, CDH1 associated with hereditary diffuse gastric cancer and STK11 associated with Peutz–Jeghers syndrome.

For ovarian cancer, the most commonly associated hereditary syndrome is HBOC and Lynch syndrome associated with mutations in the MLH1, MSH2, MSH6, PMS2 and EPCAM genes.

MCO: What does the BRCA mutation entail for both men and women?

Dr. Voian: For breast cancer, the inherited risk associated with a BRCA1 and BRCA2 mutation in females is 45 to 84 percent, compared with an approximate 12 percent risk in the general population.5-7 Women who have already had breast cancer have an increased risk for a new primary contralateral breast cancer, up to a 64 percent risk in their lifetime.6 For ovarian cancer, the inherited risk is anywhere from 11 to 62 percent with the BRCA mutation, compared with approximately 2 percent in the general population.5-9 For male breast cancer, the inherited risk associated with a BRCA2 mutation is up to 8 percent, compared with a less than 1 percent risk in the general population.10-11
The risk of prostate cancer is less pronounced with an inherited BRCA2 mutation at 20 percent, compared with 16 percent in the general population. In some families, an increased incidence of melanoma and/or pancreatic cancer may exist with an inherited BRCA mutation.

**MCO:** Describe the results of genetic testing. How do the results influence further care?

**Dr. Voian:** A positive result confirms the hereditary cancer susceptibility syndrome and the predisposition for cancer associated with a specific gene. The medical management recommendations follow the established guidelines, and the options include surveillance, chemoprevention and risk-reducing surgeries. Other family members can carry the same mutation; therefore, genetic counseling with or without genetic testing is recommended.

In the event of a negative result, if there is a known mutation in the family, then the individual does not have the risks associated with that mutation and will follow the screening recommendations for the general population. For a negative result with no known mutation in the family, the result is considered uninformative. Sometimes additional genetic testing is indicated in these cases. If, after all genetic testing, the individual is still negative for a detectable mutation, the medical management recommendations are based on personal and family history of cancer and clinical symptoms. A patient may also have a variant of uncertain significance, which is when there is a change in the gene identified, but it is unknown whether that change is harmful or benign. In this latter scenario, the medical management is again based on personal and family history of cancer and clinical symptoms.

**MCO:** How do you typically present the genetic testing results to the patient?

**Dr. Voian:** We schedule an in-person follow-up consultation to disclose and discuss the genetic test results and the impact of those results on their medical management, in addition to consultation with family members tailored to each case.

**MCO:** How are genetic tests regulated?

**Dr. Voian:** All laboratories that do genetic testing and share results must be Clinical Laboratory Improvement Amendments (CLIA)–certified. CLIA certification provides federal standards for quality, accuracy and reliability of tests. The clinical validity for some genetic tests is required by the U.S. Food and Drug Administration. New York requires that genetic tests be performed in laboratories that hold a state permit for its residents. The clinical utility is determined by the health care providers and health insurance companies.²

**MCO:** Is there research being done to improve genetic testing for cancer?

**Dr. Voian:** Yes, there is ongoing research to identify gene mutations in rare genes or new genes that are associated with an increased risk for cancer. For example, familial breast cancer research is being performed by Dr. Mary-Claire King at the University of Washington in Seattle, and at the Cleveland Clinic. Dr. Charis Eng is looking for mutations in the PTEN gene and at new genes associated with Cowden syndrome.

**MCO:** Overall, do you think genetic testing and counseling is saving lives?

**Dr. Voian:** Absolutely. Identifying individuals who carry a gene mutation that predisposes them for a significant increased risk for cancer will offer options to prevent and detect cancer at an earlier stage. Risk-reducing surgeries such as mastectomy for breast cancer, salpingo-oophorectomy for ovarian cancer and colectomy for colorectal cancer are ultimately lifesaving procedures.

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**References**