Molecular Genetics

in the Community Setting
Positioning your cancer program for success

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Molecular testing is a broad term that in the clinical setting describes any diagnostic test involving analysis of DNA or RNA. Molecular tests can be broadly divided into four major categories of use:[1]

1. Diagnosis and management of classical genetic disorders
2. Prediction of susceptibility to common complex diseases
3. Modulation of drug therapy (pharmacogenomics)
4. Development of prognostic indicators and targeted therapies for cancer (and other diseases).

In the oncology setting, molecular testing is routinely used in categories 1 and 4—identifying patients and families at increased risk of cancer due to hereditary factors and identifying specific molecular markers within tumors to make decisions about treatment. In this article, we outline current and future uses of molecular testing in oncology care, and the role genetic counselors can play in incorporating these tests into care in the community setting.

The number of molecular tests available for clinical use has exploded over the past 10 years. UnitedHealth Center for Health Reform and Modernization recently published a working paper reporting that nearly $500 million was spent in 2010 on genetic and molecular diagnostic testing for UnitedHealthcare (UHC) members alone, with 16 percent of this (roughly $80 million) spent on cancer-related testing.[2] Combined with data from Medicare and Medicaid, UHC further estimates that $5 billion was spent on molecular tests nationwide and growth trajectories estimate that this number could rise as high as $15 to $25 billion by 2021.[2]

Increased use of molecular testing is likely to contribute to increased overall healthcare spending, but *appropriate* use of testing could also improve health outcomes, including outcomes in the oncology setting, which could have an opposite effect on healthcare costs.

Molecular Testing & Cancer Treatment

The National Cancer Institute defines cancer as "a term used for diseases in which abnormal cells divide without control and are able to invade other tissues." The abnormal behaviors of cancer cells result from changes (or mutations) in genes that control the processes of cell division, growth, and death. These mutations are usually not inherited, but can occur as a result of environmental insult (e.g., UV light) or randomly during the normal process of copying DNA before cell division (see Figure 1, page 28).

Historically, most standard chemotherapeutic agents worked by killing rapidly dividing cells, including not only cancer cells but also healthy cells that divide rapidly under normal circumstances—in the hair follicles, bone marrow, and the lining of the digestive tract for example. Indiscriminate killing of rapidly dividing cells leads to side effects, including hair loss, decreased blood cell counts, and GI symptoms. The goal of

Figure 1. Loss of Normal Growth Control

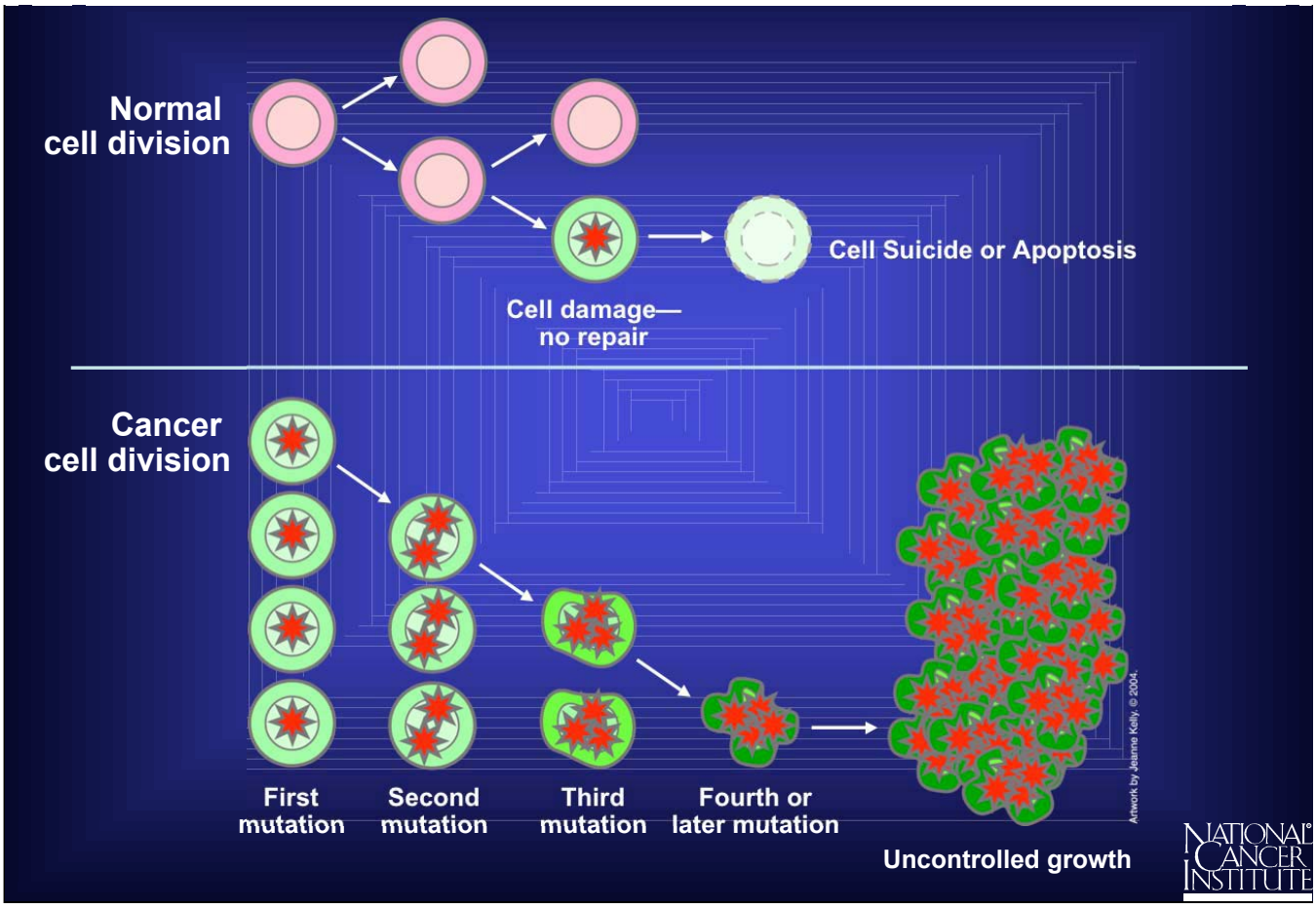


Figure 1. Accumulated mutations lead to uncontrolled growth and invasion. Molecular testing can be used to identify the mutations in cancer cells, with the goal of targeting specific therapies to treat cancers with different types of mutations. Source: National Cancer Institute, *www.cancer.gov.*

molecular testing is to identify specific behaviors of cancer cells and underlying genetic changes that are *not present* in most normal cells. Therapies can then be chosen that *target* the genetic changes and unique behaviors of cancer cells with the hope of increasing efficacy and decreasing side effects, a strategy often referred to as "personalized" care.

There are several well-established examples of genetic aberrations identifiable through molecular testing that are already used to guide treatment decisions, and a growing number of targeted therapies that are FDA approved and in clinical trials.[3] Large research consortia, including The Cancer Genome Atlas[4] and the Cancer Genome Project,[5] are working on sequencing cancer genomes for many different types of cancer to better characterize and catalog all genetic mutations in order to improve our understanding of how and why tumors behave as they do. There is hope that this research could also lead to strategies for earlier detection and even cancer prevention. As a result of this work with cancer genomes, the number of targets and related therapies is likely to expand dramatically over time.

Molecular Testing & Hereditary Risk

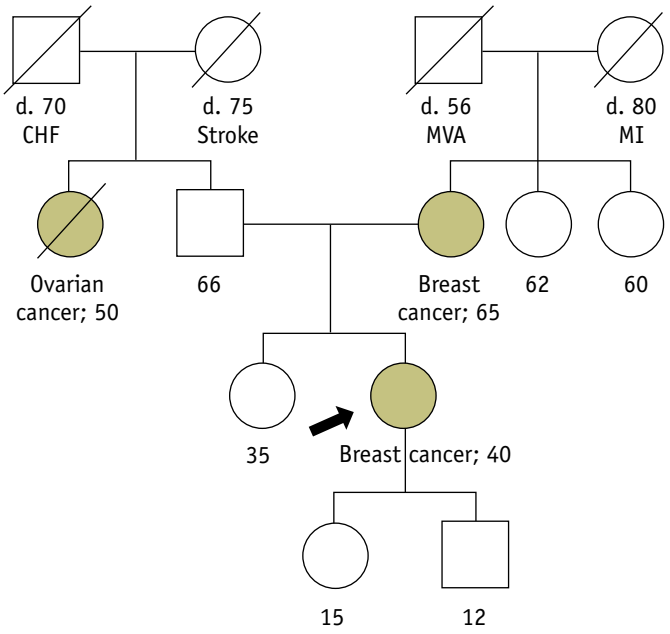
Through July 2012, the Cancer Genome Project had reported 488 genes important in cancer development and progression.[5] Of these, 90 percent have an impact when a mutation occurs in cancer cells, and 20 percent are important in causing hereditary risk (10 percent have a role at both levels).[6] Thus, in the oncology setting, molecular testing has an important role in identifying patients and families at risk for hereditary cancer susceptibility.

Testing for mutations in the *BRCA1* and *BRCA2* genes has been clinically available since 1996, and is considered to be standard of care for women diagnosed with breast cancer under age 45, women with triple negative (ER-, PR-, HER2-) breast cancers under age 60, and women with family history of breast and/or ovarian cancer.[7] Similarly, 2 to 4 percent of all colon cancer diagnoses are caused by Lynch syndrome, and identification of these patients and families through molecular testing is critical to their care.[8]

Advances in Molecular Testing

Until recently, molecular testing typically involved selecting one or a few very specific tests for specific patients based on

Figure 2. Impact of Molecular Testing on Cancer Care



SQUARES: Denote male family members
CIRCLES: Denote female family members
CHF: Congestive heart failure
MVA: Motor vehicle accident
MI: Myocardial infarction

In this example, patient presents with breast cancer at age 40.

Molecular testing initiated at diagnosis:
- Analysis of ER/PR/HER2-Neu status
- If ER positive: gene signature panel for recurrence risk and chemotherapy decision
- Referral to genetics for *BRCA1/BRCA2* gene testing

Genetic Counseling Issues

Before additional testing ordered:
- Interpretation of molecular testing thus far
- Timing of testing: to be used for surgical decisions or better to wait until patient has had time to deal emotionally with diagnosis?
- Screening recommendations for at-risk family members with or without genetic test results as they are likely to still have moderately increased risk.

After test results are available:
- If *BRCA* mutation positive, discussion of prophylactic bilateral salpingo-oophorectomy
- Implications for family:
  - Not entirely clear which side of the family a *BRCA* mutation came from. Test parents.
  - Patient worried about daughter, but typically not necessary to test minors for *BRCA* mutation
  - Educate about cancer risks for males
- If no mutation identified, provide risk assessment based on family history.

clinical criteria. For example, testing for *BRCA1/BRCA2* mutations in a woman diagnosed with breast cancer at age 35 and with a family history of breast cancer, or testing for *EGFR* mutations in metastatic non-small cell lung cancer (NSCLC) for treatment planning. With the rapid advances in next generation sequencing technology, it is becoming technically easier and less expensive to order panels of molecular tests that include multiple genes.

Existing clinically available tumor panels can test for up to 739 specific mutations in 46 different cancer genes with potential to impact treatment decisions. Next-generation panels for hereditary risk are also available, and currently existing panels offer testing for mutations in up to 23 different genes implicated in cancer risk on a single blood sample. While there are clear advantages to this type of testing, it also leads to more possibilities for unexpected results or findings that may be difficult to interpret.[9] For example, you may find a mutation in an unexpected tumor type where there is not yet data to support a related treatment, or you may find a mutation for hereditary risk in a family that does not have any suggestive history. With this in mind, tests should be ordered in a responsible manner and with careful attention to impact on patient care. Further, tests should be clinically validated, warranted for the specific patient, and interpreted properly.

UHC surveyed 1,254 physicians of varying backgrounds and specialties in early 2012 and found that almost 75 percent of them responded that they have patients in their practices that have not had genetic testing, but who would benefit from doing so. UHC also found that the most frequently ordered tests are oncology-related (64 percent) but that only 28 percent of physicians surveyed felt comfortable interpreting results of oncology tests.[2] Given the rapid changes in genomic medicine, providers will be challenged to build and maintain satisfactory genetics knowledge when other aspects of oncology diagnosis and treatment are also constantly evolving. In 2011 a perspective piece in *Nature* suggested that "all healthcare providers must acquire competency in genomics to provide services appropriate for the scope of practice."[10]

Many professional organizations have convened special interest groups and developed educational materials for the purpose of filling genetics and genomics knowledge gaps for their members. Community cancer centers can help clinicians remain up-to-date by providing genetics-focused CME events. With the help of genetics specialists, programs can focus on topics that are of broad interest to staff and have the potential to alter clinical care in a positive way. Inclusion of genetic counselors in multidisciplinary care teams can also help to meet this need, given their special expertise in understanding implications of genetic testing and in conveying these ideas to patients.

The Genetic Counselor Role in Multidisciplinary Cancer Programs

Most community cancer centers now provide multidisciplinary care in oncology. Some institutions have implemented truly multidisciplinary clinics in which patients meet with multiple providers at one visit to learn of their treatment options in detail. Multidisciplinary tumor boards and case conferences are also frequently used to collaboratively care for patients. Typically, these care teams consist of surgeons, medical oncologists, radiation oncologists, pathologists, nurses, and other practitioners depending on institutional resources.[11] In recent years, however, it has become important to include genetics specialists on these teams as well, as reflected in ACCC's *Cancer Program Guidelines*.[12] This staff could include genetic counselors (practitioners that have specialized graduate degrees and experience in the areas of medical genetics and counseling), medical geneticists, and/or nurses with specialized training.

Because molecular testing and genetic risk assessment can impact surgical and treatment decisions, the gathering of family history and discussions about molecular testing are often initiated at, or shortly after, the time of cancer diagnosis. Outcomes of these tests may impact the work of other team members. For example, a 40-year-old woman with a newly-diagnosed breast cancer may opt to undergo testing for mutations in the *BRCA1* and *BRCA2* genes prior to determining the extent of her surgical treatment (lumpectomy vs. mastectomy +/- contralateral prophylactic mastectomy). This same patient may also benefit from molecular profiling of her tumor to determine her recurrence risk prior to considering chemotherapeutic options (see Figure 2, page 29). Genetic counselors and other genetics specialists may lend expertise and aid in conveying these often complicated options to patients, including the differences between molecular testing for hereditary risk and molecular testing of a tumor for treatment information (see Figure 3, below).

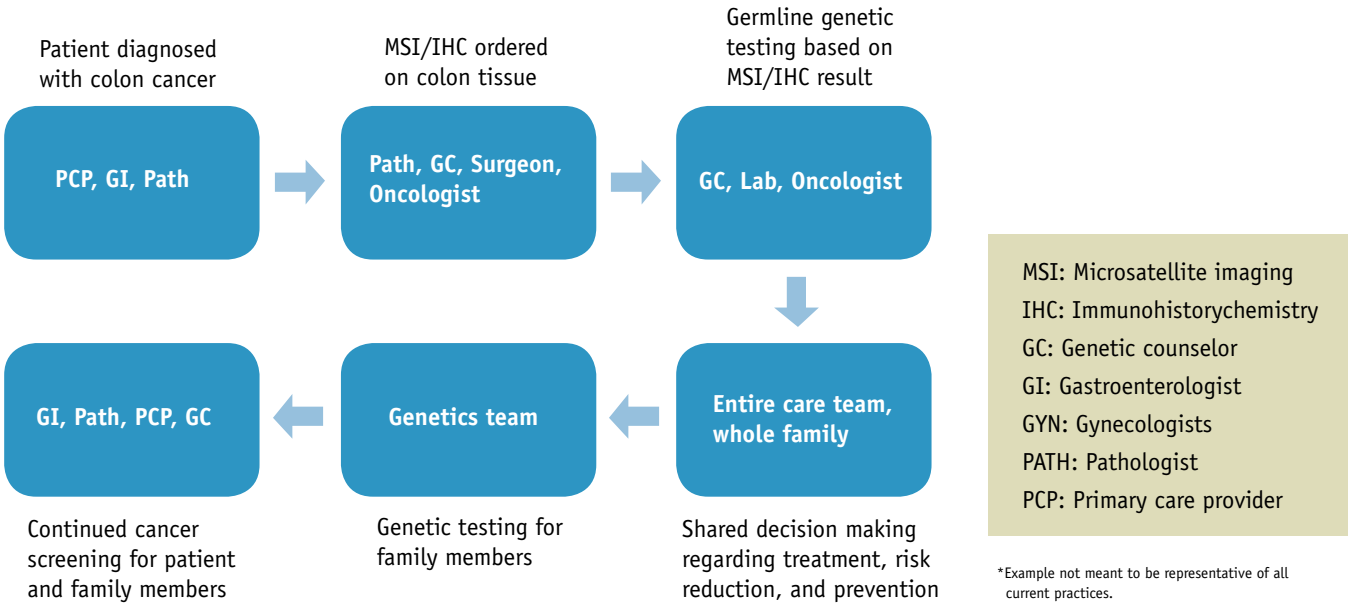
Recognizing the importance and impact of genetic testing in clinical care, some accreditation bodies, including the American College of Surgeons Commission on Cancer (CoC) and the National Accreditation Program for Breast Centers (NAPBC), have included the provision of genetic risk assessment in their most recent standards.[13,14] Many professional organizations, including the American Society of Clinical Oncology[15] and the Society of Gynecologic Oncologists[16], have position statements regarding cancer genetic testing that specifically state that testing should be performed in the context of genetic counseling.

Structuring Genetic Counseling Services

Over the years with increasing demands on institutional resources and more widespread use of molecular testing, several models of genetic service delivery have emerged in oncology. The Service Delivery Model Task Force of the National Society of Genetic Counselors recently summarized four commonly-used genetic counseling clinical models:[17]

- ***In-person genetic counseling.*** A traditional model where patients present in-person for genetic counseling.
- ***Telephone genetic counseling.*** Genetic counseling that is delivered by telephone.

Figure 3. Simplified Example of Multidisciplinary Involvement in Colon Cancer Case*



*Example not meant to be representative of all current practices.

- ***Group genetic counseling.*** When multiple individuals present for genetic counseling at one time.
- ***Telegenetics.*** Web-based and telemedicine where genetic counseling is provided remotely.

In many instances, a cancer center may choose to employ a combination of these services to best meet the growing needs of their patients. Cancer genetic services are most commonly provided by a dedicated genetic counselor or other specialist directly employed by the institution. When this model is not possible, however, an institution may consider options for contracting with a genetic counselor to provide telephone counseling or counseling via telegenetics, which uses video conferencing capabilities. Some genetic counselors provide contract work directly, while others provide services through institutional contract with their primary employer. In either model, the genetic counselor works as part of the comprehensive cancer care team and communicates directly with referring physicians to determine the appropriate personalized management plan for each patient.

There are several ways to bill for cancer genetic services and genetic counseling can be directly reimbursed using CPT code 96040. Typically, each institution determines the most appropriate model for its given situation, which could depend on institution-specific credentialing guidelines, types of providers and payers, and/or state licensing requirements. The National Society of Genetic Counselors has compiled information in this area, including electronic courses that broadly review some of the most common billing practices. These resources can be found online at *www.nsgc.org*.

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MORE FROM ACCC

Access additional resources from ACCC's "Molecular Testing in the Community Oncology Setting" education project at *www.accc-cancer.org/moleculartesting*. Read project key findings and the final report, including annotated bibliography and case studies. View the archived "Molecular Testing 101" webinar presented by Jessica Everett, MS, CGC, and Leigha Senter, MS, CGC, for this project.

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