ASSOCIATION OF CANCER CARE CENTERS

GERMLINE VS SOMATIC TESTING FOR CANCER: HEREDITARY CANCER SYNDROMES

BACKGROUND

Hereditary cancer syndromes, also known as inherited cancer syndrome or genetic cancer syndrome, describe gene changes that are passed down from parent to child and that may increase a person's risk of developing a disease. Referred to as variants by the genetics community or mutations by oncologists, these inherited genetic predispositions may cause some individuals to develop cancer, often at an early age.

Some examples of hereditary cancer syndromes include[1]:

- Hereditary breast and ovarian cancer syndrome (HBOC)
- Li–Fraumeni syndrome
- Lynch syndrome
- Multiple endocrine neoplasia types 1 and 2
- Peutz-Jeghers syndrome.

Clinical practice guidelines currently recommend that germline testing be offered to EVERY newly diagnosed patient with breast cancer (age <65), ovarian cancer, pancreatic cancer, or metastatic prostate cancer.[2] Guidelines also recommend germline testing for patients with many other cancers who meet criteria for screening and testing.

HEREDITARY (GERMLINE) TESTING: genetic testing that may reveal a hereditary cancer syndrome or may identify patients who may be eligible for certain types of targeted therapy.

BIOMARKER OR TUMOR (SOMATIC) TESTING: often performed using a multigene panel and/or other tests (eg, protein expression) to identify patients who may be eligible for targeted therapy and/or immunotherapy. Testing is usually performed on tumor tissue or blood.

Patients diagnosed with a suspected hereditary cancer should receive genetic testing to:

- Confirm if they have a hereditary cancer syndrome
- Guide treatment decisions
- Personalize when and how to screen for other types of high-risk cancers
- Inform family members about hereditary cancer risk and prevention strategies (ie, cascade genetic testing).

Germline variants also may be found in patients with cancer types for which germline testing is not routinely indicated. The results of a large database study found germline variants in 6.6% of bladder cancers and 5.8% of lung cancers.[3]

TIP

Differentiate Germline vs Somatic Genetic Testing

Hereditary genetic testing may also be called germline testing or genetic testing for an inherited variant. Hereditary genetic testing should not be confused with somatic (or tumor) genomic testing. Some terms, particularly those related to the testing method, may refer to either germline or somatic testing. Therefore, be sure to clarify whether the testing term is being used for germline or somatic testing or both diagnostic types.

- **Molecular testing, gene or genetic testing, gene sequencing:** these terms may refer to germline or somatic testing.
- **Next-generation sequencing (NGS):** NGS refers to a testing methodology that may be used for germline or somatic testing.

These distinctions can be confusing for healthcare professionals and are quite confusing for patients. Therefore, take the time to clearly explain the differences between the multiple genetic tests being ordered; these differences include the purpose, benefits, and limitations of testing. Patients must be informed about their care, especially if they decline testing because they mistakenly believe they already had genetic testing.

For example, a somatic genetic test report may indicate that a patient has a BRCA variant. Unless germline testing is also performed, it may not be possible to know if the variant was inherited. Some laboratories may perform paired somatic-germline testing (also called tumor-normal) to identify variants that are inherited vs those that are not. However, unless the paired testing is clinically validated to identify germline variants, hereditary cancer testing should be used to confirm suspected inherited variants.[4]

Some testing terminologies that may cause confusion include:

- **Variant:** The term refers to a change in the DNA sequence of a gene. This term is often used by genetic counselors. Germline variants are changes in DNA that are inherited at the time of conception and present in all cells. Somatic variants, on the other hand, are changes in DNA that occur after birth and are classified differently than germline variants.
- **Mutation:** Oncologists may prefer to use the term mutation rather than variant. The terms are not technically equivalent, but they are often used interchangeably in lay and professional literature.
- Other terms may be used to refer to specific changes in the DNA sequence of a gene, and some have very precise definitions that cannot be used interchangeably; these include *alteration, rearrangement, insertion, deletion, copy number changes, point mutation, and fusions.*

TIP

Be Clear About Variant Classification

Guidelines from organizations like the American College of Medical Genetics and Genomics and the Association for Molecular Pathology provide the foundation for germline variant classification.[5] In 2022, the Clinical Genome Resource, the Cancer Genomics Consortium, and the Variant Interpretation for Cancer Consortium published standards for the classification of somatic variants in cancer (**Table 1**).[6]

Table 1. Published Standards for Classification of Germline and Somatic Variants in Cancer[6]

Germline variants	Somatic variants
Benign	Benign
Likely benign	Likely benign
Variant of uncertain significance	Variant of uncertain significance
Likely pathogenic	Likely oncogenic
Pathogenic	Oncogenic

Gene variants may be reclassified as research results supply more information on their relevance. This is particularly true for variants of uncertain significance (VUS). A VUS may later be reclassified as being pathogenic or as likely benign. The results of one study showed that 24.9% of variants classified as VUS were reclassified over a 10-year period.[7]

TIP

Form Partnerships with Genetic Counselors

Certified genetic counselors (CGCs) are trained to identify patients who may be suspected of having a hereditary cancer syndrome. CGCs are integral members of the multidisciplinary cancer care team—they can offer valuable counseling before testing for patients who are recommended for germline testing or who are at risk for hereditary cancer syndromes. In addition, CGCs can help interpret the meaning of germline test results in the context of the patient's medical and family histories and educate patients on other cancer risks and/or review medical recommendations for cancer screenings/risk reduction practices based on their personalized results and family history. CGCs can also assist in shaping and developing testing algorithms, clinical workflows, and protocols to ensure that all appropriate patients are offered testing as well as refer patients to financial advocates or patient assistance resources for those facing financial barriers.

Genetic counseling is very helpful for patients found to harbor a pathogenic variant for a hereditary cancer syndrome and for facilitating cascade testing for their at-risk family members; it also is useful for patients with negative or VUS results in the presence of a concerning family history (familial cancer). Germline variants may be found in patients with tumors; however, their risk for hereditary cancer syndromes is not recognized. CGCs can help ensure that staff members receive continuing education to stay current on the latest recommendations for germline testing.[8]

TIP

Develop Tools for Germline Testing in Patients with Cancer

Tools such as algorithms or clinical pathways can remind clinicians to refer appropriate patients for genetic counseling and hereditary testing. Some examples include:

- EVERY patient diagnosed with breast cancer (age <65), ovarian cancer, pancreatic cancer, or metastatic prostate cancer should be referred for genetic counseling and germline testing.
- EVERY patient with colorectal cancer should receive screening testing for microsatellite instability/mismatch repair. Based on those results, appropriate patients should be referred for genetic counseling and germline testing.
- EVERY patient with breast cancer should complete a family history questionnaire. Based on those results and other patient factors (eg, age, subtype of cancer), appropriate patients should be referred for genetic counseling and germline testing.
- Germline testing should be performed in patients with advanced-stage breast, ovarian, pancreatic, or prostate cancers to determine eligibility for PARP inhibitor therapy.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are available for the following types of hereditary cancers:

- Genetic/Familial High-Risk Assessment: Colorectal[9]
- Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic[10]

TIP

Recognize That Somatic Testing May Reveal Germline Variants

Broad multigene somatic panels are routinely ordered in patients with advanced cancers. Remember that those test reports may reveal variants suspected to be germline variants. As noted earlier, if a somatic test report indicates a BRCA variant, one of the next steps should be clinically validated hereditary or germline testing to confirm whether this is a germline variant, since a pathogenic germline variant would indicate a hereditary cancer syndrome.

Learn more: accc-cancer.org/cancer-diagnostics

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