Pan-Cancer Hereditary Cancer Susceptibility Panels

A pan-cancer hereditary cancer susceptibility panel includes genes that are associated with inherited susceptibility to several different types of cancer (e.g., breast cancer, colon cancer, stomach cancer, etc.).

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel is considered **medically necessary** when the member meets **BOTH** A and B:

   A. The member has one of the following:

      1. A personal history, or a close relative with a personal history, of one of the following cancers less than or equal to 50 years of age:

         a) Breast cancer, **OR**

         b) Colorectal cancer, **OR**

         c) Endometrial cancer, **OR**

      2. The member has a personal history of one of the following:

         a) Pancreatic cancer at any age, **OR**

         b) Metastatic prostate cancer at any age**, OR**

         c) Ovarian, peritoneal, or fallopian tube cancer at any age, **OR**

      3. The member's personal or family history is suspicious for more than one hereditary cancer syndrome, **AND**

   B. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*.

II. Genetic testing using a pan-cancer hereditary cancer susceptibility panel is considered **investigational** for all other indications.

III. Hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used.

RATIONALE AND REFERENCES

Pan-Cancer Hereditary Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline defines multigene testing as analysis of a set of genes that fare associated with one or more cancer phenotypes in a family. NCCN states that in some families, there is suspicion for more than one hereditary cancer syndrome. In those cases, phenotype-directed testing via a “tailored multigene panel” is a more efficient and cost-effective method of testing. They state that “intermediate penetrant (moderate-risk) genes” may also be included in the multigene panels (p. EVAL-A 3 of 11).

These guidelines also recommend consideration of RNA studies, to further define the meaning of variants of unknown significance. Research studies designed to explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered (p. EVAL-A, 9 of 11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026
https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline recommends germline multigene panel testing in individuals with a personal history of colorectal cancer who are under age 50 at diagnosis as well as for other Lynch-syndrome related cancers, including ovarian and pancreatic cancer (p. HRS-3). Test selection should include at a minimum selected genes associated with colorectal cancer risk but additional genes can be included based on a patient’s personal and family history of cancer (p. HRS-A, 2 of 3).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors released a position statement (Adopted 2017, reaffirmed 2020 and 2023) endorsing the use of multigene panels when clinically warranted and appropriately applied, stating the following:

> These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices.
>
> Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost.

Use of Multi-Gene Panel Testing. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests. Released March 14, 2017. Reaffirmed 2020 and 2023.

American Society of Clinical Oncology (ASCO)

ASCO released guidelines in 2024 regarding appropriate use of multigene panel germline testing for individuals with cancer. As part of the guideline, they recommend germline genetic testing via a multigene panel for patients with cancer who have suspicion for more than one gene related to that cancer type (Table 4, p. 2605). Several genes are listed in Table 1 (p. 2603), which they recommend be included for specific populations of people with cancer (Table 4, p. 2605).

Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. Practice Guideline from The American Society of Clinical Oncology. https://ascopubs.org/doi/pdfdirect/10.1200/JCO.24.00662. Published May 17, 2024.

DEFINITIONS

1. **Adenomatous polyposis** are conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract.
2. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
3. **Close relatives** include first, second, and third degree blood relatives:
    a. **First-degree relatives** are parents, siblings, and children
    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
4. **Adjuvant treatment with olaparib therapy** may be indicated for cancer defined as
    a. Triple-negative breast cancer treated with either:
        i. Adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**
        ii. Neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, **OR**
    b. Hormone receptor positive disease treated with either:
        i. Adjuvant chemotherapy with four or more positive pathologically confirmed lymph nodes, **OR**
        ii. Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and grade (G)] of 3 or higher.
5. **High-risk prostate cancer** is defined by NCCN as an individual who has one or more of the following high-risk features, but does not meet criteria for very-high-risk features:

a. cT3-cT4
b. Grade Group 4 or 5
a. PSA > 20ng/ml

6. **Juvenile polyps** are associated with Juvenile Polyposis Syndrome. These polyps are exophytic and eroded. They typically contain the following: marked edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.

7. **Lynch syndrome-related cancer** is defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.

8. **Maori ancestry** describes individuals who are of indigenous New Zealand ethnic background.

9. **Very-high-risk prostate cancer** is defined by NCCN as an individual who has at least two of the following:
    a. cT3-cT4
    b. PSA >40 ng/mL
    a. Grade Group 4 or 5