

NCCN Guideline Updates: Hereditary Breast and Ovarian Cancers

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The field of hereditary cancer is quickly evolving. In an effort to ensure patients receive the highest quality of health care, the NCCN guidelines are updated annually. Highlights from the recent updates to the “Genetic/Familial High-Risk Assessment: Breast and Ovarian” section are below.

Hereditary Breast and/or Ovarian Cancer Syndrome (HBOC) is the most common known cause of hereditary breast and hereditary ovarian cancer. HBOC is caused by *BRCA1* and *BRCA2* gene mutations:

- Several of the criteria for BRCA gene testing are now less stringent. While much of the criteria remains the same, now females (and males) qualify for BRCA gene testing if they:
 - Received a diagnosis of breast cancer *at any age* AND have one close blood relative with breast cancer diagnosed younger than 50 years old OR at least one relative with epithelial ovarian cancer at any age.
 - Received a diagnosis of breast cancer *at any age* AND have with at least two close blood relatives with pancreatic cancer or aggressive prostate cancer (Gleason score greater than or equal to 7) at any age.
 - Have no personal history of cancer; clinical judgment should be used to determine if the patient has a reasonable likelihood of a mutation.
- Interpretation of test results:
 - The limitations of interpreting test results for an unaffected individual should be discussed.
- HBOC management for women:
 - For women 25-30 years old, the best breast cancer screening strategy is uncertain. Some data suggests that mammograms should only be added after 30 years old. This is still under study.
 - After salpingo-oophorectomy, pathology should be reviewed due to the high rate of occult neoplasms.
 - Although tamoxifen and raloxifene have been shown to significantly reduce the risk of breast cancer for the average women. These drugs have not been studied in BRCA gene mutation carriers.

Li-Fraumeni Syndrome (LFS) often presents in youth in the form of brain tumors, sarcomas, leukemia and lymphomas. The risk for female breast cancer is high, and often occurs before 30 years old. LFS is caused by *TP53* gene mutations:

- Updates to the *TP53* genetic testing criteria include the following:
 - LFS testing should be considered in individuals who test negative for a BRCA mutation under the age of 35 years old (formerly under 30 years old).
 - Tumors no longer considered to be associated with LFS include gastrointestinal stromal tumors, desmoid tumor, and angiosarcoma (in addition to Ewing’s sarcoma).
- Management of LFS

- Patients with LFS are highly sensitive to radiation, and there are theoretical concerns about the safety of mammograms in this population. This version of the guidelines state that, following physician consultation, annual MRI-only screening may be sufficient for women aged 20-30 years old.
- The specific types of cancer observed in LFS vary somewhat between families. Additional surveillance should be considered based on family history.

Cowden Syndrome (CS) is associated with increased risk for cancers of the breast, uterine, thyroid, kidney, and possibly colon cancer and melanoma. About 80% of Cowden syndrome is caused by *PTEN* gene mutations:

- Updates to *PTEN* genetic testing criteria include the following:
 - Traditionally, non-medullary thyroid cancer has been part of the major *PTEN* testing criteria. However, follicular thyroid cancer is overrepresented in CS more than other forms of non-medullary thyroid cancer. Now “follicular thyroid cancer” replaces “non-medullary thyroid cancer” as a major testing criterion.
 - The following were added to the minor criteria: colon cancer, esophageal glycogenic acanthosis (greater than or equal to 3), papillary or follicular variant of papillary thyroid cancer, testicular lipomatosis, and vascular anomalies (including multiple intracranial developmental venous anomalies).
 - Fibrocystic breast disease, fibromas, and uterine fibroids were removed from the criteria, as the literature is insufficient as to whether these should be included.

Additional Syndromes: A new page was added that includes additional hereditary breast and/or ovarian cancer syndromes that have already been established. The syndromes and the genes associated with them include the following:

- Hereditary Diffuse Gastric Cancer Syndrome: caused by *CDH1* gene mutations.
 - The risk for diffuse gastric cancer is 67-83%
 - The risk for lobular breast cancer is 39-52%.
- Peutz-Jeghers Syndrome: caused by *STK11/LKB1* gene mutations.
 - Breast cancer risk is 44-50%
 - Ovarian cancer is 18-21%, usually ovarian sex cord tumors.
 - (The risks for other cancers, including colon and pancreatic cancer, are increased and are listed in a separate section of the guidelines).
- Lynch syndrome: caused by mutations in the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* genes.
 - Ovarian cancer risk is 9%
 - The data regarding increased risk for breast cancer is controversial.
 - (The risks for other cancers, including colon and endometrial, are increased and included in a separate section of the guidelines).

Updates for All Hereditary Cancer Syndromes:

- Patients of reproductive age should be counseled about the options of prenatal diagnosis and pre-implantation genetic diagnosis (PGD).
- Sometimes genetic test results are uninformative, and it is not clear whether the patient does or does not have a mutation. These results are called ‘variants of uncertain significance (VUS)’. Updated NCCN guidelines state that when a patient tests positive for a VUS, testing other family members for the same VUS should not be used for clinical purposes.

- A footnote has been added for all syndromes stating that women should be familiar with their breasts and that periodic BSEs may be helpful, particularly if performed at the end of menses.

Hereditary Cancer Panels:

Hereditary cancer panels, which use next generation sequencing, are now included in the NCCN guidelines. The guidelines state that these are intended for individuals who have tested negative for high penetrance genes and for those whose family histories are suggestive of more than one syndrome. Additionally, the guidelines address the complexities of panel testing, which include unknown percentage of VUSs, lack of certainty regarding some cancer risk, and lack of complete guidelines for management of mutation-positive patients. The guidelines iterate that due to the complexity, “cancer panels should only be ordered in consultation with a cancer genetics professional”.

Testing Guidelines in Practice:

Testing criteria used by health insurance companies is based largely off of NCCN guidelines. However, it usually takes some time before NCCN updates are reflected in health insurance testing criteria. Therefore, in practice, some patients who meet NCCN guidelines for testing do not meet insurance testing criteria, and will likely decline testing because they would have to pay out-of-pocket. If testing is not time-sensitive, it is appropriate to advise these patients to re-contact their genetic counselor with a few months to determine whether their insurance company’s criteria have been updated. Limited financial assistance is available for insured patients who have steep out-of-pocket testing costs. As always, financial assistance remains available for patients who do not have insurance at UT Southwestern.

Contact Information:

As always, if you have any questions or would like to refer a patient to UT Southwestern’s cancer genetics team in Fort Worth at the Moncrief Cancer Institute or in Dallas, please call (214)645-2563.

Reference:

NCCN Clinical Practice Guidelines in Oncology. “Genetic/Familial High-Risk Assessment: Breast and Ovarian”. version 2.2013. Accessed 5/8/2013.

http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf