Abstract

The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide recommendations for genetic testing and counseling and risk assessment and management for hereditary cancer syndromes. Guidelines focus on syndromes associated with an increased risk of breast and/or ovarian cancer and are intended to assist with clinical and shared decision-making. These NCCN Guidelines Insights summarize major discussion points of the 2015 NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian panel meeting. Major discussion topics this year included multigene testing, risk management recommendations for less common genetic mutations, and salpingectomy for ovarian cancer risk reduction. The panel also discussed revisions to genetic testing criteria that take into account ovarian cancer histology and personal history of pancreatic cancer.

From 1Fox Chase Cancer Center; 2The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; 3The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; 4St. Jude Children’s Research Hospital/The University of Tennessee Health Science Center; 5Huntsman Cancer Institute at the University of Utah; 6UCSF Helen Diller Family Comprehensive Cancer Center; 7University of Alabama at Birmingham Comprehensive Cancer Center; 8FORCE-Facing Our Risk of Cancer Empowered; 9Dana-Farber/Brigham and Women’s Cancer Center; 10Robert H. Lurie Comprehensive Cancer Center of Northwestern University; 11University of Colorado Cancer Center; 12Stanford Cancer Institute; 13The University of Texas MD Anderson Cancer Center; 14UC San Diego Moores Cancer Center; 15Duke Cancer Institute; 16University of Michigan Comprehensive Cancer Center; 17Memorial Sloan Kettering Cancer Center; 18Moffitt Cancer Center; 19Fred & Pamela Buffett Cancer Center; 20Massachusetts General Hospital Cancer Center; 21University of Washington Medical Center/Seattle Cancer Care Alliance; 22Roswell Park Cancer Institute; 23City of Hope Comprehensive Cancer Center; 24Sidney Kimmel Comprehensive Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; 25Mayo Clinic Cancer Center; 26Vanderbilt Ingram Cancer Center; and 27National Comprehensive Cancer Network.

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NCCN Guidelines Insights

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Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015

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Learning Objectives:
Upon completion of this activity, participants will be able to:
• Integrate into professional practice the updates to NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian

Disclosure of Relevant Financial Relationships

Editor:
Kerrin M. Green, MA, Assistant Managing Editor, JNCCN—Journal of the National Comprehensive Cancer Network
Ms. Green has disclosed that she has no relevant financial relationships.

CE Planners:
Deborah J. Moonan, RN, BSN, Director, Continuing Education
Ms. Moonan has disclosed that she has no relevant financial relationships.
Ann Gianola, MA, Senior Manager, Continuing Education Accreditation and Program Operations
Ms. Gianola has disclosed that she has no relevant financial relationships.
Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations
Ms. Gregory has disclosed that she has no relevant financial relationships.
Rashmi Kumar, PhD, Senior Manager, Clinical Content, NCCN
Dr. Kumar has disclosed that she has no relevant financial relationships.

Individuals Who Provided Content Development and/or Authorship Assistance:
Mary B. Daly, MD, PhD, Panel Chair, has disclosed that he has no relevant relationships.
Robert Pilarski, MS, CGC, Panel Vice-Chair, has disclosed that he is a Scientific Advisor for Invitae.
Allison Kurian, MD, MSc, Panel Member, has disclosed that he receives Research Support from Myriad Genetic Laboratories, Inc., Invitae, and Ambry Genetics.
Saundra S. Buys, MD, Panel Member, has disclosed that she has no relevant financial relationships.
Myra J. Wick, MD, PhD, Panel Member, has disclosed that she has no relevant financial relationships.
Mary Dwyer, MS, CGC, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.
Susan D. Darlow, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION

An individual with a cancer diagnosis meeting any of the following:
- A known mutation in a cancer susceptibility gene within the family
- Early-age-onset breast cancer
- Triple negative (ER-, PR-, HER2-) breast cancer ≤50 y
- Two breast cancer primaries in a single individual
- Breast cancer at any age, and
  - ≥1 close blood relative with breast cancer ≤50 y, or
  - ≥1 close blood relative with invasive ovarian cancer at any age, or
- ≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or
- From a population at increased risk
- Personal and/or family history of three or more of the following (especially if early onset):
  - Pancreatic cancer
  - Prostate cancer (Gleason score 7+)
  - Sarcoma
  - Adrenocortical carcinoma
  - Brain tumors
  - Endometrial cancer
  - Thyroid cancer
  - Kidney cancer
  - Dermatologic manifestations

An individual with no personal history of cancer but with a family history of any of the following:
- A known mutation in a cancer susceptibility gene within the family
- ≥2 breast cancer primaries in a single individual
- ≥2 individuals with breast cancer primaries on the same side of family
- ≥1 invasive ovarian cancer primary
- First- or second-degree relative with breast cancer ≤45 y
- Personal and/or family history of three or more of the following (especially if early onset):
  - Pancreatic cancer
  - Prostate cancer (Gleason score 7+)
  - Sarcoma
  - Adrenocortical carcinoma
  - Brain tumors
  - Endometrial cancer
  - Thyroid cancer
  - Kidney cancer
  - Dermatologic manifestations
  - Multiple primary cancers in same individual
- Male breast cancer

Overview

Family studies have long documented an increased risk of several forms of cancer among first- and second-degree relatives of affected individuals. These individuals may have an increased susceptibility to cancer as the result of one or more genetic mutations present in parental germline cells; cancers developing in these individuals may be classified as hereditary or familial cancers. Hereditary cancers are often characterized by mutations associated with a high probability of cancer development, vertical transmission through a parent, and an association with other types of tumors. They often have an early age of onset and exhibit an autosomal dominant inheritance pattern. Advances in molecular genetics have allowed researchers to identify a number of genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, BRCA1/2, PTEN, TP53).

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial
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HEdERATIVE BREAST AND ORDAEv. OVARIAN CANCER SYNDROME TESTING CRITERIA.a,b

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancerb + one or more of the following: • Diagnosed ≤50 y with: ◦ An additional breast cancer primary ◦ 21 close blood relatives with breast cancer at any age ◦ 21 close relative with pancreatic cancer ◦ 21 relative with prostate cancer (Gleason score ≥7) ◦ An unknown or limited family historyb • Diagnosed ≤50 y with a: ◦ Triple negative breast cancer ◦ Diagnosed at any age with: ◦ 21 close blood relatives with breast cancer diagnosed ≤50 y ◦ 22 close blood relatives with breast cancer at any age ◦ 21 close blood relative with invasive ovarian cancer ◦ 22 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age ◦ A close male blood relative with breast cancer ◦ For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be requiredb • Personal history of invasive ovarian cancer • Personal history of male breast cancer

Personal history of prostate cancer (Gleason score ≥7) at any age with 21 close blood relative with breast (≤50 y) and/or invasive ovarian and/or pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with 21 close blood relative with breast (≤50 y) and/or ovarian cancer and/or pancreatic cancer at any age
- Personal history of pancreatic cancer, and Ashkenazi Jewish ancestry
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed); • First- or second-degree blood relative meeting any of the above criteria • Third-degree blood relative who has breast cancer and/or invasive ovarian cancer and who has 22 close blood relatives with breast cancer (at least one with breast cancer ≤50 y) and/or invasive ovarian cancer

bFor further details regarding the nuances of genetic counseling and testing, see BRCAV-A.

cFor the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

dTwo breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate (isolated) primary tumors either synchronously or asynchronously.

eClose blood relatives include first-, second-, and third-degree relatives on same side of family. (See BRCAV-B)

fTesting for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other HBOC criteria are met. Founder mutations exist in other populations.

High-Risk Assessment: Breast and Ovarian focus primarily on assessment of mutations in the genes BRCA1/2, TP53, and PTEN. The main focus of these NCCN Guidelines is on the management of breast and ovarian cancer risk, and genetic testing and counseling in individuals with these particular genetic mutations. These guidelines were developed with an acute awareness of the preliminary nature of much of the knowledge regarding the clinical application of the rapidly emerging field of molecular genetics, and with an appreciation of the need for flexibility when applying these guidelines to individual families. They are intended to serve as a resource for health care providers to identify individuals who may benefit from cancer risk assessment and genetic counseling, to provide genetic professionals with an updated tool for the assessment of individual breast cancer and ovarian cancer risk and to guide decisions related to genetic testing, and to facilitate a multidisciplinary approach in the management of individuals at increased risk of hereditary breast and/or ovarian cancer.

Genetic Evaluation and Testing

Genetic testing is a complex process involving several phases. First, an initial risk assessment is performed to determine whether genetic assessment should be undertaken. Next, a patient would undergo a formal risk assessment, including a detailed family history, a personal medical and surgical history, a focused physical examination, and an evaluation of the patient’s needs and concerns. Testing may be offered; counseling should be performed both before and after testing. Before the 2015 update, recommendations regarding testing and counseling principles (eg, consideration of cancer risk in relatives) were scattered throughout the guidelines, often as footnotes. For the 2015 guidelines update, much of this information was consolidated
and moved to a new set of pages titled “Principles of Cancer Risk Assessment and Counseling” (available online, in the full version of these guidelines, at NCCN.org [BR/OV-A]). Given the complexity of genetic testing and the rapid evolution of molecular diagnostics, the panel agreed that listing the principles on a single set of pages, as opposed to throughout the guidelines as footnotes, would clarify the panel’s position on testing principles.

For the most recent guidelines update, the panel revised recommendations regarding multigene testing. Minor modifications were also made to testing criteria for genetic mutations, including clarification regarding ovarian cancer histology and review of BRCA1/2 testing criteria for those with a personal history of pancreatic cancer and with Ashkenazi Jewish ancestry.

**Multigene Testing**

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. In this approach, referred to as multigene testing, a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes are simultaneously analyzed. The recent introduction of multigene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. This approach may detect mutations not found in single-gene testing. Multigene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available.

The NCCN Guidelines panel had added information regarding multigene testing for the 2014 update. This new section included a list of advantages and disadvantages of multigene testing, examples of when this testing may be particularly advantageous and cost-effective, and issues to consider (e.g., clinical
MULTI-GENE TESTING

Overview of multi-gene testing
• The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.
• Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, than multi-gene testing, may be more efficient and/or cost-effective.
• There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.
• As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
• Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene tests are necessarily clinically actionable. As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives. In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
• There is an increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes.
• It is for these and other reasons that multigene testing are ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

Implications of moderate-penetrance genes included in a panel). The panel also included recommendations for both the provider and laboratories. During the panel meeting for the 2015 update, several members noted that this section should be more concise, because some of the most important points were difficult to identify in the presented text. The panel’s recommendations regarding multigene testing now more clearly emphasize the following (GENE-1, this page):
• Multigene testing should ideally be offered in the context of professional genetic expertise.
• Multigene testing may be more efficient and/or cost-effective for patients who have a family history suggestive of an inherited cancer syndrome and in the setting of clinical features common to more than one hereditary syndrome or more than one gene.
• Multigene testing may also be warranted in those who have tested negative (indeterminate) for a single inherited syndrome but whose personal or family history remains strongly suggestive of an inherited susceptibility.
• Both the laboratory and test panel should be chosen carefully and limitations understood.

The panel also noted that multigene testing may include moderate-penetrance genes. Currently, there are limited data and no specific guidelines regarding degree of cancer risk associated with some moderate-penetrance genes and management for gene carriers. These issues are compounded by the low incidence rates of hereditary disease, making it difficult to conduct adequately powered studies. The approach to risk management after detection of a mutation in a moderate-risk gene and how best to communicate risk to relatives are currently unknown. Ideally, testing should only be performed for genes that are clinically actionable. The panel now provides recommendations regarding risk manage-
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### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS

<table>
<thead>
<tr>
<th>Intervention Warranted based on gene and/or risk level</th>
<th>Recommend MRI (20% risk of breast cancer)</th>
<th>Recommend RRSO</th>
<th>Discuss Option of RRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;br&gt;BRCA1, BRCA2, CDH1, PTEN, TP53</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;br&gt;BRCA1, BRCA2, CDH1, PTEN, TP53</td>
<td>BRCA1, BRCA2, Lynch syndrome&lt;br&gt;BRCA1, BRCA2, CDH1, PTEN, TP53</td>
</tr>
<tr>
<td>Insufficient evidence for intervention</td>
<td>BARD1, BRIP1</td>
<td>BARD1, BRIP1, PALB2, RAD51C, RAD51D</td>
<td>ATM, BARD1, BRIP1, CHEK2, PALB2, STK11</td>
</tr>
</tbody>
</table>

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*Other genes may be included in multi-gene testing.
*Intervention may still be warranted based on family history or other clinical factors.
*See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
*May be modified based on family history or specific gene mutation.
*See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

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ment for less common moderate-penetrance genes (see later discussion).

Finally, the panel noted that multigene tests increase the likelihood of detecting a variant of unknown significance (VUS). The considerable possibility of detecting a VUS adds to the complexity of counseling for multigene testing.

**Ovarian Cancer Histology and Genetic Mutations**

During the meeting for the 2015 guidelines update, the panel debated whether the criteria for genetic risk evaluation should be more specific regarding ovarian cancer histology. The histology of ovarian cancers in carriers of a BRCA1/2 mutation is more likely to be characterized as serous adenocarcinoma and high grade compared with ovarian cancers in nonmutation carriers. However, endometrioid and clear cell ovarian cancers have also been reported in BRCA1/2 carriers. Mutations are also associated with nonmucinous ovarian carcinoma as opposed to mucinous. Mucinous epithelial ovarian carcinomas may be associated with other gene mutations, such as KRAS and TP53 mutations. Nonepithelial ovarian carcinomas (eg, germ cell and sex cord stromal tumors) are not significantly associated with BRCA1/2 mutations, but they may be associated with other cancer genetic syndromes, such as Peutz-Jeghers syndrome. Current data indicate that ovarian low-malignant-potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with BRCA1/2 mutations.
other cancer genetic syndromes may be associated with ovarian cancer that is mucinous or non-epithelial.

**Pancreatic Cancer Risk and BRCA1/2 Mutations**

BRCA1/2 mutations are associated with an increased propensity for developing pancreatic cancer. In an analysis of samples from patients with familial pancreatic cancer (kindreds in which ≥3 family members had pancreatic cancer, at least 2 of whom were first-degree relatives), BRCA2 mutations were detected in 17% of patient samples.27 Patients with pancreatic cancer who also have Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a BRCA1/2 mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, and with mutations in BRCA2 (4%–11%) being more common than BRCA1 (1%–8%).29–31 In 211 Ashkenazi Jewish patients with breast cancer who had a family history of pancreatic cancer, 6.6% had a BRCA1 mutation and 7.6% had a BRCA2 mutation.32

Regarding testing criteria for BRCA1/2 mutations, the panel previously recommended that criteria for those with a personal history of pancreatic cancer would be the same as for those with a personal history of prostate cancer; specifically, a personal history of pancreatic or prostate cancer, with at least 1 close relative with breast cancer diagnosed at age 50 years or younger and/or invasive ovarian cancer and/or pancreatic or prostate cancer diagnosed at any age. Given the elevated risk for pancreatic cancer in BRCA1/2 carriers24,25,27,28,33 relative to the risk for prostate cancer,36 and the short survival of most patients with pancreatic cancer (which limits the ability to perform genetic testing in these individuals in the future), the panel argued that less stringent criteria are warranted for testing in those with a personal history of pancreatic cancer. Based on concerns raised by 2 panel members, the panel now recommends that a family history of prostate cancer is no longer a criterion for testing in those with a personal history of pancreatic cancer. Furthermore, a personal history of pancreatic cancer combined with Ashkenazi Jewish ancestry warrants testing, given the considerable rates of BRCA1/2 mutations in Ashkenazi Jewish patients with pancreatic cancer (HBOC-1, page 156).29–31

**Risk Management Recommendations**

The panel’s recommendations regarding screening and risk reduction for those found to have a genetic mutation associated with hereditary cancer are based on existing evidence. Changes made for the 2015 update include refinement of risk management recommendations for less common genetic mutations associated with breast and/or ovarian cancer, and recommendations regarding ovarian cancer risk-reducing surgery in BRCA1/2 mutation carriers.

**Less Common Genetic Mutations Associated With Breast/Ovarian Cancer**

In these NCCN Guidelines, the panel focuses specifically on assessment of known high-penetrance mutations (ie, BRCA1/2, TP53, PTEN). In the 2014 update, the panel added CDH1, STK11/LKB1, and Lynch syndrome to the guidelines as other genes associated with increased breast and/or ovarian cancer risk. Although evidence is limited, other genes have been shown to be associated with increased cancer risk, including ATM, CHEK2, PALB2, BARD1, BRIP1, RAD51C, and RAD51D.

During the 2015 guidelines update meeting, the panel debated the possibility of including information and recommendations for these less common genes, including population frequency, estimated cancer risks, and management strategies. The panel ultimately decided that providing this amount of detailed information in the guidelines for all of the rare genes noted would be premature, given the current state of the evidence. Risk management recommendations should be evidence-based and matched to cancer risk and should only be made for genes that are clinically actionable. Because risk may differ between breast and ovarian cancers, different recommendations may need to be made for these 2 cancer types.

Based on this logic, the panel created a new table summarizing which gene mutations are associated with breast and/or ovarian cancer risk, and when breast MRI, risk-reducing mastectomy (RRM), and risk-reducing salpingo-oophorectomy (RRSO) should be recommended or considered (ADDIT-2, page 159). Breast MRI is recommended when the gene mutation is associated with at least a 20% lifetime risk of breast cancer. This threshold was identified in breast cancer risk models dependent on family history (see NCCN Guidelines for Breast Cancer Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2015).
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Cancer Screening and Diagnosis and for Breast Cancer Risk Reduction for more information; available at NCCN.org). Most of the recommendations in this new table are extrapolated from BRCA studies, because no strong evidence exists regarding risk management recommendations for the other genes. Genes for which there is little to no existing evidence suggesting an association with breast and/or ovarian cancer risk are noted in a row titled “Insufficient evidence for intervention.” Intervention may be warranted based on family history or other clinical factors. The recommendations in this table can be used to inform which genes may be included in multigene testing (see earlier discussion).

Salpingectomy in BRCA1/2 Mutation Carriers
Salpingectomy (surgical removal of the fallopian tube) has recently gained attention as a potential procedure to reduce the risk of ovarian cancer. Salpingectomy rates are increasing, especially in women younger than 50 years. Its use is supported by the finding that high-grade serous carcinomas may originate in the fallopian tube. This procedure allows patients to avoid the disadvantages of oophorectomy, such as lack of ovarian preservation and onset of early menopause. Salpingectomy has been shown to be a safe and feasible procedure when performed at the same time as hysterectomy.

Despite evidence regarding the safety and feasibility of salpingectomy, more data are needed regarding its efficacy in reducing the risk of ovarian cancer. Furthermore, BRCA1/2 carriers who undergo salpingectomy without oophorectomy may not get the 50% reduction in breast cancer risk associated with oophorectomy. During the 2015 update meeting, a panel member presented data showing that, although ovarian carcinomas often originate in the fallopian tube, a significant minority (>20%) originates in the ovary. For these reasons, the panel included a statement that salpingectomy is not the standard of care, and risk-reducing salpingectomy alone or outside the context of a clinical trial is not recommended (HBOC-A, page 157).

Summary and Conclusions
In summary, the panel discussed several pertinent issues this year, including multigene testing, risk management recommendations for less common genetic mutations, and salpingectomy for ovarian cancer risk reduction. The panel also made the following changes to the 2015 recommendations:

- Consolidated recommendations regarding testing and counseling principles into a new set of pages, titled “Principles of Cancer Risk Assessment and Counseling.”
- Added more specific language regarding ovarian cancer histology criteria for genetic risk evaluation, and
- Revised testing criteria for BRCA1/2 mutations for those with a personal history of pancreatic cancer and who have Ashkenazi Jewish ancestry.

The evidence base for genetic testing and counseling and risk assessment and management for hereditary cancer syndromes is rapidly evolving. It is essential for recommendations to reflect the current state of the evidence.

References

Instructions for Completion

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Posttest Questions

1. According to the 2015 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, BRCA1/2 mutations are associated with the following ovarian cancer histologies:
   a. Nonmucinous
   b. High-grade serous
c. Borderline epithelial
da. a and b
e. all of the above

2. True or False: Very few (<10%) ovarian cancers start in the ovary.

3. According to the 2015 NCCN Guidelines for Genetic/Familial High-Risk Assessment (Breast and Ovarian), which of the following statements regarding multigene testing are correct:
   a. Multigene testing only includes high-penetration genes.
   b. Multigene testing decreases the likelihood of finding a variant of unknown significance.
c. Multigene testing may be cost-effective for patients who have an inherited cancer syndrome that can be explained by more than one gene.
d. Interlaboratory differences in variant interpretation are not a concern with multigene testing.