NCCN Guidelines® Insights

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

Featured Updates to the NCCN Guidelines

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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.
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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

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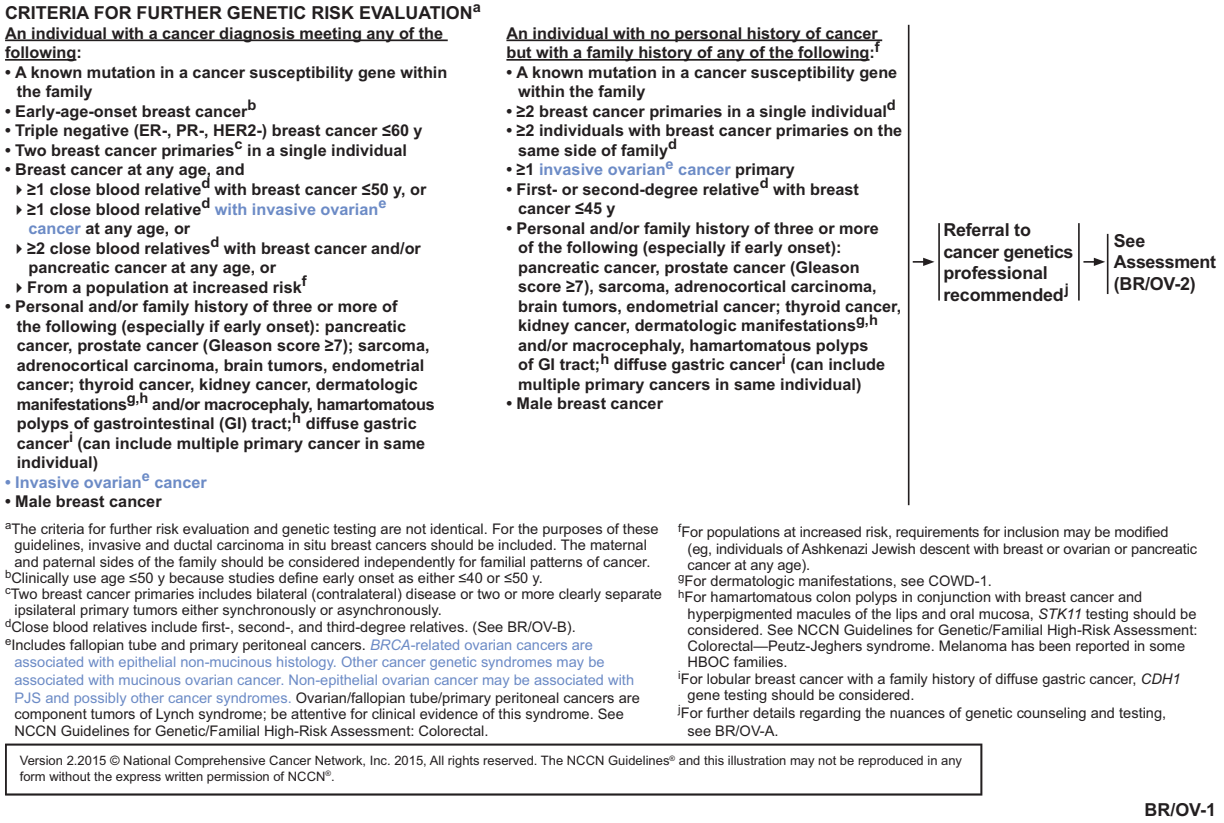

[a]The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.
[b]Clinically use age ≤50 y because studies define early onset as either ≤40 or ≤50 y.
[c]Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
[d]Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-B).
[e]Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial non-mucinous histology. Other cancer genetic syndromes may be associated with mucinous ovarian cancer. Non-epithelial ovarian cancer may be associated with PJS and possibly other cancer syndromes. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome; be attentive for clinical evidence of this syndrome. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[f]For populations at increased risk, requirements for inclusion may be modified (eg, individuals of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).
[g]For dermatologic manifestations, see COWD-1.
[h]For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, *STK11* testing should be considered. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal—Peutz-Jeghers syndrome. Melanoma has been reported in some HBOC families.
[i]For lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.
[j]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

BR/OV-1

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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.[1,2] 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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HEREDITARY BREAST AND/OR 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 cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - ◊ An additional breast cancer primary[c]
    - ◊ ≥1 close blood relative[d] with breast cancer at any age
    - ◊ ≥1 close relative with pancreatic cancer
    - ◊ ≥1 relative with prostate cancer (Gleason score ≥7)
    - ◊ An unknown or limited family history[a]
  - Diagnosed ≤60 y with a:
    - ◊ Triple negative breast cancer
  - Diagnosed at any age with:
    - ◊ ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ◊ ≥2 close blood relatives[d] with breast cancer at any age
    - ◊ ≥1 close blood relative[d] with invasive ovarian[e] cancer
    - ◊ ≥2 close blood relatives[d] with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - ◊ A close male blood relative[d] with breast cancer
    - ◊ For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of invasive ovarian[e] cancer
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[d] with breast (≤50 y) and/or invasive ovarian[e] and/or pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with breast (≤50 y) and/or invasive ovarian[e] 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[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or invasive ovarian[e] cancer and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or invasive ovarian[f] cancer

HBOC testing criteria met → See Follow-up (HBOC-2)

If HBOC testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
[b]For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[c]Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
[d]Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)
[e]Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial non-mucinous histology. Other cancer genetic syndromes may be associated with mucinous ovarian cancer. Non-epithelial ovarian cancer may be associated with PJS and possibly other cancer syndromes. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome; be attentive for clinical evidence of this syndrome. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[f]Testing 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.

HBOC-1

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

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HBOC SYNDROME MANAGEMENT (1 of 2)

WOMEN

- **Breast awareness[1] starting at age 18 y.**
- **Clinical breast exam, every 6–12 mo,[2] starting at age 25 y.**
- **Breast screening[3]**
  - **Age 25–29 y, annual breast MRI[4] screening (preferred) or mammogram if MRI is unavailable or individualized based on family history if a breast cancer diagnosis before age 25 is present.**
  - **Age 30–75 y, annual mammogram and breast MRI[4] screening.**
  - **Age >75 y, management should be considered on an individual basis.**
  - **For women with a *BRCA* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.**
- **Discuss option of risk-reducing mastectomy**
  - **Counseling may include a discussion regarding degree of protection, reconstruction options, and risks.**
- **Recommend risk-reducing salpingo-oophorectomy (ideally in consultation with a gynecologist oncologist),[5] typically between 35 and 40 y, and upon completion of child bearing. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer- Principles of Surgery.**
  - **Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy to a recommended maximum age of natural menopause, and related medical issues.**
  - **Salpingectomy alone is not the standard of care and is discouraged outside a clinical trial. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer by 50%.[6]**
- **Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.**
- **For those patients who have not elected risk-reducing salpingo-oophorectomy, while there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening. Transvaginal ultrasound for ovarian cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion starting at age 30–35 y. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.**
- **Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).**
- **Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.**

Continued on next page

[1]Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.

[2]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6–12 mo is the concern for interval breast cancers.

[3]The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Annual screening strategies in *BRCA1* and *BRCA2* gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118:2021-2030.

[4]High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women.

[5]Given the high rate of occult neoplasms, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (See Discussion for details.) See the College of American Pathologists, Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary. See NCCN Guidelines for Ovarian Cancer for treatment of findings.

[6]SGO Clinical Practice Statement: Salpingectomy for Ovarian Cancer Prevention November 2013.

HBOC-A
1 OF 2

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 revision 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.[3]

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 (eg, clinical

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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.

References (GENE-2)

See Breast and Ovarian Management Based on Genetic Test Results (ADDIT-2)

GENE-1

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.[4–6] These issues are compounded by the low incidence rates of hereditary disease, making it difficult to conduct adequately powered studies.[4] 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.[7] 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[a]

	Recommend MRI[c] (>20% risk of breast cancer[d])	Recommend RRSO	Discuss Option of RRM
Intervention Warranted based on gene and/or risk level	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* Lynch syndrome[e]	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53*
Insufficient evidence for intervention[b]	*BARD1* *BRIP1*	*BARD1* *BRIP1* *PALB2* *RAD51C* *RAD51D*	*ATM* *BARD1* *CHEK2* *PALB2* *STK11*

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

ADDIT-2

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).[3,5–9] 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.[10–15] Mutations are also associated with nonmucinous ovarian carcinoma as opposed to mucinous.[16,17] Mucinous epithelial ovarian carcinomas may be associated with other gene mutations, such as *KRAS* and *TP53* mutations.[18] Nonepithelial ovarian carcinomas (eg, germ cell and sex cord stromal tumors) are not significantly associated with *BRCA1/2* mutations,[19] but they may be associated with other cancer genetic syndromes, such as Peutz-Jeghers syndrome.[20–23] Current data indicate that ovarian low-malignant-potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with *BRCA1/2* mutations.[16]

Based on these study findings, the following modifications were made to the genetic risk evaluation guidelines (BR/OV-1, page 155):

- "Epithelial ovarian cancer" was replaced with "invasive ovarian cancer."
- The footnote was modified to indicate that *BRCA*-related ovarian cancers are associated with epithelial nonmucinous histology, although

other cancer genetic syndromes may be associated with ovarian cancer that is mucinous or nonepithelial.

Pancreatic Cancer Risk and *BRCA1/2* Mutations

BRCA1/2 mutations are associated with an increased propensity for developing pancreatic cancer.[24–28] 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* carriers[24,25,27,28,33] relative to the risk for prostate cancer,[28,33] 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

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Cancer Screening and Diagnosis and for Breast Cancer Risk Reduction for more information; available at NCCN.org).[34,35] 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.[36] Its use is supported by the finding that high-grade serous carcinomas may originate in the fallopian tube.[37–39] This procedure allows patients to avoid the disadvantages of oophorectomy, such as lack of ovarian preservation and onset of early menopause.[40] Salpingectomy has been shown to be a safe and feasible procedure when performed at the same time as hysterectomy.[36,41]

Despite evidence regarding the safety and feasibility of salpingectomy, more data are needed regarding its efficacy in reducing the risk of ovarian cancer.[37,42] 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.[43–46] 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.

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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
   d. 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-penetrance 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.