NCCN Guidelines® Insights
Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide recommendations for genetic testing and counseling for hereditary cancer syndromes and risk management recommendations for patients who are diagnosed with a syndrome. Guidelines focus on syndromes associated with an increased risk of breast and/or ovarian cancer. The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. The NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding risk management for carriers of moderately penetrant genetic mutations associated with breast and/or ovarian cancer.

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Release date: January 3, 2017; Expiration date: January 3, 2018

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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Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a,b]

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast starting at age 40 y[c] • RRM: Consider based on family history	**No increased risk of OC**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. The 7271T>G missense mutation may act in a dominant–negative fashion, resulting in a lifetime breast cancer risk as high as 60% by age 80 (which is higher than truncating mutations, where risks are in the range of 30-40%). Counsel for risk of autosomal recessive condition in offspring.		
BRCA1	**Increased risk of BC** • See BRCA Mutation-Positive Management	**Increased risk of OC** • See BRCA Mutation-Positive Management	Prostate cancer • See BRCA Mutation-Positive Management
BRCA2	**Increased risk of BC** • See BRCA Mutation-Positive Management	**Increased risk of OC** • See BRCA Mutation-Positive Management	Pancreas, Prostate, Melanoma • See BRCA Mutation-Positive Management
BRIP1	**No increased risk of BC**	**Increased risk of OC** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
CDH1	**Increased risk of lobular BC** • Screening: Annual mammogram and consider breast MRI with contrast starting at age 30 y[c] • RRM: Consider based on family history	**No increased risk of OC**	Diffuse gastric cancer • See NCCN Guidelines for Gastric Cancer

BC: Breast cancer
OC: Ovarian cancer
RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

[a]Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.
[b]The following genes and others are found on some of the panels but there is insufficient evidence to make *any* recommendations for breast MRI, RRSO, or RRM: BARD1, FANCC, MRE11A, MUTYH heterozygotes, REQL, RAD50, RET1, SLX4, SMARCA4, or XRCC2.
[c]May be modified based on family history or specific gene mutation.

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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

Hereditary cancers are often characterized by mutations associated with increased risk for certain cancers (ie, a high penetrance phenotype) and transmission to offspring through the mother and/or father.[1,2] An individual suspected of being at risk for hereditary cancer should be offered genetic counseling.[3,4] The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian were developed with the intent to (1) serve as a resource for healthcare providers to identify individuals who may benefit from cancer risk assessment and genetic counseling; (2) provide genetic counselors with an updated tool for the assessment of individual breast and ovarian cancer risk and to guide decisions related to genetic testing; and (3) facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancer.

Advances in molecular genetics have identified a number of genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, *BRCA1/2*, *TP53*,

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Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CHEK2	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast age 40 y[c] • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift mutations. The risks for most missense mutations are unclear.		
MSH2, MLH1, MSH6, PMS2, EPCAM	**Unknown or insufficient evidence for BC risk[d]** • Manage based on family history	**Increased risk of OC** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
NBN	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast age 40 y[c] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for OC risk**	Unknown or insufficient evidence
	Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating mutation. Although risks for other mutations have not been established it is prudent to manage patients with other truncating mutations similarly to those with 675del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of BC** • Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	• Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to NF specialist for evaluation and management.
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y.		

[a]Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.
[c]May be modified based on family history or specific gene mutation.
[d]There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.

BC: Breast cancer
OC: Ovarian cancer
RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued

CDH1) and provided a means of characterizing the specific gene mutation or mutations present in certain individuals and families exhibiting an increased risk for cancer. 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. Multigene testing should focus on identifying a mutation known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of a mutation. For some of the genes included as part of multigene testing, especially some low- to moderate-risk genes, there is currently a lack of evidence regarding proper risk management strategies that should follow testing.[5]

Risk Management Recommendations for Moderate-Penetrance Genes Associated With Breast and/or Ovarian Cancer

Penetrance, as it applies to genetic mutations, refers to the probability of a clinical condition, such as breast or ovarian cancer, developing in the presence of a specific genotype. In the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the panel primarily focuses on assessment of known high-penetrance mutations (ie, *BRCA1/2*, *TP53*, *PTEN*) and recommendations for genetic testing, counseling, and management strategies in individuals with these mutations. The following sections include a description of moderate-penetrance genes that the panel argues warrant additional screening beyond what is recommended in the general population (ie, those without the specific gene mutation). These include mutations for *ATM*, *BRIP1*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, and *STK11*. Risk management for genetic mutations associated with Lynch syndrome and neurofibromatosis type 1 are also described. During the 2017 guidelines update meeting, the panel extensively revised their risk management recommendations for these moderate-penetrance genes (see GENE-2, GENE-3, GENE-4, pages 11–13)

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BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]

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Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast at 30 y • RRM: Consider based on family history.	**Unknown or insufficient evidence for OC risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of BC** • See Cowden Syndrome Management	**No increased risk of OC**	See Cowden Syndrome Management
RAD51C	**Unknown or insufficient evidence for BC risk**	**Increased risk of OC** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Unknown or insufficient evidence for BC risk**	**Increased risk of OC** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of BC** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal • RRM: Evidence insufficient, manage based on family history.	**Increased risk of non-epithelial OC** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
TP53	**Increased risk of BC** • See Li-Fraumeni Syndrome Management	**No increased risk of OC**	See Li-Fraumeni Syndrome Management

[a]Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.

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GENE-4

The question of when to initiate risk management in mutation carriers of moderate-penetrance genes was discussed at length during the panel meeting for the 2017 update. This included consideration and adoption of an absolute-risk approach as proposed by Tung et al.[6] Specifically, these investigators posited that, for carriers of moderately penetrant genetic mutations (ie, *ATM*, *CHEK2*, *NBN*), screening with mammography should begin when the estimated 5-year risk of developing breast cancer exceeds 1%, consistent with recommendations for the average-risk population. Likewise, breast MRI screening in these carriers should begin when the estimated 5-year risk of developing breast cancer exceeds 2.2%. However, they also noted that, for practical reasons, it is reasonable to begin MRI and mammographic screening at the same time. It is important to note that the age at which breast screening is recommended may be impacted by the presence of risk factors such as family history of breast cancer, especially early-onset breast cancer.[6] There is currently insufficient evidence to recommend risk-reducing mastectomy in carriers of moderately penetrant genetic mutations,[6] although this option may be considered and discussed in the context of a personal or family history of breast cancer.

There is insufficient evidence to recommend a specific age at which risk-reducing salpingo-oophorectomy (RRSO) should be considered in carriers of moderately penetrant genetic mutations associated with ovarian cancer (ie, *BRIP1*, *RAD51C*, *RAD51D*). The decision to perform RRSO should not be made lightly, given the impact of premature menopause. Therefore, Tung et al,[6] who performed an analysis of ovarian cancer risk in carriers of moderately penetrant genetic mutations, argued that RRSO should not be considered until a woman's expected lifetime risk of developing ovarian cancer exceeds 2.6%, which is the expected lifetime risk of a woman with a *BRCA*-negative family history of ovarian cancer. A discussion about risk-reducing surgery may be

initiated earlier if there is a family history of early-onset ovarian cancer.

Lower penetrance genes that may be included as part of multigene testing, but for which there is currently insufficient evidence of an association with breast and/or ovarian cancer, include: *BARD1*, *FANCC*, *MRE11A*, *MUTYH* heterozygotes, *REQL*, *RAD50*, *RET1*, *SLX4*, *SMARCA4*, and *XRCC2*. Risk management recommendations for these genes should take into account family history and other clinical factors.

ATM Mutations

Mutations in the *ATM* (ataxia-telangiectasia mutated) gene may increase the risk for breast cancer. A meta-analysis of 3 cohort studies of relatives with ataxia-telangiectasia showed an estimated relative risk of 2.8 (90% CI, 2.2–3.7; *P*<.001).[7] In a sample of 488 women with nonmetastatic breast cancer, 1% had an *ATM* mutation.[8] An analysis of 82 Dutch patients with early-onset breast cancer showed that 8.5% (n=7) of the patients had a detected *ATM* mutation.[9]

The association between specific types of *ATM* genetic variants and breast cancer susceptibility is less clear,[10–12] with some evidence showing that certain missense mutations may act in a dominant-negative fashion to increase cancer risk, relative to truncating mutations.[10,11] A meta-analysis including 5 studies showed that *ATM* mutation carriers have a 38% lifetime risk of developing breast cancer, with carriers of the c.7271T>G missense mutation having a 69% risk of developing breast cancer by age 70 years.[13] An analysis of 27 families in which pathogenic *ATM* variants were identified showed an association between the c.7271T>G variant and increased risk of breast cancer (hazard ratio [HR], 8.0; 95% CI, 2.3–27.4; *P*<.001).[14]

Results of the case-control WECARE study suggested that radiation exposure may be associated with increased risk of contralateral breast cancer in women who are carriers of rare *ATM* missense variants predicted to be deleterious.[15] However, a meta-analysis including 5 studies showed that radiation therapy (with conventional dosing) is not contraindicated in patients with a heterozygous *ATM* mutation.[13] Therefore, there is currently insufficient evidence to recommend against radiation therapy in women who are carriers diagnosed with cancer.

The panel recommends annual mammogram for women with a mutated *ATM* gene beginning at age 40 years, with consideration of annual breast MRI. Risk-reducing mastectomy may also be considered based on family history. Given the association between *ATM* and development of the autosomal recessive condition ataxia telangiectasia, counseling for carriers of *ATM* mutations should include a discussion of reproductive options.

BRIP1 Mutations

In an observational study including 1,915 unselected ovarian cancer cases, 1.4% of patients had a mutation in the *BRCA1* interaction protein C-terminal helicase 1 gene (*BRIP1*),[16] which is a Fanconi anemia gene. An analysis of 3,236 women with epithelial ovarian cancer, 3,431 controls, and 2,000 unaffected high-risk women from an ovarian cancer screening trial (UKFOCSS) showed that *BRIP1* is associated with an increased risk for ovarian cancer (*P*<.001), with the relative risk (RR) for invasive epithelial ovarian cancer being 11.22 (95% CI, 3.22–34.10; *P*<.001) and 14.09 for high-grade serous disease (95% CI, 4.04–45.02; *P*<.001).[17] An analysis of an Icelandic population (656 ovarian cancer cases, 3,913 controls) also showed an association between *BRIP1* and increased risk of ovarian cancer (odds ratio [OR], 8.13; 95% CI, 4.74–13.95; *P*<.001).[18] The cumulative lifetime risk of developing ovarian cancer by age 80 years in *BRIP1* mutation carriers is estimated to be 5.8% (95% CI, 3.6–9.1).[17]

Tung et al[6] argued that RRSO should not be considered in these mutation carriers until their cumulative risk exceeds that of a woman with a first-degree relative with a non–*BRCA*-related ovarian cancer (≈2.64%). For *BRIP1* mutation carriers, this would be around age 50 to 55 years. However, some women may have additive risk factors (eg, multiple family members with ovarian cancer, lack of parity),[19] and delaying the discussion of RRSO until age 50 years may miss some cases of early-onset ovarian cancer. Therefore, the panel recommends that RRSO in *BRIP1* mutation carriers be considered beginning at age 45 to 50 years. Ultimately, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in these mutation carriers.

BRIP1 is not believed to be significantly associated with increased risk of breast cancer, and no single truncating variant has been found to be associated with increased risk of breast cancer.[20] *BRIP1*

is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of *BRIP1* mutations should include a discussion of reproductive options.

CDH1 Mutations

Germline mutations in *CDH1* are associated with hereditary diffuse gastric cancer and lobular breast cancer, and studies have reported a cumulative lifetime risk for breast cancer of 39% to 52%.[21,22] Given the considerable risk for lobular breast cancer in women with a *CDH1* mutation, the panel recommends screening with annual mammogram (or consideration of breast MRI) beginning at age 30 years. Screening may be considered earlier in patients with a family history of early-onset breast cancer. The option of risk-reducing mastectomy should be discussed for these carriers.

CHEK2 Mutations

Another breast cancer susceptibility gene that has been identified is *CHEK2* (cell cycle checkpoint kinase 2). In a study of *BRCA*-negative patients with breast cancer who have a strong family history of breast or ovarian cancer, a *CHEK2* mutation was detected in 5%.[23] Deleterious *CHEK2* mutations have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America.[24–26] The cumulative lifetime risk for breast cancer in women with *CHEK2* mutations and familial breast cancer has been estimated to range from approximately 28% to 37%, and is higher in women with stronger family histories of breast cancer than those without.[27,28] The estimated relative risk of breast cancer, based on data from 2 large case-control studies, was 3.0 (90% CI, 2.6–3.5).[7]

Studies investigating the association between breast cancer risk and specific *CHEK2* variants have primarily been based on the truncating variant 1100delC. An analysis from the Copenhagen General Population Study (N=86,975) showed that *CHEK2* 1100delC heterozygotes had an increased risk of breast cancer when analyses were stratified by age and sex (HR, 2.08; 95% CI, 1.51–2.85).[29] A case-control study (10,860 cases and 9,065 controls) performed by the CHEK2 Breast Cancer Case-Control Consortium of Europe and Australia showed that the 1100delC variant is associated with an increased risk of breast cancer, even in women unselected for family history (OR, 2.34; 95% CI, 1.72–3.20; $P<.001$).[30] Another case-control study (44,777 cases and 42,997 controls) showed that heterozygous 1100delC carriers have a significantly increased risk of developing estrogen receptor (ER)–positive breast cancer (OR, 2.55; 95% CI, 2.10–3.10; $P<.001$), but not ER-negative breast cancer (OR, 1.32; 95% CI, 0.93–1.88; $P=.12$).[31] Results from a meta-analysis including 18 case-control studies (26,336 cases and 44,219 controls) showed that the missense variant I157T is associated with increased risk of breast cancer (OR, 1.58; 95% CI, 1.42–1.75; $P<.001$).[32]

The panel recommends annual mammogram beginning at age 40 years for women with a mutated *CHEK2* gene, with consideration of annual breast MRI. Forty years was chosen by the panel as the age at which to begin breast screening, taking into account the average 5-year risk of breast cancer in *CHEK2* mutation carriers (see "*ATM* Mutations," opposite page), based on risk data that only takes into account frameshift mutations such as 1100delC.[6] There are no data on the benefit of risk-reducing mastectomy for women with *CHEK2* mutations,[6] but this procedure may be considered based on family history.

MLH1, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* Mutations

Women with Lynch syndrome are at increased risk of endometrial and ovarian cancers (up to 60% and 24%, respectively).[33–36] Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women who have completed childbearing and carry a *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* mutation.[37–42] No clear evidence supports routine screening for gynecologic cancers in these mutation carriers. Annual endometrial sampling may be considered, but the benefit is uncertain.[37,42–46] Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific,[37,43–47] but there may be circumstances in which these tests may be helpful.

Some studies have suggested that female *MLH1* mutation carriers may be at increased risk for breast cancer, with one study estimating an 18.6% cumulative risk to age 70 years (95% CI, 11.3–25.9).[48] However, not enough evidence currently exists for

the panel to recommend breast screening for women with Lynch syndrome beyond that which is recommended for the average-risk population.

More information regarding risk management recommendations for Lynch syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

NBN Mutations

The *NBN* gene is responsible for producing the protein nibrin. Women with heterozygous *NBN* mutations are at increased risk of developing breast cancer (OR, 3.1, 95% CI, 1.4–6.6; *P*=.004).[49] A meta-analysis including 7 studies showed a significant association between the variant 657del5 and breast cancer risk (OR, 2.42; 95% CI, 1.54–3.80).[50] An analysis of women with breast cancer in Poland (N=562) showed that this founder mutation is associated with early-onset breast cancer (OR, 8.36; 95% CI, 2.57–27.27; *P*<.001).[51] The panel recommends annual mammogram for women with a mutated *NBN* gene beginning at age 40 years, with consideration of annual breast MRI. Forty years was chosen by the panel as the age at which to begin breast screening, taking into account the average 5-year risk of breast cancer in these mutation carriers (see earlier discussion).[6] This recommendation is based primarily on data derived from the Slavic truncating mutation 657del5.[49–52] There are no data on the benefit of risk-reducing mastectomy for women with *NBN* mutations. Therefore, risk-reducing mastectomy is not recommended in these mutation carriers, but this procedure may be considered based on family history. The *NBN* gene is associated with development of the autosomal recessive condition Nijmegen breakage syndrome. Therefore, counselling for carriers of *NBN* mutations should include a discussion of reproductive options.

NF1 Mutations

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary cancer syndrome that is caused by an *NF1* mutation. NF1 is associated with increased risk of malignant peripheral nerve sheath tumors, other central nervous system tumors, and gastrointestinal stromal tumors.[53–56] A population-based study in Finland of 1,404 patients with NF1 showed an estimated lifetime cancer risk of 59.6%.[53] This study showed a significant association between NF1 and an increased risk of breast cancer (standardized incidence ratio [SIR], 3.04; 95% CI, 2.06–4.31; *P*<.001). Among patients with breast cancer, NF1 was associated with poorer survival, with 5-year survival rates of 67.9% compared with 87.8% in patients without NF1. Excess incidence was highest in women younger than age 40 years (SIR, 11.10; 95% CI, 5.56–19.50; *P*<.001). A population-based study in England of 848 patients with NF1 also showed an increased risk of breast cancer (SIR, 3.5; 95% CI, 1.9–5.9), especially among women younger than 50 years (SIR, 4.9; 95% CI, 2.4–8.8).[57] Cumulative lifetime risk of developing breast cancer by age 50 years was 8.4% in this sample.

Given the increased risk of early-onset breast cancer in these mutation carriers, annual breast screening with mammography should begin at age 30 years.[58] Screening with breast MRI could also be considered. A prospective study of patients with NF1 from the United Kingdom (N=448) showed that breast cancer risk in these mutation carriers is not significantly increased at age 50 years and beyond.[56] Case-control analyses of women with NF1 from England showed that RR estimates for women aged 30 to 39 years was 6.5 (95% CI, 2.6–13.5) and 4.4 for women aged 40 to 49 years (95% CI, 2.5–7.0).[59] RR estimates then decrease for women aged 50 to 59 years (RR, 2.6; 95% CI, 1.5–4.2), and continue to decrease as age increases (RR, 1.9; 95% CI, 1.0–3.3 for age 60–69 years, and RR, 0.8; 95% CI, 0.2–2.2 for age 70–79 years). These studies show that, beginning at age 50 years, breast cancer risk in women with NF1 may not significantly differ from that of women in the general population. Therefore, breast MRI screening in patients with NF1 may be discontinued at age 50 years. There are no data regarding the benefit of risk-reducing mastectomy for women with *NF1* mutations. Therefore, risk-reducing mastectomy is not recommended in these patients, but this procedure may be considered based on family history. Complications related to NF1 may appear early in life, and these have the potential to be severe.[60] Therefore, referral to a neurofibromatosis specialist for management is recommended.

PALB2 Mutations

PALB2 (partner and localizer of *BRCA2*) is a Fanconi anemia gene. Mutations in this gene are associated with increased risk for breast cancer, with studies of women with breast cancer showing that

1% to 3% harbor a pathogenic *PALB2* mutation.[61–64] A meta-analysis of 3 studies estimated a relative risk of 5.3 (90% CI, 3.0–9.4).[7] Breast cancer risk increases with age in women with a *PALB2* mutation, with a 14% lifetime risk by age 50 years and a 35% lifetime risk by age 70 years.[65] The risk also increases with increasing number of relatives affected with breast cancer. Breast cancer risk by age 70 years for those with no first-degree relative with breast cancer was 33% compared with 58% in those with 2 first-degree relatives.[65] In a recently published Polish study of patients with breast cancer who underwent genetic testing, contralateral breast cancer was reported in 10% of *PALB2* carriers.[64] This study also showed that the 10-year survival rate among *PALB2* carriers with breast cancer was 48%, compared with 72% in *BRCA1* mutation carriers and 75% in noncarriers ($P<.001$). Further, 10-year survival among those with tumors ≥2 cm was substantially worse (32.4%) than those with tumors <2 cm (82.4%; HR, 7.04; 95% CI, 2.47–20.07; $P<.001$).

The panel recommends annual mammogram for *PALB2* mutation carriers beginning at age 30 years, because this is the age when the average 5-year risk of breast cancer in these mutation carriers exceeds 1%.[6,65] Breast MRI screening may also be considered, as well as risk-reducing mastectomy. Though some studies suggest that there may be an association between *PALB2* and increased ovarian cancer risk,[16,66] there is currently insufficient evidence to consider RRSO in these mutation carriers. *PALB2* is associated with Fanconi anemia, inherited in an autosomal recessive manner.[67] Therefore, counseling for carriers of *PALB2* mutations should include a discussion of reproductive options.

RAD51C and *RAD51D* Mutations

Genes in the *RAD51* protein family are involved in homologous recombination and DNA repair. *RAD51C* and *RAD51D* have been shown to be associated with an increased risk of ovarian cancer. In an observational study including 1,915 unselected ovarian cancer cases, 1.1% of patients had either a *RAD51C* or *RAD51D* mutation.[16] In a comparison of 1,132 probands with a family history of ovarian cancer and 1,156 controls, *RAD51C* was associated with an increased risk of ovarian cancer (RR, 5.88; 95% CI, 2.91–11.88; $P<.001$).[68] Analyses from the same trial (911 probands and 1,060 controls) also showed an association between *RAD51D* and an increased risk of ovarian cancer (RR, 6.30; 95% CI, 2.86–13.85; $P<.011$).[69] In a case-control analysis of 3,429 women with epithelial ovarian cancer and 2,772 controls, both *RAD51C* (OR, 5.2; 95% CI, 1.1–24; $P=.035$) and *RAD51D* (OR, 12.0; 95% CI, 1.5–90; $P=.019$) were associated with an increased risk for ovarian cancer.[70]

The cumulative risk of developing ovarian cancer in carriers of a *RAD51C* mutation does not approach 2.6% (ie, the expected lifetime risk of a woman with a first-degree relative with ovarian cancer) until age 60 to 64 years, with a cumulative risk of 1.5% between the ages of 55 and 59 years.[6,70] In carriers of a *RAD51D* mutation, the cumulative risk approaches 2.6% around age 50 to 54 years. As with carriers of a *BRIP1* mutation, there may be the presence of additive risk factors that may increase the risk of early-onset ovarian cancer. Therefore, the panel recommends that RRSO in *RAD51C* and *RAD51D* mutation carriers be considered beginning at age 45 to 50 years. As with *BRIP1* mutations, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in *RAD51C* and *RAD51D* mutation carriers.

There is currently insufficient evidence that mutations in *RAD51C* and *RAD51D* are associated with increased risk of breast cancer. Therefore, carriers of these gene mutations are advised to follow guidelines for women at average risk of developing breast cancer. *RAD51C* is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of *RAD51C* mutations should include a discussion of reproductive options.

STK11 Mutations

Germline mutations in *STK11* are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers as well as breast or nonepithelial ovarian cancers. Breast cancer risk in women with Peutz-Jeghers syndrome is 8% at age 40 years, 13% at age 50 years, 31% at age 60 years, and 45% at age 70 years.[71] There are no data on the benefit of risk-reducing mastectomy for women with *STK11* mutations. Therefore, risk-reducing mastectomy is

not recommended in these patients, but this procedure may be considered based on family history. Information regarding screening for patients with Peutz-Jeghers syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

Summary and Conclusions

During the panel meeting for the 2017 update, members discussed a number of important updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, including principles of multigene testing and risk management recommendations for moderately penetrant genetic mutations associated with breast and/or ovarian cancer. In the guidelines, risk management recommendations are described for carriers of the following mutations: *ATM*, *BRIP1*, *CDH1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, and *STK11*. Recommendations for genetic mutations associated with Lynch syndrome and NF1 are also described. Multigene testing should be offered in the context of professional genetic counseling. Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries. The evidence supporting risk management recommendations for mutations in genes of moderate, low, and uncertain penetrance is continuing to evolve, and it is important for these recommendations to reflect the current evidence base.

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Posttest Questions

1. According to the 2017 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the following gene mutations are associated with increased risk of breast cancer:
   a. *ATM*
   b. *CHEK2*
   c. *PALB2*
   d. a and b
   e. a and c
   f. all of the above
2. True or False: A 62-year-old woman with an *NF1* mutation and no family history of breast cancer should receive an annual breast MRI with contrast.
3. According to the 2017 NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, at which age should a woman with a *BRIP1* mutation and no family history of ovarian cancer consider RRSO?
   a. 18 years
   b. 30 years
   c. 40 years
   d. 48 years