Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021

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ABSTRACT

The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic focus primarily on assessment of pathogenic or likely pathogenic variants associated with increased risk of breast, ovarian, and pancreatic cancer and recommended approaches to genetic testing/counseling and management strategies in individuals with these pathogenic or likely pathogenic variants. This manuscript focuses on cancer risk and risk management for BRCA-related breast/ovarian cancer syndrome and Li-Fraumeni syndrome. Carriers of a BRCA1/2 pathogenic or likely pathogenic variant have an excessive risk for both breast and ovarian cancer that warrants consideration of more intensive screening and preventive strategies. There is also evidence that risks of prostate cancer and pancreatic cancer are elevated in these carriers. Li-Fraumeni syndrome is a highly penetrant cancer syndrome associated with a high lifetime risk for cancer, including soft tissue sarcomas, osteosarcomas, premenopausal breast cancer, colon cancer, gastric cancer, adrenocortical carcinoma, and brain tumors.

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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.

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All recommendations are category 2A unless otherwise noted.

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

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The complete NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Panel members can be found on page 102. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES

(This can include *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, and *TP53* among others. See GENE-A for a more complete list.)^{a,b,c,d}

Testing is clinically indicated in the following scenarios:

1. Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2. Individuals meeting the criteria below but tested negative with previous limited testing (eg, single gene and/or absent deletion/duplication analysis) interested in pursuing multi-gene testing
3. **Personal history of cancer**
 - Breast cancer with at least one of the following:
 - ▶ Diagnosed at age ≤45 y; or
 - ▶ Diagnosed at age 46–50 y with:
 - ◊ Unknown or limited family history;^e or
 - ◊ A second breast cancer diagnosed at any age; or
 - ◊ ≥1 close blood relative^f with breast, ovarian, pancreatic, or prostate cancer at any age
 - ▶ Diagnosed at age ≤60 y with triple-negative breast cancer;
 - ▶ Diagnosed at any age with:
 - ◊ Ashkenazi Jewish ancestry; or
 - ◊ ≥1 close blood relative^f with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic,^g intraductal/ciribiform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer at any age; or
 - ◊ ≥3 total diagnoses of breast cancer in patient and/or close blood relatives^f
 - ▶ Diagnosed at any age with male breast cancer
 - Epithelial ovarian cancer^h (including fallopian tube cancer or peritoneal cancer) at any age
 - Exocrine pancreatic cancer at any age (See CRIT-3*)
 - Prostate cancer at any age with:
 - ▶ Metastatic,^g intraductal/ciribiform histology, or high- or very-high-risk group (see NCCN Guidelines for Prostate Cancerⁱ);
 - ▶ Any NCCN risk group (see NCCN Guidelines for Prostate Cancer) with the following family history:
 - ◊ Ashkenazi Jewish ancestry; or
 - ◊ ≥1 close relative^f with breast cancer at age ≤50 y or ovarian, pancreatic, metastatic,^g or intraductal/ciribiform prostate cancer at any age; or
 - ◊ ≥2 close relatives^f with either breast or prostate cancer (any grade) at any age
 - A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
 - Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (see CRIT-4*) or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria (see CRIT-5*)
 - To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancerⁱ

Footnotes
on CRIT-2A*

Continued on next page

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CRIT-1

Overview

Specific patterns of hereditary breast and ovarian cancers have been found to be linked to pathogenic or likely pathogenic variants in the *BRCA1/2* genes.^{1,2} In addition, Li-Fraumeni syndrome (LFS), a very rare hereditary cancer syndrome, is related to germline pathogenic or likely pathogenic variants in the *TP53* gene.³ These hereditary syndromes share several features beyond elevation of breast cancer risk. These syndromes arise from germline pathogenic or likely pathogenic variants that are not within sex-linked genes; hence, the variants can be inherited from either parent. The syndromes are associated with breast cancer onset at an early age and development of other types of cancer, and exhibit an autosomal dominant inheritance pattern. Offspring of an individual with one of these hereditary syndromes have a 50% chance of inheriting the pathogenic or likely pathogenic variant. In addition, individuals with these hereditary syndromes share increased risks for multiple cases of early-onset disease as well as bilateral disease. The pathogenic or likely pathogenic variants associated with these hereditary syndromes are

considered to be highly penetrant. In addition, the manifestations (ie, expression) of these hereditary syndromes are often variable in individuals within a single family (eg, age of onset, tumor site, number of primary tumors). The risk of developing cancer in individuals with one of these hereditary syndromes depends on numerous variables including the gender and age of the individual.

Before 2020, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (Breast, Ovarian, and Pancreatic as of 2020) focused largely on testing criteria for *BRCA1/2* and appropriate risk management for carriers of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant. Based on strong evidence that genes beyond *BRCA1/2* confer markedly increased risk of breast and/or ovarian cancers, these guidelines have been expanded; see GENE-A in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at NCCN.org). This manuscript focuses on cancer risk and risk management for BRCA-related breast/ovarian cancer syndrome and LFS.

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST AND/OR OVARIAN CANCER SUSCEPTIBILITY GENES
(This can include *BRCA1*, *BRCA2*, *CDH1*, *PALB2*, *PTEN*, and *TP53* among others. See GENE-A for a more complete list.)^{a,b,c,d}

Testing is clinically indicated in the following scenarios (continued):

4. Family history of cancer

- An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making).^f
 - ▶ If the affected relative has pancreatic cancer or prostate cancer (metastatic, intraductal/criform, or NCCN Guidelines for Prostate Cancer - High- or Very-High-Risk Group), only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.
- An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)^g

Testing may be considered in the following scenarios (with appropriate pre-test education and access to post-test management):

1. Multiple primary breast cancers, first diagnosed between the ages of 50 and 65 y
2. An Ashkenazi Jewish individual^h
3. An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%–5% probability of *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)^h

There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios:

1. Women diagnosed with breast cancer at age >65 y, with no close relative^f with breast, ovarian, pancreatic, or prostate cancer
2. Men diagnosed with localized prostate cancer with Gleason Score <7 and no close relative^f with breast, ovarian, pancreatic, or prostate cancer

Criteria met → See GENE-1*

If 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†

Footnotes on CRIT-2A*

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CRIT-2

BRCA-Related Breast/Ovarian Cancer Syndrome

Both the *BRCA1* and *BRCA2* genes encode for proteins involved in tumor suppression. *BRCA1/2* pathogenic or likely pathogenic variants can be highly penetrant, although the probability of cancer development in carriers of *BRCA1/2* pathogenic or likely pathogenic variants is variable, even within families with the same variant.^{4–6} At present, it is unclear whether penetrance is related only to the specific pathogenic or likely pathogenic variant identified in a family or whether additional factors, either genetic or environmental, affect disease expression. It is generally accepted, however, that carriers of *BRCA1/2* pathogenic or likely pathogenic variants have an excessive risk for both breast and ovarian cancer that warrants consideration of more intensive screening and preventive strategies.

Testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes, including *BRCA1* and *BRCA2*, can be viewed on CRIT-1 and CRIT-2 (pages 78 and 79).

Breast Cancer Risk

Estimates of penetrance range from a 41%–90% life-time risk for breast cancer, with an increased risk for

contralateral breast cancer.^{7–15} A prospective cohort study including 9,856 unaffected *BRCA1/2* carriers showed that a cumulative risk of breast cancer by 80 years of age was 72% for carriers of a pathogenic *BRCA1* variant and 69% for carriers of a *BRCA2* variant.¹⁶ Estimates of cumulative risk for contralateral breast cancer 20 years after breast cancer diagnosis are 40% for carriers of a pathogenic *BRCA1* variant and 26% for carriers of a pathogenic *BRCA2* variant.¹⁶

The evidence that a pathogenic variant in *BRCA1/2* is associated with poor survival outcomes for breast cancer has been inconsistent.^{17,18} A meta-analysis including 13 studies showed that carriers of a pathogenic *BRCA1* variant with breast cancer had worse overall survival (OS) compared with those without a *BRCA* mutation (hazard ratio [HR], 1.50; 95% CI, 1.11–2.04), while harboring a *BRCA2* mutation was not significantly associated with worse survival.¹⁹ A more recent meta-analysis including 60 studies and 105,220 patients with breast cancer also found that carriers of a pathogenic *BRCA1* variant had worse OS compared with noncarriers (HR, 1.30; 95% CI, 1.11–1.52; *P*=.001).²⁰ Carriers of a pathogenic *BRCA2* variant had worse breast cancer-specific survival compared with noncarriers (HR, 1.29; 95% CI, 1.03–1.62;

TESTING CRITERIA FOR LI-FRAUMENI SYNDROME^a

FOLLOW-UP

- Individual from a family with a known *TP53* pathogenic/likely pathogenic variant
- Classic Li-Fraumeni syndrome (LFS) criteria:^p
 - ▶ Combination of an individual diagnosed at age <45 years with a sarcoma^q
AND
A first-degree relative diagnosed at age <45 years with cancer
AND
An additional first- or second-degree relative in the same lineage with cancer diagnosed at age <45 years, or a sarcoma at any age
- Chompret criteria:^{r,s}
 - ▶ Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age
OR
 - ▶ Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years
OR
 - ▶ Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history
OR
 - ▶ Breast cancer before 31 years of age
- Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing^t

LFS testing
criteria met

→ See GENE-1*

If LFS testing
criteria not
met, consider
testing
for other
hereditary
syndromes, if
appropriate

Individualized
recommendations
according to
personal and
family history

^a For further details regarding the nuances of genetic counseling and testing, see EVAL-A.

^p Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 1988;48:5358-5362.

^q To date, there have been no reports of Ewing sarcoma, gastrointestinal stromal tumor (GIST), desmoid tumor, or angiosarcoma in *TP53* pathogenic/likely pathogenic variant carriers.

*Available online, in these guidelines, at NCCN.org.

^r Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. *J Med Genet* 2001;38:43-47.

^s Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from *TP53* mutation carriers. *J Clin Oncol* 2015;33:2345-2352.

^t This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic *TP53* pathogenic/likely pathogenic variants are common in many tumor types in absence of a germline pathogenic/likely pathogenic variant.

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CRIT-4

$P=.03$), though OS was not significantly different. This meta-analysis also showed that, among patients with triple-negative breast cancer, *BRCA1/2* mutations are associated with better OS (HR, 0.49; 95% CI, 0.26–0.92; $P=.03$). However, this subgroup analysis only included 2 studies. A third meta-analysis including 66 studies also showed that a *BRCA2* mutation was associated with worse breast cancer-specific survival (HR, 1.57; 95% CI, 1.29–1.86), but study results were too heterogeneous for the analysis to be conclusive.²¹ Results of the prospective cohort Prospective Outcomes in Sporadic versus Hereditary breast cancer (POSH) study including 2,733 women with breast cancer showed no significant differences in OS between carriers of a pathogenic *BRCA1/2* variant and noncarriers 2, 5, and 10 years after diagnosis.²²

BRCA1/2 pathogenic variants are associated with early-onset breast cancer. In a sample of 21,401 families who met German Consortium for Hereditary Breast and Ovarian Cancer testing criteria for *BRCA1/2* mutations, a mutation was detected in 13.7% of families with a single case of breast cancer diagnosed at younger than 36 years of age.²³ An analysis of 6,478 patients who

were diagnosed with breast cancer before 50 years of age showed that carriers of a pathogenic *BRCA1* variant had worse OS compared with patients who were not carriers of a pathogenic *BRCA1/2* variant (HR, 1.28; 95% CI, 1.05–1.57; $P=.01$), but this association was no longer statistically significant when taking into account disease and treatment characteristics (HR, 1.20; 95% CI, 0.97–1.47; $P=.09$).²⁴ *BRCA2* mutations were not significantly associated with decreased OS in these analyses, except for the first 5 years of follow-up (HR, 1.56; 95% CI, 1.06–2.28; $P=.02$). There may be a genetic anticipation effect in carriers of a pathogenic *BRCA1/2* variant in that age of disease onset may become lower over time as *BRCA1/2* mutation testing has become more common, with an increase in knowledge about improved breast cancer screening in carriers of a pathogenic *BRCA1/2* variant.²⁵ However, an analysis of 176 families with a known *BRCA1/2* variant and more than 2 family members with breast or ovarian cancer in consecutive generations showed that this decrease in age of onset across generations may be due to a cohort effect, specifically lifestyle or environmental factors such as increased use of oral contraceptives and increased obesity rates.²⁶

**BRCA PATHOGENIC/LIKELY PATHOGENIC
VARIANT-POSITIVE MANAGEMENT**

WOMEN

- Breast awareness^a starting at age 18 years.
 - Clinical breast exam, every 6–12 months,^b starting at age 25 years.
 - Breast screening^{c,d}
 - ▶ Age 25–29 years, annual breast MRI^e screening with contrast^f (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
 - ▶ Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI^e screening with contrast.
 - ▶ Age >75 years, management should be considered on an individual basis.
 - ▶ For women with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram with consideration of tomosynthesis and breast MRI should continue as described above.
 - Discuss option of risk-reducing mastectomy
 - ▶ Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
 - Recommend risk-reducing salpingo-oophorectomy (RRSO),^g typically between 35 and 40 years, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. 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, hormone replacement therapy, and related medical issues.
 - Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
 - Limited data suggest that there may be a slightly increased risk of serous uterine cancer among women with a *BRCA1* pathogenic/likely pathogenic variant. The clinical significance of these findings is unclear. Further evaluation of the risk of serous uterine cancer in the *BRCA* population needs to be undertaken. The provider and patient should discuss the risks and benefits of concurrent hysterectomy at the time of RRSO for women with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery. Women who undergo hysterectomy at the time of RRSO are candidates for estrogen alone hormone replacement therapy, which is associated with a decreased risk of breast cancer compared to combined estrogen and progesterone, which is required when the uterus is left in situ (Chlebowski R, et al. JAMA Oncol 2015;1:296-305).
 - Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
 - For those patients who have not elected RRSO, transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion starting at age 30–35 y.
 - Consider risk reduction agents as options for breast and ovarian cancer, including discussion of risks and benefits (See Discussion for details).
- (See NCCN Guidelines for Breast Cancer Risk Reduction[†]).

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Footnotes on
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Continued

BRCA-A
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Some histopathologic features have been reported to occur more frequently in breast cancers of individuals with a germline *BRCA1/2* pathogenic or likely pathogenic variant. For example, several studies have shown that *BRCA1*-related breast cancer is more likely to be characterized as ER-/PR-negative and HER2-negative (ie, “triple negative”).^{15,27–32} Studies have reported *BRCA1* mutations in 7%–16% of patients with triple-negative breast cancer.^{15,32–39} The incidence of *BRCA2* mutations range from 1% to 17% in studies of triple-negative breast cancer cases unselected for age or family history.^{15,36,37,39–41} One cohort study showed that hormone receptor-positive disease (ER+ and/or PR+) is associated with an absolute lifetime risk of 40% in carriers of a pathogenic *BRCA2* variant.¹⁵ A case-control study showed that the 20-year survival rate in carriers of a pathogenic *BRCA2* variant with ER-positive tumors was 62.2%, compared with 83.7% in those with ER-negative tumors, though this difference was only statistically significant in those younger than age 50 (n=199; 68.3% vs 91.3%, respectively; *P*=.03).⁴² A case-control study of carriers of the Icelandic founder *BRCA2* variant 999del5 showed that ER-positive disease was

associated with increased mortality risk, compared with those with ER-negative disease (HR, 1.94; 95% CI, 1.22–3.07; *P*=.005).⁴³ However, prevalence of ER-negative disease was not significantly greater in carriers of a pathogenic *BRCA2* variant than in noncarriers (75.6% vs 70.2%, respectively; *P*=.11).

Among patients with triple-negative disease, carriers of a pathogenic *BRCA1/2* variant were diagnosed at a younger age compared with noncarriers.^{34,44} In a study of a large cohort of patients with triple-negative breast cancer (n=403), the median age of diagnosis among carriers of a pathogenic *BRCA1* variant (n=65) was 39 years.³³ Patients in this population-based study were unselected for family history or age. Among the group of patients with early-onset (age at diagnosis <40 years) triple-negative breast cancer (n=106), the incidence of *BRCA1* mutations was 36%; the incidence was 27% among those diagnosed before 50 years of age (n=208). Result from the prospective cohort POSH study showed that, among 558 patients with triple-negative breast cancer, 2-year OS was greater in carriers of a pathogenic *BRCA1/2* variant than in noncarriers (95% vs 91%, respectively; HR, 0.59; 95% CI, 0.35–0.99; *P*=.047), but

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

MEN

- Breast self-exam training and education starting at age 35 years
- Clinical breast exam, every 12 months, starting at age 35 years
- Consider annual mammogram screening in men with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family (whichever comes first)^h
- Starting at age 40 years: (See Guidelines for Prostate Cancer Early Detection[†])
 - ▶ Recommend prostate cancer screening for *BRCA2* carriers
 - ▶ Consider prostate cancer screening for *BRCA1* carriers

MEN AND WOMEN

- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.
- Education regarding signs and symptoms of cancer(s), especially those associated with *BRCA* gene pathogenic/likely pathogenic variants.
- No specific screening guidelines exist for melanoma, but general melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure.
- For pancreatic cancer screening recommendations, see PANC-A*.

RISK TO RELATIVES

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

REPRODUCTIVE OPTIONS

- For individuals of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.

^a 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.

^b 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.

^c The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, Lee JM, Kong CY, et al. Cancer 2012;118:2021-2030.

^d Lehman CD, Lee JM, DeMartini WB, et al. Screening MRI in women with a personal history of breast cancer. J Natl Cancer Inst 2016;108.

^e The criteria for high-quality breast MRI include a dedicated breast coil, the ability to perform biopsy under MRI guidance, radiologists experienced in breast MRI, and regional availability. Breast MRI is preferably performed on days 7–15 of a menstrual cycle for premenopausal women.

^f Breast MRI is preferred due to the theoretical risk of radiation exposure in pathogenic/likely pathogenic variant carriers.

^g 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.

^h There are only limited data to support screening for breast cancer in men. Gao Y, et al Radiology 2019;293:282-291.

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BRCA-A
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5- and 10-year OS did not differ significantly between these groups.²²

Male carriers of a pathogenic *BRCA1/2* variant also have a greater risk for cancer susceptibility.⁴⁵ Among male patients with breast cancer unselected for family history, 4%–14% tested positive for a germline *BRCA2* mutation.^{46–49} For males carrying a pathogenic *BRCA2* variant, the cumulative lifetime risk for breast cancer has been estimated at 7%–8%.^{50,51} The cumulative lifetime risk for male carriers of a pathogenic *BRCA1* variant is 1.2%.⁵¹ In contrast, for men who are not carriers of a pathogenic *BRCA1/2* variant, the lifetime risk for breast cancer has been estimated at approximately 0.1% (1 in 1,000).^{48,52}

Ovarian Cancer Risk

Increased risks for cancers of the ovary, fallopian tube, and peritoneum are observed in carriers of a pathogenic *BRCA1/2* variant.^{53–55} In the setting of an invasive ovarian cancer diagnosis, a pathogenic *BRCA1* variant has been found in 3.8%–14.5% of women, and a pathogenic *BRCA2* variant has been found in 4.2%–5.7% of women.^{13,56–59} Carriers of a pathogenic *BRCA1* variant

have an estimated 48.3% (95% CI, 38.8%–57.9%) cumulative risk of ovarian cancer by age 70, whereas the cumulative risk by age 70 is 20.0% (95% CI, 13.3%–29.0%) for carriers of a pathogenic *BRCA2* variant.⁶⁰

Several studies have reported more favorable survival outcomes among carriers of a pathogenic *BRCA1/2* variant in patients with ovarian cancer compared with noncarrier patients.^{61–67} Survival outcomes appear to be most favorable for carriers of a pathogenic *BRCA2* variant.^{61,66,68} Additionally, *BRCA2* mutations were associated with significantly higher response rates (compared with noncarriers or with *BRCA1* mutation carriers) to primary chemotherapy. In contrast, *BRCA1* mutations were not associated with prognosis or improved chemotherapy response.⁶⁶

The histology of ovarian cancers in carriers of a pathogenic *BRCA1/2* variant is more likely to be characterized as serous adenocarcinoma and high grade compared with ovarian cancers in nonmutation carriers, although endometrioid and clear cell ovarian cancers also have been reported in the former population.^{55,57,69–72} Mutations are also associated with nonmucinous ovarian carcinoma as opposed to mucinous.^{56,58} Mucinous

LI-FRAUMENI SYNDROME MANAGEMENT
IN ADULTS**BREAST CANCER RISK FOR WOMEN**

- Breast awareness^a starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 20 y.^b
- Breast screening
 - ▶ Age 20–29^b y, annual breast MRI^c screening with contrast.^d
 - ▶ Age 30–75 y, annual breast MRI^c screening with contrast and mammogram with consideration of tomosynthesis.
 - ▶ Age >75 y, management should be considered on an individual basis.
 - ▶ For women with a *TP53* pathogenic/likely pathogenic variant who are treated for breast cancer, and who have not had a bilateral mastectomy, screening with annual breast MRI and mammogram with consideration of tomosynthesis should continue as described above.
- Discuss option of risk-reducing mastectomy
 - ▶ Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.

OTHER CANCER RISKS

- Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers and second malignancies in cancer survivors every 6–12 mo.
- Colonoscopy and upper endoscopy every 2–5 y starting at 25 y or 5 y before the earliest known colon cancer in the family (whichever comes first).
- Annual dermatologic examination starting at 18 y.
- Annual whole body MRI^{e,f,g} (category 2B).
- Annual brain MRI (category 2B) may be performed as part of the whole body MRI or as a separate exam.

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

^b Or at the age of the earliest diagnosed breast cancer in the family, if younger than age 20 y.

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

^d Or mammogram with consideration of tomosynthesis, if MRI is unavailable. Breast MRI is preferred because of concerns regarding the risk of radiation exposure in pathogenic/likely pathogenic variant carriers.

^e Whole body MRI is not uniformly available. If whole body MRI is not available, then individuals with LFS are encouraged to participate in clinical trials or consider alternate comprehensive imaging methods. Other components of screening are being evaluated in protocols, including biochemical screening and regular blood screening for hematologic malignancies.

^f Ballinger M, Best A, Mai P, et al. Baseline surveillance in Li-Fraumeni syndrome using whole-body magnetic resonance imaging: a meta-analysis. *JAMA Oncol* 2017;3:1634–1639.

^g Screening through whole body MRI has been broadly demonstrated to be feasible and of potential utility in the early detection of cancer among classic LFS families, though it also results in the detection of false-positive findings and possible cancer overdiagnosis. Furthermore, screening utility has not been evaluated among those with a germline *TP53* pathogenic/likely pathogenic variant without a classic family history of LFS, who are increasingly identified through multi-gene panel tests.

Continued

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epithelial ovarian carcinomas may be associated with other gene mutations, such as *TP53* mutations,⁷³ which are implicated in LFS (see “Li-Fraumeni Syndrome,” page 92). Nonepithelial ovarian carcinomas (eg, germ cell and sex cord-stromal tumors) are not significantly associated with a *BRCA1/2* mutation.⁷⁴ Current data show that ovarian low malignant potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with a *BRCA1/2* mutation.⁵⁶

In studies of women carrying a pathogenic *BRCA1/2* variant who underwent risk-reducing salpingo-oophorectomy (RRSO), occult gynecologic neoplasia, both invasive carcinoma and intraepithelial lesions, were identified in 4.5%–9% of cases based on rigorous pathologic examinations of the ovaries and fallopian tubes.^{75–78} Tubal intraepithelial carcinoma (TIC) is thought to represent an early precursor lesion for serous ovarian cancers, and TIC (with or without other lesions) was detected in 5%–8% of cases from patients carrying a pathogenic *BRCA1/2* variant who underwent RRSO.^{75,79,80} The fimbriae or distal tube was reported to be the predominant site of origin for these early malignancies found in carriers of a pathogenic *BRCA1/2* variant.^{75,80,81}

Although TIC appeared to present more frequently among carriers of a pathogenic *BRCA1/2* variant compared with noncarriers undergoing RRSO,^{80,81} TIC has also been documented among patients with serous carcinomas unselected for family history or *BRCA* mutation status.⁸² Because TIC was identified in individuals who underwent surgery for risk reduction (for carriers of a pathogenic *BRCA1/2* variant) or other gynecologic indications, the incidence and significance of these early lesions within the general population is unclear.

Prostate Cancer Risk

Germline *BRCA1/2* mutations are associated with increased risk for prostate cancer,^{83–86} with this association being strongest for advanced or metastatic prostate cancer.^{87–90} Carriers of a pathogenic *BRCA1* variant have an estimated 29% (95% CI, 17%–45%) cumulative lifetime risk of prostate cancer, whereas the cumulative lifetime risk is 60% (95% CI, 43%–78%) for carriers of a pathogenic *BRCA2* variant.⁹¹ A study of a large cohort of patients from Spain with prostate cancer (n=2,019) showed that carriers of a pathogenic *BRCA1/2* variant had significantly higher rates of aggressive prostate cancer (Gleason

LI-FRAUMENI SYNDROME MANAGEMENT
IN ADULTS

OTHER ASPECTS OF MANAGING LFS

- This screening and management of LFS is complex; it is preferred that individuals with LFS be followed at centers with expertise in the management of this syndrome.
- Because of the remarkable risk of additional primary neoplasms, screening may be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).
- Address limitations of screening for many cancers associated with LFS.
- Pediatricians should be apprised of the risk of childhood cancers in affected families and review screening recommendations for children with LFS.^h
- Therapeutic RT for cancer should be avoided when possible; diagnostic radiation should be minimized to the extent feasible without sacrificing accuracy.
- Provide additional surveillance based on family history of cancer.
- Provide education regarding signs and symptoms of cancer.
- Address psychosocial and quality-of-life aspects of the complex management of LFS.
- There is controversy over how to manage cancer risk in incidental *TP53* carriers who do not meet classic LFS criteria; some data suggest lower cancer risks in *TP53* pathogenic/likely pathogenic carriers who do not have a family history consistent with LFS.

REPRODUCTIVE OPTIONS

- For individuals of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.

RISK TO RELATIVES

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

TESTING CONSIDERATIONS

- Somatic *TP53* variants frequently confound germline testing results. Late post-zygotic aberrant clonal expansions (ACEs) containing a pathogenic *TP53* variant, limited to the hematologic compartment or to a tumor, may be detected in the blood or saliva through germline testing, particularly using NGS technology. The phenomenon of ACE is well described and is most often due to CHIP, which can be demonstrated in healthy populations at increasing frequency with increasing age (Jaiswal S, et al. *N Engl J Med* 2014;371:2488-2498; Genovese G, et al. *N Engl J Med* 2014;371:2477-2487). This finding has important clinical implications regarding potential application of unwarranted clinical interventions. Further, the finding of clonal hematopoiesis itself may portend adverse clinical outcomes, such as the development of hematologic neoplasia and increased non-hematologic mortality.
- Blood and/or saliva is an unsuitable source of DNA for germline testing for cases with a history of hematologic abnormalities. Careful examination of the patient's complete blood count (CBC) and peripheral blood smear may be warranted in all cases reporting the discovery of a *TP53* pathogenic/likely pathogenic variant, and testing of non-lymphoid ancillary tissues may help to delineate bona fide mosaic involvement of different germ layers (Weitzel J, et al. *Genet Med* 2018;20:809-816).

^h For additional information on the management of children with LFS, see Kratz C, et al. *Clin Cancer Res* 2017;23:e38-e45.

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score ≥ 8), nodal involvement, and distant metastasis compared with noncarriers.⁹² In a sample of 692 men with metastatic prostate cancer, unselected for family history or age at diagnosis, 5.3% carried a *BRCA2* mutation, and 0.9% carried a *BRCA1* mutation.⁸⁹ In addition, analyses from a treatment center database showed that *BRCA1/2* and *ATM* mutation rates were highest in patients with metastatic disease (8.2%). This study also showed that carriers with prostate cancer had significantly decreased survival, compared with patients who were noncarriers (5 vs 16 years, respectively; $P < .001$).⁸⁸ This association remained statistically significant when controlling for race, age, prostate-specific antigen, and Gleason score. Ashkenazi Jewish ancestry is also associated with *BRCA1/2* pathogenic variants in men with prostate cancer, with rates for *BRCA1* being 0%–2% and rates for *BRCA2* being 1%–3%.^{83,93–96}

Pancreatic Cancer Risk

Before more widespread testing of individuals with pancreatic cancer for germline variants in cancer predisposition genes, studies showed that *BRCA1/2* mutation rates in pancreatic cancer cases ranged from

1%–11% for *BRCA1* and 0%–17% for *BRCA2*.^{97–105} However, some of these studies included only patients with familial pancreatic cancer^{100,101,104} or those of Ashkenazi Jewish ancestry,¹⁰² both of whom may have a greater likelihood of testing positive for a *BRCA1/2* mutation. More recent studies that used panel testing confirm that some pancreatic cancers harbor actionable *BRCA1/2* pathogenic or likely pathogenic variants (0%–3% for *BRCA1* and 1%–6% for *BRCA2*).^{106–111} Patients with pancreatic cancer and Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* pathogenic variant, with prevalence of detected mutations in this group ranging from 5.5%–19%, with mutations being more common for *BRCA2*.^{102,103,105,112}

More information on genes associated with pancreatic cancer can be found in the full version of these NCCN Guidelines at NCCN.org.

Other Cancer Risks

Some studies have suggested an increased risk specifically of serous uterine cancer in carriers of a pathogenic *BRCA1/2* variant.^{113–116} Analyses from a multicenter prospective cohort study including 1,083 women carrying a pathogenic

BRCA1 variant who underwent RRSO without hysterectomy showed an increased risk for serous and/or serous-like endometrial cancer.¹¹⁷ However, it has been suggested that the increased risk for endometrial cancer observed in some carriers of *BRCA1/2* pathogenic or likely pathogenic variants may be due to the use of tamoxifen therapy by these women rather than the presence of a gene mutation.^{118,119} A meta-analysis including 5 studies of patients with uterine serous cancer and Ashkenazi Jewish ancestry showed that *BRCA1/2* pathogenic/likely pathogenic variant prevalence was greater in women with uterine serous cancer than in controls (also of Ashkenazi Jewish ancestry) (OR, 5.4; 95% CI, 2.2–13.1).¹¹³ In a retrospective case control study including 2,627 Jewish Israeli women (88% Ashkenazi Jewish) who were carriers of a pathogenic *BRCA1/2* variant, risk of developing uterine cancer was increased, with an observed-to-expected ratio of 3.98 (95% CI, 2.17–6.67; $P<.001$).¹¹⁶ This association persisted regardless of uterine cancer histology. Despite some evidence of increased risk of uterine cancer in carriers of a pathogenic *BRCA1/2* variant, the absolute risk is low.

Studies that investigated associations between *BRCA2* mutation and cutaneous melanoma have drawn inconsistent conclusions, though there is some evidence of an association.¹²⁰ One study showed that women carrying a pathogenic *BRCA2* variant have an elevated risk for leukemia (standardized incidence ratio [SIR], 4.76; 95% CI, 1.21–12.96; $P=.03$), particularly women who have received chemotherapy (SIR, 8.11; 95% CI, 2.06–22.07; $P=.007$).¹²¹ Analyses of data from the Swedish Family Cancer Database showed that carriers of a pathogenic *BRCA1/2* variant who also have family history of breast and ovarian cancer are at increased risk of gastric cancer by age 70 (SIR, 1.88; 95% CI, 1.05–3.12).¹²² A 1999 analysis from the Breast Cancer Linkage Consortium suggested that this risk might be particularly elevated in carriers of a pathogenic *BRCA2* variant (RR, 2.59; 95% CI, 1.46–4.61).¹²³ Finally, an analysis of 490 families with a known *BRCA1/2* pathogenic or likely pathogenic variant showed an increased risk for ocular melanoma in carriers of a pathogenic *BRCA2* variant (RR, 99.4; 95% CI, 11.1–359.8), though absolute risk is low.¹²⁴

Risk Management

Recommendations for the medical management of BRCA-related breast/ovarian cancer syndrome are based on an appreciation of the early onset of disease, the increased risk for ovarian cancer, and the risk for male breast cancer in carriers of a pathogenic *BRCA1/2* variant (see BRCA-A 1 and BRCA-A 2, pages 81 and 82). An individual from a family with a known *BRCA1/2* pathogenic or likely pathogenic variant who tests negative for the familial variant should be followed according to the

recommendations for the general population in the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at NCCN.org).

Screening Recommendations

The emphasis on initiating screening considerably earlier than standard recommendations is a reflection of the early age of onset seen in hereditary breast/ovarian cancer.¹²⁵ For a woman who is a carrier of a *BRCA1/2* pathogenic or likely pathogenic variant, training in breast awareness with regular monthly practice should begin at 18 years of age, and clinical breast examinations should be conducted every 6–12 months, beginning at 25 years of age. Between the ages of 25 and 29 years, the woman should have annual breast MRI screening with contrast (to be performed on days 7–15 of menstrual cycle for premenopausal women) or annual mammograms only if MRI is not available. The age to begin screening can be individualized if family history includes a breast diagnosis prior to 30 years of age.^{125–129} Breast MRI screening is preferred over mammogram in the 25- to 29-year age group. High-quality breast MRI screening should consist of the following: dedicated breast coil, ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Between 30 and 75 years of age, annual mammogram and breast MRI with contrast should both be done. After 75 years of age, management should be considered on an individual basis. In women treated for breast cancer who have not had bilateral mastectomy, mammography and breast MRI screening with contrast should continue as recommended based on age.

Mammography has served as the standard screening modality for detection of breast cancer during the past few decades. There are currently no data indicating that mammography on its own reduces mortality in women with genetically increased risk for breast cancer.¹³⁰ Also, false-negative mammography results are common and have been correlated with factors such as presence of a *BRCA1/2* mutation and high breast tissue density,^{131–134} both of which may occur more frequently among younger women. Rapidly growing or aggressive breast tumors—also more common among younger women—have also been associated with decreased sensitivity of mammographic screening methods.^{131,135} Prospective studies on comparative surveillance modalities in women at high risk for familial breast cancer (ie, confirmed *BRCA1/2* pathogenic variant or suspected mutation based on family history) have consistently reported higher sensitivity of MRI screening (77%–94%) compared with mammography (33%–59%) in detecting breast cancers. False-positive rates were higher with MRI in some reports, resulting in a slightly lower or similar specificity with MRI screening (81%–98%) compared with mammography (92%–100%).^{125–127,136–138}

The sensitivity with ultrasound screening (33%–65%) appeared similar to that of mammography in this high-risk population.^{125,136–138} In a prospective screening trial (conducted from 1997–2009) that evaluated the performance of annual MRI and mammography in women (aged 25–65 years; n=496) with confirmed pathogenic *BRCA1/2* variant, sensitivity with MRI was significantly higher compared with mammography during the entire study period (86% vs 19%; $P<.0001$).¹³⁹ Factors such as age, mutation type, or invasiveness of the tumor did not significantly influence the relative sensitivity of the 2 screening modalities. Importantly, the large majority (97%) of cancers detected by MRI screening were early-stage tumors.¹³⁹ At a median follow-up of 8 years from diagnosis, none of the surviving patients (n=24) had developed distant recurrence. In an analysis of 606 women with either a family history of breast cancer or who harbor a genetic mutation associated with increased risk for breast cancer, sensitivity of breast MRI screening was reported to be 79%, while specificity was reported to be 86%.¹⁴⁰

All of these studies discussed previously evaluated a screening strategy that was conducted on an annual basis, and many of the studies included individuals without known *BRCA1/2* mutation status. A study of 1,219 carriers of a pathogenic *BRCA1* variant and 732 carriers of a pathogenic *BRCA2* variant showed that the increased sensitivity of mammography over MRI was greater for carriers of a pathogenic *BRCA2* variant (12.6%) than for carriers of a pathogenic *BRCA1* variant (3.9%).¹⁴¹ In a retrospective study, a different screening interval was evaluated, using alternating mammography and MRI screening every 6 months in women with a confirmed pathogenic *BRCA1/2* variant (n=73).¹⁴² After a median follow-up of 2 years, 13 breast cancers were detected among 11 women; 12 of the tumors were detected by MRI screening but not by mammography obtained 6 months earlier. The sensitivity and specificity with MRI screening was 92% and 87%, respectively.¹⁴²

The optimal surveillance approach in women at high risk for familial breast cancer remains uncertain, especially for women between the ages of 25 and 30 years. Although earlier studies have reported an unlikely association between radiation exposure from mammography and increased risk for breast cancer in carriers of a pathogenic *BRCA1/2* variant,^{143,144} a report from a large cohort study suggested an increased risk in women exposed to radiation at a young age.¹⁴⁵ A retrospective cohort study (from the GENE-RAD-RISK study) showed that exposure to diagnostic radiation (including mammography) before 30 years of age was associated with increased risk for breast cancer in women with a confirmed pathogenic *BRCA1/2* variant (n=1,993).¹⁴⁵ Thus, one of the potential benefits of incorporating MRI modalities into surveillance strategies may include

minimizing the radiation risks associated with mammography, in addition to the higher sensitivity of MRI screening in detecting tumors. The use of MRI, however, may potentially be associated with higher false-positive results and higher costs relative to mammography. The combined use of digital mammography (2-dimensional [2D]) in conjunction with digital breast tomosynthesis (DBT) appears to improve cancer detection and reduce false-positive call-back rates.^{146–155} Tomosynthesis allows acquisition of 3-dimensional (3D) data using a moving X-ray and digital detector. These data are reconstructed using computer algorithms to generate thin sections of images. The combined use of 2D and digital breast tomosynthesis results in double the radiation exposure compared with mammography alone. However, this increase in radiation dose falls below dose limits of radiation set by the U.S. FDA for standard mammography. The radiation dose can be minimized by newer tomosynthesis techniques that create a synthetic 2D image,^{147,156,157} which may obviate the need for a conventional digital image. When mammography is performed, the panel recommends that tomosynthesis be considered. In carriers of a *BRCA1/2* pathogenic or likely pathogenic variant who are younger than 30 years of age, breast MRI screening is preferred over mammography due to the potential radiation exposure risk and less sensitivity for detection of tumors associated with mammography.

The appropriate imaging modalities and surveillance intervals are still under investigation. In a report based on a computer simulation model that evaluated different annual screening strategies in carriers of a pathogenic *BRCA1/2* variant, a screening approach that included annual MRI starting at 25 years of age combined with alternating digital mammography/MRI starting at 30 years of age was shown to be the most effective strategy when radiation risks, life expectancy, and false-positive rates were considered.¹⁵⁸ Future prospective trials are needed to evaluate the different surveillance strategies in individuals at high risk for familial breast cancer. Annual MRI as an adjunct to screening mammogram and clinical breast examination for women aged 25 years or older with a genetic predisposition to breast cancer is supported by guidelines from the ACS.¹²⁸

Posttest counseling in women with a confirmed *BRCA1/2* pathogenic or likely pathogenic variant (or highly suspected of having the variant based on presence of known pathogenic or likely pathogenic variant in the family) includes discussion of risk-reducing mastectomy and/or RRSO. Counseling for these risk-reducing surgeries should include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, breast reconstructive options, management of menopausal symptoms, and discussion of reproductive desires. It is important to address the psychosocial and

quality-of-life aspects of undergoing risk-reducing surgical procedures.¹⁵⁹

Studies assessing whether ovarian cancer screening procedures are sufficiently sensitive or specific have yielded mixed results. The UK Collaborative Trial of Ovarian Cancer Screening, which assessed multimodality screening with transvaginal ultrasound (TVUS) and CA-125 versus either TVUS alone or no screening, showed that multimodality screening is more effective at detecting early-stage cancer; however, after a median of 11 years of follow-up, a significant mortality reduction was not observed.^{160,161} In phase II of the UK Familial Ovarian Cancer Screening Study, 4,348 women with an estimated lifetime ovarian cancer risk no less than 10% underwent ovarian cancer screening via serum CA-125 tests every 4 months (with the risk of ovarian cancer algorithm [ROCA] used to interpret results) and TVUS (annually or within 2 months if abnormal ROCA score).¹⁶² Thirteen patients were diagnosed with ovarian cancer as a result of the screening protocol, with 5 of the 13 being diagnosed with early-stage cancer. Sensitivity, positive predictive value, and negative predictive value of the screening protocol for detecting ovarian cancer within 1 year were 94.7%, 10.8%, and 100%, respectively. A third study including 3,692 women who were at increased familial/genetic risk of ovarian cancer (ie, known pathogenic *BRCA1/2* variant in the family and/or family history of multiple breast and/or ovarian cancers) showed that a ROCA-based screening protocol (ie, serum CA-125 testing every 3 months with annual TVUS annually or sooner depending on CA-125 test results) identified 6 incidental ovarian cancers, of which 50% were early stage.¹⁶³ The results of these studies suggest a potential stage shift when a ROCA-based ovarian cancer screening protocol is followed in high-risk women, though it remains unknown whether this screening protocol impacts survival. RRSO remains the current standard of care for ovarian cancer risk management in carriers of a pathogenic *BRCA1/2* variant. For women who have not elected RRSO, TVUS and serum CA-125 may be considered at the clinician's discretion starting at 30 to 35 years of age.

Men testing positive for a *BRCA1/2* pathogenic or likely pathogenic variant should have an annual clinical breast examination and undergo training in breast self-examination with regular monthly practice starting at 35 years of age. Data to support breast screening in men are limited. A 12-year longitudinal observational study evaluated the outcomes of mammography screening in 1,869 men who were at increased risk of developing breast cancer (ie, personal or family history of breast cancer and/or germline genetic mutation associated with breast cancer, mostly *BRCA1* and *BRCA2*).¹⁶⁴ Node-negative breast cancer was identified in 5 men (18 per

1,000 examinations), which is greater than the cancer detection rates in both average-risk and high-risk women who undergo breast screening. Harboring a genetic mutation (n=47) was associated with breast cancer (OR, 7; 95% CI, 2-29; *P*=.006). Annual mammogram screening in men with gynecomastia may be considered, beginning at age 50 or 10 years before the earliest known breast cancer in the family (whichever comes first).

Screening for prostate cancer starting at 40 years of age is recommended for carriers of a pathogenic *BRCA2* variant and should be considered for carriers of a pathogenic *BRCA1* variant.⁸⁶ See the NCCN Guidelines for Prostate Cancer Early Detection (available at NCCN.org). For both men and women testing positive for a *BRCA1/2* pathogenic or likely pathogenic variant, general melanoma risk management is indicated, such as annual full body skin exam and minimizing ultraviolet exposure. There are no specific screening guidelines for melanoma, though more information can be found at the website for the National Council on Skin Cancer Prevention (www.skincancer.org). Information on pancreas screening can be found in PANC-A in these guidelines online at NCCN.org).

Risk-Reduction Surgery

Bilateral Total Mastectomy

Two meta-analyses show that prophylactic bilateral mastectomy reduces the risk for breast cancer.^{165,166} Only one of these analyses showed that risk-reducing surgery is significantly associated with reduced mortality.¹⁶⁶ Retrospective studies and small prospective studies provide support for concluding that risk-reducing mastectomy (RRM) provides a high degree of protection against breast cancer in women carrying a pathogenic *BRCA1/2* variant.¹⁶⁷⁻¹⁷⁰

The NCCN Guidelines Panel supports discussion of the option of RRM for women on a case-by-case basis. Counseling regarding the degree of protection offered by such surgery and the degree of cancer risk should be provided. Because risk of breast cancer remains increased with age in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant,⁹ age and life expectancy should be considered during this counseling, as should family history.

It is important that the potential psychosocial effects of RRM are addressed. A 2018 Cochrane review including 20 studies that evaluated psychosocial effects of RRM showed that patients are generally satisfied with their decision, with reported decreases in worry about breast cancer, but negative impacts on body image and sexuality have also been reported. Additional research is needed to further evaluate the psychosocial impact of RRM.¹⁷¹ RRM is also associated with long-term

physical symptoms, such as lower sensitivity to touch, pain, tingling, infection, and edema.¹⁶⁶ Multidisciplinary consultations are recommended before surgery and should include discussions of the risks and benefits of surgery and surgical breast reconstruction options. Immediate breast reconstruction is an option for many women following RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction.¹⁷² Nipple-sparing mastectomy has been suggested to be a safe and effective risk reduction strategy for patients carrying a *BRCA1/2* pathogenic or likely pathogenic variant,¹⁷³ although more data and longer follow-up are needed.

Bilateral Salpingo-Oophorectomy

Women with a confirmed *BRCA1/2* pathogenic or likely pathogenic variant are at increased risk for both breast and ovarian cancers (including fallopian tube cancer and primary peritoneal cancer).^{53,54} Although the risk for ovarian cancer is generally considered to be lower than the risk for breast cancer in carriers of a pathogenic *BRCA1/2* variant,^{7,8,174} the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have lent support for the performance of bilateral RRSO after completion of childbearing in these women.

An observational prospective study of 5,783 women carrying a pathogenic *BRCA1/2* variant showed that ovarian cancer is more prevalent in individuals carrying a pathogenic *BRCA1* (4.2%) variant than those carrying a pathogenic *BRCA2* (0.6%) variant.¹⁷⁵ In carriers of a pathogenic *BRCA1* variant, prevalence of ovarian, fallopian tube, and peritoneal cancers found during risk-reducing surgery was 1.5% for those younger than 40 years of age and 3.8% in those between the ages of 40 and 49 years.¹⁷⁵ The highest incidence rate for carriers of a pathogenic *BRCA1* variant was observed between the ages of 50 and 59 years (annual risk, 1.7%); for carriers of a pathogenic *BRCA2* variant, the highest incidence rate was observed between the ages of 60 and 69 years (annual risk, 0.6%). Therefore, the recommended age for RRSO should be younger for women carrying a *BRCA1* pathogenic or likely pathogenic variant than for women carrying a *BRCA2* variant.

The effectiveness of RRSO in reducing the risk for ovarian cancer in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant has been demonstrated in a number of studies. For example, results of a meta-analysis involving 10 studies of carriers of a pathogenic *BRCA1/2* variant showed an approximately 80% reduction in the risk for ovarian or fallopian cancer following RRSO.¹⁷⁶ In a large prospective study of women who carried a deleterious *BRCA1/2* variant (n=1079),

RRSO significantly reduced the risk for *BRCA1*-associated gynecologic tumors (including ovarian, fallopian tube, or primary peritoneal cancers) by 85% compared with observation during a 3-year follow-up period (HR, 0.15; 95% CI, 0.04–0.56; *P*=.005).¹⁷⁷ An observational study of 5,783 women carrying a pathogenic *BRCA1/2* variant showed that risk-reducing oophorectomy reduces risk for ovarian, fallopian, or peritoneal cancer by 80% (HR, 0.20; 95% CI, 0.13–0.30) and all-cause mortality by 77% (HR, 0.23; 95% CI, 0.13–0.39).¹⁷⁵ RRSO reduces mortality at all ages in carriers of a pathogenic *BRCA1* variant, but among carriers of a pathogenic *BRCA2* variant, RRSO is only associated with reduced mortality in those between the ages of 41 and 60 years.¹⁷⁵

A 1%–4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.^{76,176,178–180} An analysis of 36 carriers of a *BRCA1/2* pathogenic variant who developed peritoneal carcinomatosis following RRSO showed that 86% were carriers of a *BRCA1* pathogenic variant specifically.¹⁸¹ When comparing to 113 carriers of a pathogenic *BRCA1/2* variant who did not develop peritoneal carcinomatosis following RRSO, women who eventually developed peritoneal carcinomatosis were older at time of RRSO (*P*=.025) and had a greater percentage of serous tubal intraepithelial carcinoma in their RRSO specimen (*P*<.001), supporting the removal of the fallopian tubes as part of the risk-reducing procedure. Further, an analysis from a multicenter prospective cohort study (n=1,083) showed an increased risk for serous and/or serous-like endometrial cancer in women carrying a pathogenic *BRCA1* variant who underwent RRSO without hysterectomy.¹¹⁷

RRSO may provide an opportunity for gynecologic cancer detection in high-risk women. An analysis of 966 RRSO procedures showed that invasive or intraepithelial ovarian, tubal, or peritoneal neoplasms were detected in 4.6% of carriers of a pathogenic *BRCA1* variant and 3.5% of carriers of a pathogenic *BRCA2* variant.¹⁸² Carrying a pathogenic *BRCA1/2* variant was associated with detection of clinically occult neoplasms during RRSO (*P*=.006).

In early studies, RRSO was reported to reduce the risk for breast cancer in carriers of a pathogenic *BRCA1/2* variant.^{165,176,179,180,183–186} In the case-control international study by Eisen et al, a 56% (OR, 0.44; 95% CI, 0.29–0.66; *P*<.001) and a 43% (OR, 0.57; 95% CI, 0.28–1.15; *P*=.11) breast cancer risk reduction (adjusted for oral contraceptive use and parity) was reported following RRSO in carriers of a *BRCA1* and a *BRCA2* pathogenic variant, respectively.¹⁸³ A study comparing breast cancer risk in women with carrying a pathogenic *BRCA1/2* variant who had undergone RRSO with carriers of these mutations who opted for surveillance only also showed reduced breast cancer risk in women who underwent RRSO (HR,

0.47; 95% CI, 0.29–0.77).¹⁸⁰ These studies were further supported by a meta-analysis that found similar reductions in breast cancer risk of approximately 50% for carriers of a pathogenic *BRCA1/2* variant following RRSO.¹⁷⁶

Results of a prospective cohort study suggested that RRSO may be associated with a greater reduction in breast cancer risk for carriers of a pathogenic *BRCA2* variant compared with carriers of a pathogenic *BRCA1* variant.¹⁷⁷ Another retrospective analysis including 676 women with stage I or II breast cancer and a pathogenic *BRCA1/2* variant showed that oophorectomy was associated with decreased risk of mortality from breast cancer in carriers of a pathogenic *BRCA1* variant (HR, 0.38; 95% CI, 0.19–0.77, $P=.007$), but not in carriers of a carriers of a pathogenic *BRCA2* variant ($P=.23$).¹⁸⁷

The reduction in breast cancer risk following RRSO was questioned in a prospective cohort study from the Netherlands (N=822), which did not find a statistically significant difference in breast cancer incidence between carriers of a pathogenic *BRCA1/2* variant who opted for an RRSO and women who did not, regardless of whether the mutation was for *BRCA1* or *BRCA2*.¹⁸⁸ Study investigators argued that previous study findings showing a 50% decrease in breast cancer risk may have been influenced by bias, specifically inclusion of patients with a history of breast or ovarian cancer in the comparison group and immortal person-time bias. One study that corrected for immortal person-time bias as a result of this analysis continued to find a protective effect of RRSO on breast cancer incidence in carriers of a pathogenic *BRCA1/2* variant (HR, 0.59; 95% CI, 0.42–0.82, $P<.001$).¹⁸⁹ Another prospective cohort analysis including 1,289 carriers of a pathogenic *BRCA1/2* variant unaffected with breast cancer (196 eventually being diagnosed) also showed that, when RRSO was treated as a time-dependent variable, it was no longer associated with breast cancer risk.¹⁹⁰ A meta-analysis including 19 studies of the association between RRSO and breast cancer risk and mortality showed a protective effect in studies published earlier than 2016, but not in studies published in 2016 or later ($n=3$).¹⁸⁴

Results from one of the earlier studies showed that greater reductions in breast cancer risk were observed in women carrying a pathogenic *BRCA1* variant who had an RRSO at 40 years of age or younger (OR, 0.36; 95% CI, 0.20–0.64), relative to carriers of a pathogenic *BRCA1* variant aged 41 to 50 years who had this procedure (OR, 0.50; 95% CI, 0.27–0.92).¹⁸³ A nonsignificant reduction in breast cancer risk was found for women aged 51 years or older, although only a small number of women were included in this group.¹⁸³ However, results from another early study also suggested that RRSO after 50 years of age is not associated with a substantial decrease in breast

cancer risk.¹⁷⁹ A 2017 study showed that oophorectomy was not significantly associated with decreased risk of breast cancer in carriers of a pathogenic *BRCA1/2* variant ($n=3,722$).¹⁹¹ However, stratified analyses in carriers of a pathogenic *BRCA2* variant who were diagnosed with breast cancer before 50 years of age showed that oophorectomy was associated with an 82% reduction in breast cancer (HR, 0.18; 95% CI, 0.05–0.63; $P=.007$). The risk reduction in carriers of a pathogenic *BRCA1* variant was not statistically significant ($P=.51$). A 2020 study including 853 premenopausal carriers of a pathogenic *BRCA1/2* variant showed that premenopausal RRSO decreased breast cancer risk in *BRCA1* pathogenic variant carriers (HR, 0.45; 95% CI, 0.22–0.92), but not in *BRCA2* pathogenic variant carriers (HR, 0.77; 95% CI, 0.35–1.67).¹⁹² Analysis for this study began observation 6 months after genetic testing to avoid event-free time bias.

Studies suggest a benefit of RRSO on breast cancer risk, but the magnitude of the effect is not well-understood, and evidence is mixed regarding age at which RRSO should be undertaken, and the specific mutation (*BRCA1* vs *BRCA2*) carried.

Two systematic reviews showed that hormone-replacement therapy (HRT) does not negate the reduction in breast cancer risk associated with the surgery.^{193,194} One of these reviews showed that breast cancer risk tended to be lower in women who received estrogen only, compared with estrogen plus progesterone (OR, 0.62; 95% CI, 0.29–1.31).¹⁹³ It is important to have a discussion about the potential risks and benefits of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.^{195,196}

Salpingectomy (surgical removal of the fallopian tube with retention of the ovaries) rates are increasing, especially in women younger than 50 years of age.¹⁹⁷ Despite some evidence regarding the safety and feasibility of this procedure,^{197,198} more data are needed regarding its efficacy in reducing the risk for ovarian cancer.^{159,199} Further, carriers of a pathogenic *BRCA1/2* variant who undergo salpingectomy without oophorectomy may not get the reduction in breast cancer risk that research suggests carriers of a pathogenic *BRCA1/2* variant who undergo oophorectomy may receive. Therefore, at this time, the panel does not recommend risk-reducing salpingectomy alone as the standard of care in carriers of a pathogenic *BRCA1/2* variant. Clinical trials of interval salpingectomy with delayed oophorectomy are ongoing (eg, ClinicalTrials.gov identifiers: NCT02321228, NCT01907789).

Some studies suggest a link between *BRCA1/2* pathogenic/likely pathogenic variants and development of serous uterine cancer (primarily with *BRCA1*),

although the overall risk for uterine cancer was not increased when controlling for tamoxifen use.^{113,114,117} Women who undergo hysterectomy at the time of RRSO are candidates for estrogen alone HRT, which is associated with a decreased risk of breast cancer, compared with combined estrogen and progesterone, which is required when the uterus is left in situ.²⁰⁰ For patients who choose to undergo RRSO, the provider may discuss the risks and benefits of concurrent hysterectomy, but more data are needed to determine the magnitude of the association between *BRCA1/2* variants and development of serous uterine cancer.

The NCCN Guidelines Panel recommends RRSO for women with a known *BRCA1/2* pathogenic or likely pathogenic variant, typically between 35 and 40 years of age for women with a *BRCA1* pathogenic or likely pathogenic variant. Since ovarian cancer onset tends to be later in women who test positive for a *BRCA2* pathogenic or likely pathogenic variant, it is reasonable to delay RRSO for management of ovarian cancer risk until between 40 and 45 years of age in these women, unless age at diagnosis in the family warrants earlier age for consideration of this prophylactic surgery.¹⁷⁵ Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.^{77,79} The protocol published by CAP (2009) can be consulted for details on specimen evaluation.²⁰¹ See the NCCN Guidelines for Ovarian Cancer for treatment of findings (available at NCCN.org).

The decision to undergo RRSO is a complex one and should be made ideally in consultation with a gynecologic oncologist, especially when the patient wishes to undergo RRSO before the age at which it is typically recommended (ie, 35 years of age). Topics that should be addressed include impact on reproduction, impact on breast and ovarian cancer risk, risks associated with premature menopause (eg, osteoporosis, cardiovascular disease, cognitive changes, changes to vasomotor symptoms, sexual concerns), and other medical issues. The panel recommends that a gynecologic oncologist help patients considering RRSO understand how it may impact quality of life.

Chemoprevention

The use of selective estrogen receptor modulators (ie, tamoxifen, raloxifene) has been shown to reduce the risk for invasive breast cancer in postmenopausal women considered at high risk for developing breast cancer, especially ER-positive disease.^{202–209} However, only limited data are available on the specific use of these agents in patients with *BRCA1/2* pathogenic or likely pathogenic variants. As previously discussed, patients with *BRCA1/2* pathogenic or likely pathogenic variants who are

diagnosed with breast cancer have elevated risks for developing contralateral breast tumors. In one of the largest prospective series of carriers of a pathogenic *BRCA1/2* variant evaluated, the mean cumulative lifetime risks for contralateral breast cancer were estimated to be 83% for carriers of a pathogenic *BRCA1* variant and 62% for carriers of a pathogenic *BRCA2* variant.¹² Patients carrying a pathogenic *BRCA1/2* variant who have intact contralateral breast tissue (and who do not undergo oophorectomy or receive chemoprevention) have an estimated 40% risk for contralateral breast cancer at 10 years.²¹⁰ Case-control studies from the Hereditary Breast Cancer Clinical Study Group reported that the use of tamoxifen protected against contralateral breast cancer with an odds ratio (OR) of 0.38 (95% CI, 0.19–0.74) to 0.50 (95% CI, 0.30–0.85) among carriers of a pathogenic *BRCA1* variant and 0.42 (95% CI, 0.17–1.02) to 0.63 (95% CI, 0.20–1.50) among carriers of a pathogenic *BRCA2* variant.^{211,212} This translates to an approximately 45%–60% reduction in risk for contralateral tumors among carriers of a pathogenic *BRCA1/2* variant with breast cancer. The data were not consistent in regard to the protective effects of tamoxifen in the subset of carriers of a pathogenic *BRCA1/2* variant who also underwent oophorectomy. In addition, no data were available on the estrogen receptor status of the tumors. An evaluation of the subset of healthy carriers of a pathogenic *BRCA1/2* variant in the Breast Cancer Prevention Trial revealed that breast cancer risk was reduced by 62% in carriers of a pathogenic *BRCA2* variant receiving tamoxifen relative to placebo (risk ratio, 0.38; 95% CI, 0.06–1.56).²¹³ However, an analysis of 288 women who developed breast cancer during their participation in this trial showed that tamoxifen use was not associated with a reduction in breast cancer risk in carriers of a pathogenic *BRCA1* variant.²¹³ These findings may be related to the greater likelihood for development of estrogen receptor-negative tumors in carriers of a pathogenic *BRCA1* variant, relative to carriers of a pathogenic *BRCA2* variant. However, this analysis was limited by the very small number of individuals with a pathogenic *BRCA1/2* variant (n=19; 7% of participants diagnosed with breast cancer). Common single-nucleotide polymorphisms have been identified in genes (*ZNF423* and *CTSO*) that are involved in estrogen-dependent regulation of *BRCA1* expression.²¹⁴ These gene variants were associated with alterations in breast cancer risk during treatment with selective estrogen receptor modulators, and may eventually pave the way for predicting the likelihood of benefit with these chemopreventive approaches in individual patients.

The aromatase inhibitors (AIs) exemestane and anastrozole have been demonstrated to be effective in preventing breast cancer in postmenopausal women

considered to be high-risk of developing breast cancer.^{215,216} However, to date, there is little evidence supporting the use of aromatase inhibitors as an effective chemopreventive approach for individuals with a *BRCA1/2* pathogenic or likely pathogenic variant. A retrospective study showed that aromatase inhibitors may reduce the risk of contralateral breast cancer in women with a *BRCA1/2* pathogenic or likely pathogenic variant and ER-positive breast cancer who take them as adjuvant therapy, but these data are currently published in abstract form only.²¹⁷

With respect to the evidence regarding the effect of oral contraceptives on cancer risks in women with a known *BRCA1/2* pathogenic or likely pathogenic variant, case-control studies have demonstrated that oral contraceptives reduced the risk for ovarian cancer by 45%–50% in carriers of a pathogenic *BRCA1* variant and by 60% in carriers of a pathogenic *BRCA2* variant.^{218,219} Moreover, risks appeared to decrease with longer duration of oral contraceptive use.²¹⁹ In a meta-analysis conducted in a large number of carriers of a pathogenic *BRCA1/2* variant with (n=1503) and without (n=6,315) ovarian cancer, use of oral contraceptives significantly reduced the risk for ovarian cancer by approximately 50% for both the carriers of a pathogenic *BRCA1* variant (summary relative risk [SRR], 0.51; 95% CI, 0.40–0.65) and carriers of a pathogenic *BRCA2* variant (SRR, 0.52; 95% CI, 0.31–0.87).²²⁰ Another meta-analysis including one cohort study (n=3,181) and 3 case-control studies (1,096 cases and 2,878 controls) also showed an inverse association between ovarian cancer and having ever used oral contraceptives (OR, 0.58; 95% CI, 0.46–0.73).²²¹

Studies on the effect of oral contraceptive use on breast cancer risk among carriers of a pathogenic *BRCA1/2* variant have reported conflicting data. In one case-control study, use of oral contraceptives was associated with a modest but statistically significant increase in breast cancer risk among carriers of a pathogenic *BRCA1* variant (OR, 1.20; 95% CI, 1.02–1.40), with breast cancer risk in these carriers being associated with ≥5 years of oral contraceptive use (OR, 1.33; 95% CI, 1.11–1.60), breast cancer diagnosed before 40 years of age (OR, 1.38; 95% CI, 1.11–1.72), and use of oral contraceptives before 1975 (OR, 1.42; 95% CI, 1.17–1.75).²²² Oral contraceptive use was not significantly associated with breast cancer in carriers of a pathogenic *BRCA2* variant in this study. In another case-control study, use of oral contraceptives for at least 5 years was associated with a significantly increased risk for breast cancer in carriers of a pathogenic *BRCA2* variant (OR, 2.06; 95% CI, 1.08–3.94); results were similar when only the cases with oral contraceptive use on or after 1975 were considered.²²³ Oral contraceptive use for at least 1 year was not significantly associated with breast cancer risk in carriers of a pathogenic *BRCA1*

or *BRCA2* variant in this study. In a third case-control study, the use of low-dose oral contraceptives for at least 1 year was associated with significantly decreased risks for breast cancer among carriers of a pathogenic *BRCA1* variant (OR, 0.22; 95% CI, 0.10–0.49; *P* < .001), though not for carriers of a pathogenic *BRCA2* variant.²²⁴ Two meta-analyses^{220,221} and another case-control study²²⁵ showed that oral contraceptive use is not significantly associated with breast cancer risk in carriers of a pathogenic *BRCA1/2* variant.

Differences in the study design employed by these case-control studies make it difficult to compare outcomes between studies, and likely account for the conflicting results. The design of these studies might have differed with regard to factors such as the criteria for defining the “control” population for the study (eg, non*BRCA1/2* carriers vs pathogenic variant carriers without a cancer diagnosis), consideration of family history of breast or ovarian cancer, baseline demographics of the population studied (eg, nationality, ethnicity, geographic region, age groups), age of onset of breast cancer, and formulations or duration of oral contraceptives used. Larger prospective trials are needed to elucidate the impact of oral contraceptives on breast cancer risk in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant.

Reproductive Options

The outcomes of genetic testing can have a profound impact on family planning decisions for individuals of reproductive age who are found to be carriers of a *BRCA1/2* pathogenic or likely pathogenic variant. There is evidence that *BRCA2* pathogenic or likely pathogenic variants are associated with the rare autosomal recessive condition Fanconi anemia.²²⁶ Some case reports have also identified biallelic *BRCA1* mutations causing Fanconi anemia-like disorder.^{227–229} The proband should be advised regarding possible inherited cancer risk to relatives and his/her options for risk assessment and management. Counseling for reproductive options such as prenatal diagnosis and assisted reproduction using preimplantation genetic testing (PGT) may therefore be warranted for couples expressing concern over their future offspring's carrier status of a *BRCA1/2* pathogenic or likely pathogenic variant. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options, including cost.

Prenatal diagnosis involves postimplantation genetic analysis of an early embryo, utilizing chorionic villi or amniotic fluid cell samples; genetic testing is typically conducted between week 12 and week 16 of gestation, and testing results may potentially lead to a couple's decision to terminate pregnancy.^{230,231} PGT has emerged

as an alternative method of genetic testing in early embryos. PGT involves the testing of 1 or 2 cells from embryos in very early stages of development (ie, 6–8 cells) after in vitro fertilization (IVF). This procedure allows for the selection of unaffected embryos to be transferred to the uterus,^{230,231} and may therefore offer the advantage of avoiding potential termination of pregnancy. The PGT process requires the use of IVF regardless of the fertility status of the couple (ie, also applies to couples without infertility issues), and IVF may not always lead to a successful pregnancy. Finally, the technology or expertise may not be readily available in a couple's geographic location.

Various factors, both medical and personal, must be weighed in the decision to use prenatal diagnosis or PGT. Medical considerations may include factors such as the age of onset of the hereditary cancer, penetrance, severity or associated morbidity and mortality of the cancer, and availability of effective cancer risk reduction methods or effective treatments.^{230,231} Although the use of prenatal diagnosis or PGT is relatively well established for severe hereditary disorders with very high penetrance and/or early onset, its use in conditions associated with lower penetrance and/or later onset (eg, hereditary breast or ovarian cancer syndrome) remains somewhat controversial from both an ethical and regulatory standpoint. Personal considerations for the decision to use prenatal diagnosis or PGT may include individual ethical beliefs, value systems, cultural and religious beliefs, and social and economic factors. Successful births have been reported with the use of PGT and IVF in carriers of a pathogenic *BRCA1/2* variant,^{232,233} but data in the published literature are still very limited. In addition, data pertaining to long-term safety or outcomes of PGT and assisted reproduction in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant are not yet available.

Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* pathogenic or likely pathogenic variants.³ It has been estimated to be involved in only about 1% of hereditary breast cancer cases,²³⁴ although results from other studies suggest that germline *TP53* gene mutations may be more common than previously believed, with estimates of 1 in 5,000 to 1 in 20,000.^{235,236} There are only about 300 families reported in an LFS registry maintained by an NCCN Member Institution and the NCI.²³⁷ The tumor suppressor gene, *TP53*, is located on chromosome 17,^{238,239} and the protein product of the *TP53* gene (ie, p53) is located in the cell nucleus and binds directly to DNA. It has been called the “guardian of the genome” and plays important roles in controlling the cell cycle and apoptosis.^{238–240} Germline mutations in the *TP53* gene have been observed in over 50% (and in over 70% in some

studies) of families meeting the classic definition of LFS (see “Testing Criteria for Li-Fraumeni Syndrome,” page 80).^{3,235,241} Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.²⁴²

LFS is a highly penetrant cancer syndrome associated with a high lifetime risk for cancer. An analysis from the NCI Li-Fraumeni Syndrome Study (n=286) showed a cumulative lifetime cancer incidence of nearly 100%.²⁴³ LFS is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (although Ewing's sarcoma is less likely to be associated with LFS), premenopausal breast cancer, colon cancer, gastric cancer, adrenocortical carcinoma, and brain tumors.^{3,235,237,240,244–249} Sarcoma, breast cancer, adrenocortical tumors, and certain brain tumors have been referred to as the “core” cancers of LFS since they account for the majority of cancers observed in individuals with germline *TP53* pathogenic or likely pathogenic variants, and, in one study, at least one of these cancers was found in one or more members of all families with a germline *TP53* gene mutation.²³⁵ Hypodiploid acute lymphoblastic leukemia is also associated with LFS,^{250,251} and case reports have suggested an association between melanoma and LFS.^{252,253}

The NCI Li-Fraumeni Syndrome Study (n=286) showed that the cumulative incidence rates by 70 years of age in women are 54%, 15%, 6%, and 5% for breast cancer, soft tissue sarcoma, brain cancer, and osteosarcoma, respectively.²⁴³ The cumulative incidence rates by age 70 years in men are 22%, 19%, and 11% for soft tissue sarcoma, brain cancer, and osteosarcoma, respectively. Case-control analyses from a large study including 56,480 breast tumors showed that *TP53* mutations (n=82) were significantly associated with HER2-positive disease, regardless of whether disease was ER-positive (OR, 11.95, 95% CI, 5.84–23.0) or negative (OR, 22.71, 95% CI, 10.45–45.49).¹⁵ These results are supported by two earlier retrospective studies that reported a very high frequency of HER2-positive breast tumors (67%–83% of evaluated breast tumors) among patients with germline *TP53* mutations.^{254,255} Taken together, results suggest that amplification of HER2 may arise in conjunction with germline *TP53* mutations. This association warrants further investigation, as such patients may potentially benefit from chemoprevention therapies that incorporate HER2-targeted agents.

Individuals with LFS often present with certain cancers (eg, soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood,²⁴⁶ and have an increased risk of developing multiple primary cancers during their lifetimes.²⁵⁶ Results of a segregation analysis of data collected on the family histories of 159 patients

with childhood soft tissue sarcoma showed carriers of germline *TP53* mutations to have estimated cancer risks of approximately 60% and 95% by 45 and 70 years, respectively.²⁵⁷ Although similar cancer risks are observed in men and women with LFS when gender-specific cancers are not considered, female breast cancer is commonly associated with the syndrome.²³⁵ It is important to mention that estimations of cancer risks associated with LFS are limited to at least some degree by selection bias since dramatically affected kindreds are more likely to be identified and become the subject of further study.

A number of different sets of criteria have been used to help identify individuals with LFS. For the purposes of the NCCN Guidelines, 2 sets of these criteria are used to facilitate the identification of individuals who are candidates for testing for *TP53* pathogenic or likely pathogenic variants.

Classic LFS criteria, based on a study by Li and Fraumeni involving 24 LFS kindreds, include the following²⁴⁷: a member of a kindred with a known *TP53* pathogenic or likely pathogenic variant; a combination of an individual diagnosed at 45 years of age or younger with a sarcoma and a first-degree relative diagnosed with cancer at 45 years of age or younger; and an additional first- or second-degree relative in the same lineage with cancer diagnosed at younger than 45 years of age or a sarcoma diagnosed at any age. Classic LFS criteria have been estimated to have a high positive predictive value (estimated at 56%) as well as a high specificity, although the sensitivity is relatively low (estimated at 40%).²³⁵ Thus, it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.^{249,258} Classic LFS criteria make up one set of criteria included in the guidelines to guide selection of individuals for *TP53* pathogenic or likely pathogenic variant testing (see “Testing Criteria for Li-Fraumeni Syndrome,” page 80).

Other groups have broadened the classic LFS criteria to facilitate identification of individuals with LFS.^{259–261} For example, criteria for *TP53* testing proposed by Chompret et al²⁶⁰ recommends testing for patients with multiple primary tumors of at least 2 “core” tumor types (ie, sarcoma, breast cancer, adrenocortical carcinoma, brain tumors) diagnosed at <36 years of age or patients with adrenocortical carcinoma diagnosed at any age, regardless of family history. The Chompret criteria have an estimated positive predictive value of 20% to 35%,^{235,260} and, when incorporated as part of *TP53* testing criteria in conjunction with classic LFS criteria, have been shown to improve the sensitivity to 95% (ie, the Chompret criteria added to classic LFS criteria detected 95% of patients with *TP53* mutations).²³⁵ The Chompret criteria are the second set of criteria included in the

NCCN Guidelines. Although not part of the original published criteria set forth by Chompret et al, the panel recommends adopting the 2015 Revised Chompret Criteria and testing individuals with choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype diagnosed at any age and regardless of family history (for inclusion in criterion 3), based on reports of considerable incidence of *TP53* mutations found in patients with these rare forms of cancer.^{235,245,262–264} The panel supports the broader age cut-offs proposed by Tinat et al, based on a study in a large number of families, which detected germline *TP53* mutations in affected individuals with later tumor onsets.^{262,264}

Women with early-onset breast cancer (age of diagnosis ≤30 years), with or without family history of core tumor types, are another group for whom *TP53* gene mutation testing may be considered.²⁶³ Several studies have investigated the likelihood of a germline *TP53* mutation in this population.^{235,262,265–268} Among women <30 years of age with breast cancer and without a family history, the incidence of *TP53* mutations has been reported at 3%–8%.^{235,266,268,269} Other studies have found an even lower incidence of germline *TP53* gene mutations in this population. For example, Bougeard et al²⁶² reported that only 0.7% of unselected women with breast cancer before 33 years of age were carriers of a germline *TP53* mutation. Furthermore, Ginsburg et al²⁶⁵ found no germline *TP53* mutations in 95 unselected women with early-onset breast cancer who previously tested negative for *BRCA1/2* mutations. When taking into account family history of LFS-associated tumors, the *TP53* germline mutation prevalence increases. For example, in a study including 83 patients with *BRCA1/2* mutation-negative early-onset breast cancer (age of diagnosis ≤35 years), deleterious *TP53* mutations were identified in 3 of 4 patients (75%) with a family history of at least 2 LFS-associated tumors (breast cancer, bone or soft tissue sarcoma, brain tumors, or adrenocortical carcinoma) and in 1 of 17 patients (6%) with a family history of breast cancer only.²⁶⁷ In another study, all women younger than 30 years of age with breast cancer who had a first- or second-degree relative with at least one of the core cancer types (n=5) had germline *TP53* mutations.²³⁵

A member of a family with a known *TP53* pathogenic or likely pathogenic variant is considered to be at sufficient risk to warrant variant testing, even in the absence of any other risk factors. Individuals not meeting testing criteria should be followed according to recommendations tailored to his/her personal cancer history and family history, and testing for other hereditary syndromes may be considered. If a *TP53* mutation is detected through tumor profiling, and there are clinical implications if a *TP53* mutation is identified in the germline, then germline testing for a *TP53* variant may

be considered, depending on a careful examination of the individual's personal and family history. TP53 pathogenic/likely pathogenic variants are common in tumors.^{270,271} Therefore, if a TP53 somatic mutation is found in the absence of paired germline analysis, then germline testing may not be warranted unless there is clinical suspicion of a germline pathogenic or likely pathogenic variant.

Risk Assessment, Counseling, and Management

The approach to families with other hereditary breast cancer syndromes such as LFS reflects that of hereditary breast/ovarian cancer in many ways. However, there are some syndrome-specific differences with regard to assessment and management. In the case of LFS, there are multiple associated cancers, both pediatric and adult, that should be reflected in the expanded pedigree. Cancers associated with LFS include but are not limited to premenopausal breast cancer, bone and soft tissue sarcomas, CNS tumor, adrenocortical carcinoma, hypodiploid acute lymphoblastic leukemia, unusually early onset of other adenocarcinomas, or other childhood cancers.^{235,251,256,263} Verification of these sometimes very rare cancers is particularly important.

Employment of a screening protocol that includes MRI may improve early cancer detection in individuals with LFS.²⁷² In 2017, the panel made revisions to the LFS management recommendations following revisions to the "Toronto protocol," screening recommendations developed by a multi-institutional group of experts.²⁷³ NCCN recommendations for management of LFS apply specifically to adults with LFS, and discussions with patients should address the limitations of screening for the many cancers associated with this syndrome. Pediatricians should be made aware of the risk for childhood cancers in affected families and review with these families the screening recommendations for children with LFS.²⁷³ It is also important to address the psychosocial and quality-of-life aspects of this syndrome. Given the complexity of LFS management, individuals with LFS should be followed at centers with expertise in management of this syndrome.

For those at risk for breast cancer, training and education in breast self-examination should start at 18 years of age, with the patient performing regular self-examination on a monthly basis. For members of families with LFS, breast cancer surveillance by clinical breast examination is recommended every 6 to 12 months, beginning at 20 years of age (or at the age of the earliest known breast cancer in the family, if younger than 20 years of age) because of the very early age of breast cancer onset seen in these families. Recommendations for breast screening in LFS are similar to those for *BRCA*-related breast and ovarian cancer syndrome

management, although screening is begun at an earlier age. They include annual breast MRI screening with contrast (preferred) or mammogram if MRI is not available for women aged 20 to 29 years; annual mammogram and breast MRI screening with contrast in women aged 30 to 75 years; and management on an individual basis for women older than 75 years. For women with a family history of breast cancer diagnosed earlier than 20 years of age, breast MRI screening with contrast may begin at the earliest age of diagnosis. In women treated for breast cancer who have not had bilateral mastectomy, mammography and breast MRI screening with contrast should continue as recommended based on age. When mammography is performed, the panel recommends that tomosynthesis be considered. As with carriers of a *BRCA1/2* pathogenic or likely pathogenic variant, breast MRI screening in women who are younger than 30 years of age is preferred over mammography due to the potential radiation exposure risk and less sensitivity for detection of tumors.

Although there are no data regarding risk reduction surgery in women with LFS, options for risk-reducing mastectomy should be discussed on a case-by-case basis. Counseling for risk-reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, degree of age-specific cancer risk, reconstructive options, and competing risks from other cancers. Family history and life expectancy should also be considered during this counseling.

Many of the other cancers associated with germline *TP53* pathogenic or likely pathogenic variants do not lend themselves to early detection. Thus, additional recommendations are general and include comprehensive physical examinations (including neurologic examination) every 6 to 12 months, especially when there is a high index of suspicion for second malignancies in cancer survivors and rare cancers (see Li-Fraumeni Syndrome Management in Adults [LIFR-A 1 and 2], pages 83 and 84). Clinicians should address screening limitations for other cancers associated with LFS. Colonoscopy and upper endoscopy should be done every 2 to 5 years, starting at 25 years of age, or 5 years before the earliest known colon cancer diagnosis in family history (whichever comes first). Education regarding signs and symptoms of cancer is important. Patients should be advised about the risk to relatives, and genetic counseling for relatives is recommended. Annual dermatologic examination should be done beginning at 18 years of age.

Whole-body MRI for screening of cancers associated with LFS is being evaluated in multiple international trials. Use of whole-body MRI is appealing due to its wide anatomic coverage and the potential to cut down on the number of imaging studies that a patient undergoes.²⁷⁴

A meta-analysis including 578 individuals with *TP53* mutations across 13 prospective cohorts showed that baseline whole-body MRI identified cancer in 7% of the sample, with 83% of the cancers being localized and able to treat with curative intent.²⁷⁵ In a prospective observational study, a clinical surveillance protocol for *TP53* mutation carriers from families affected by LFS was incorporated.²⁷⁶ The surveillance protocol included biochemical methods (ie, bloodwork to evaluate 17-OH-progesterone, total testosterone, dehydroepiandrosterone sulfate, androstenedione, CBC, erythrocyte sedimentation rate, and lactate dehydrogenase; and 24-hour urine cortisol) and imaging techniques, such as annual brain MRI, annual rapid whole-body MRI, ultrasound of the abdomen and pelvis, and colonoscopy.²⁷⁷ For surveillance of breast cancers, the protocol was similar to the NCCN Guidelines for LFS Management.²⁷⁶ Eleven-year follow-up of this study, which included 89 *TP53* mutation carriers, showed that this surveillance protocol may be beneficial, with 84% (16 of 19) of patients who were diagnosed with cancer and had chosen to undergo surveillance being alive at final follow-up, compared with 49% (21 out of 43) of patients who were diagnosed with cancer and had chosen to not undergo surveillance ($P=.012$).²⁷⁷ Five-year OS was greater for patients undergoing surveillance (88.8%) compared with patients not undergoing surveillance (59.6%), $P=.013$. The clinical surveillance protocol used was shown to be feasible, though further evaluation is warranted.²⁷⁶ Based on these

study results, the panel recommends annual whole-body MRI as a category 2B recommendation. This is consistent with recommendations described in the Toronto protocol.²⁷³ The panel acknowledges that this surveillance method may not be uniformly available. Patients who do not have access to whole-body MRI should be encouraged to enroll in clinical trials, or alternative comprehensive imaging methods may be used. The panel also acknowledges that whole-body MRI screening of all individuals with LFS may result in false positives and overdiagnosis.^{275,278} Further, the utility of whole-body MRI has not been evaluated in individuals with a *TP53* pathogenic/likely pathogenic variant who don't have a classic family history of LFS, a group that is increasingly being identified through multigene testing. The brain may be examined as part of whole-body MRI or as a separate exam.

Only very limited data exist on the use of prenatal diagnostics/genetic testing for *TP53* mutations in families with LFS.^{279,280} Counseling for reproductive options such as prenatal diagnosis, PGT, and assisted reproduction may be warranted for couples expressing concern over their future offspring's carrier status of a pathogenic or likely pathogenic variant. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options. For general discussions on the topic of reproductive options and counseling considerations, see "Reproductive Options" (page 91).

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^aThe following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

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