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.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

PLEASE NOTE

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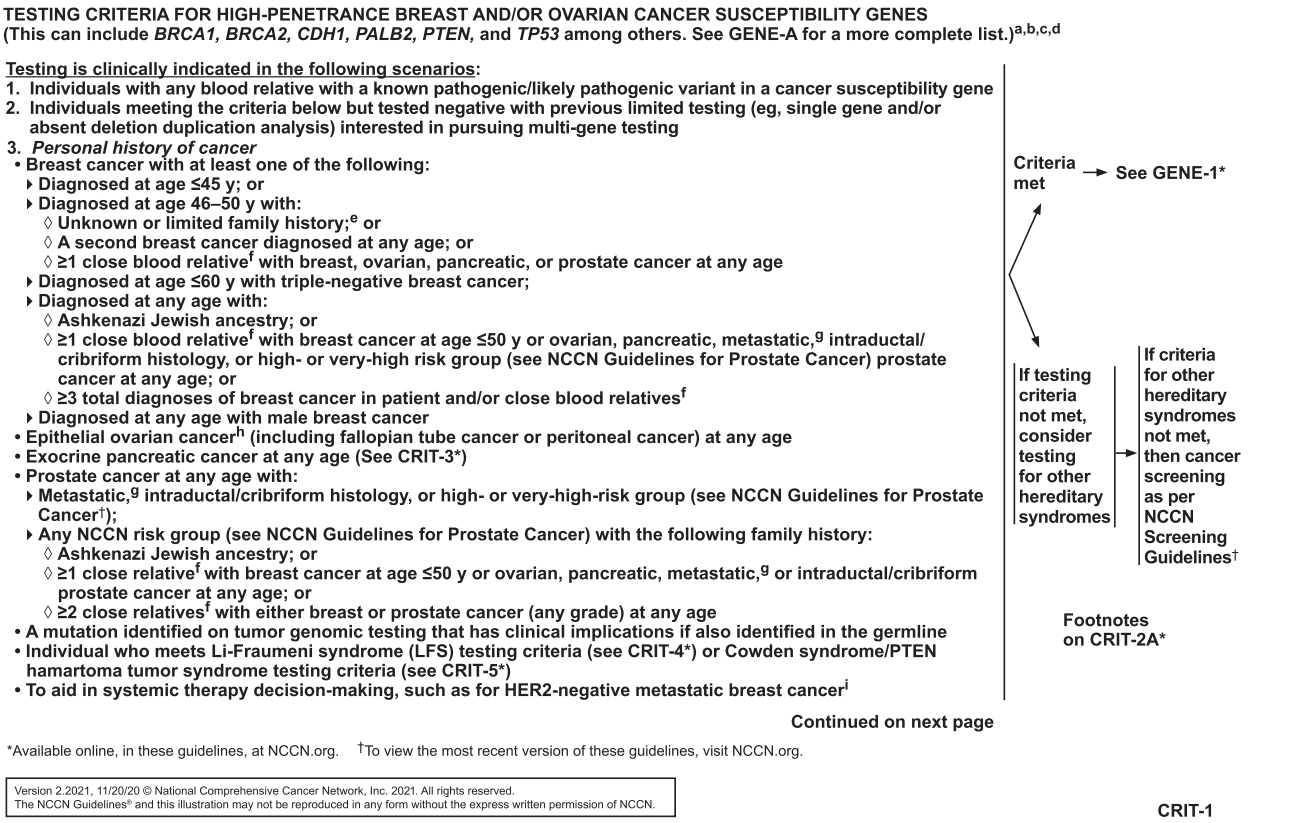
The complete NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

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.)

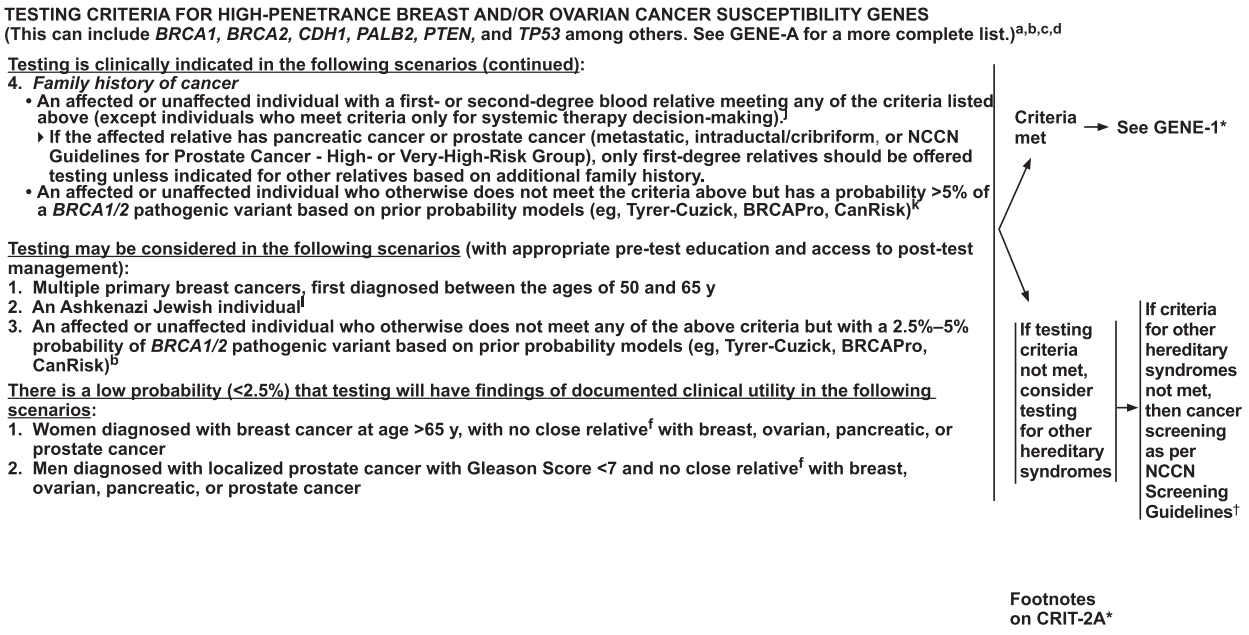
The complete and most recent version of these guidelines is available free of charge at NCCN.org.



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.



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CRIT-2

BRCA-Related Breast/Ovarian Cancer Syndrome

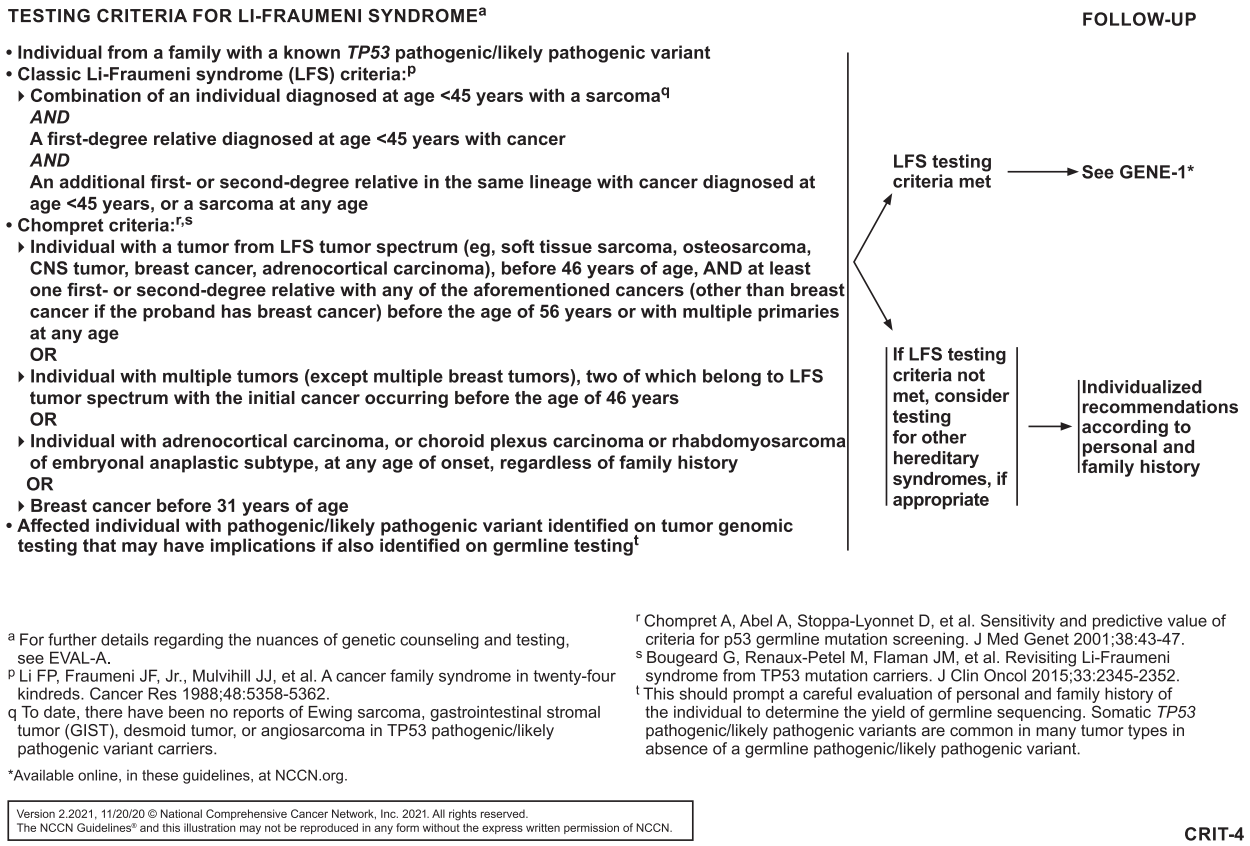
Both the *BRCA1* and *BRCA2* genes encode for proteins involved in tumor suppression. *BRCA1/2* pathogenic or likely pathogenic variants can be highly penetrant, although the probability of cancer development in carriers of *BRCA1/2* pathogenic or likely pathogenic variants is variable, even within families 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% lifetime 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;



[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.

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[†]).

[†]To view the most recent version of these guidelines, visit NCCN.org.

Footnotes on BRCA-A 2 of 2
Continued

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
2 OF 2

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

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, which may obviate the need for a conventional digital image.[147,156,157] 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 study[225] 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 following[247]: 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 al[260] 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).

References

1. Blackwood MA, Weber BL. BRCA1 and BRCA2: from molecular genetics to clinical medicine. J Clin Oncol 1998;16:1969–1977.
2. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. Cell 2002;108:171–182.
3. Schneider KA, Garber J. Li-Fraumeni syndrome. GeneReviews. Accessed December 9, 2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1311/
4. Abeliovich D, Kaduri L, Lerer I, et al. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet 1997;60:505–514.
5. Levy-Lahad E, Catane R, Eisenberg S, et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. Am J Hum Genet 1997;60:1059–1067.
6. Petrucelli N, Daly MB, Bars Culver JO, et al. BRCA1 and BRCA2 hereditary breast/ovarian cancer. GeneReviews. Accessed December 9, 2020. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1247/
7. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Br J Cancer 2000;83:1301–1308.
8. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117–1130.
9. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329–1333.
10. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Lancet 1994;343:692–695.
11. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643–646.
12. Mavaddat N, Peock S, Frost D, et al.EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013;105:812–822.
13. Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98:1694–1706.
14. van den Broek AJ, van 't Veer LJ, Hooning MJ, et al. Impact of age at primary breast cancer on contralateral breast cancer risk in BRCA1/2 mutation carriers. J Clin Oncol 2016;34:409–418.
15. Hu C, Polley EC, Yadav S, et al. The contribution of germline predisposition gene mutations to clinical subtypes of invasive breast cancer from a clinical genetic testing cohort [published online February 24,2020]. J Natl Cancer Inst, doi: 10.1093/jnci/djaa023
16. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402–2416.
17. Bordeleau L, Panchal S, Goodwin P. Prognosis of BRCA-associated breast cancer: a summary of evidence. Breast Cancer Res Treat 2010;119:13–24.
18. Verhoog LC, Berns EM, Brekelmans CT, et al. Prognostic significance of germline BRCA2 mutations in hereditary breast cancer patients. J Clin Oncol 2000; **18**(21, Suppl):119S–124S.
19. Zhong Q, Peng HL, Zhao X, et al. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. Clin Cancer Res 2015;21:211–220.

20. Baretta Z, Mocellin S, Goldin E, et al. Effect of BRCA germline mutations on breast cancer prognosis: A systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e4975.
21. van den Broek AJ, Schmidt MK, van 't Veer LJ, et al. Worse breast cancer prognosis of BRCA1/BRCA2 mutation carriers: what's the evidence? A systematic review with meta-analysis. PLoS One 2015;10:e0120189.
22. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol 2018;19:169–180.
23. Kast K, Rhiem K, Wappenschmidt B, et al. Prevalence of BRCA1/2 germline mutations in 21 401 families with breast and ovarian cancer. J Med Genet 2016;53:465–471.
24. Schmidt MK, van den Broek AJ, Tollenaar RA, et al. Breast cancer survival of BRCA1/BRCA2 mutation carriers in a hospital-based cohort of young women [published online August 1, 2017. J Natl Cancer Inst, doi: 10.1093/jnci/djw329
25. Litton JK, Ready K, Chen H, et al. Earlier age of onset of BRCA mutation-related cancers in subsequent generations. Cancer 2012;118:321–325.
26. Guindalini RS, Song A, Fackenthal JD, et al. Genetic anticipation in BRCA1/BRCA2 families after controlling for ascertainment bias and cohort effect. Cancer 2016;122:1913–1920.
27. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol 2008;26:4282–4288.
28. Eerola H, Heikkilä P, Tamminen A, et al. Relationship of patients' age to histopathol]ogical features of breast tumours in BRCA1 and BRCA2 and mutation-negative breast cancer families. Breast Cancer Res 2005;7: R465–R469.
29. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 2005;11:5175–5180.
30. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002;20:2310–2318.
31. Lee E, McKean-Cowdin R, Ma H, et al. Characteristics of triple-negative breast cancer in patients with a BRCA1 mutation: results from a population-based study of young women. J Clin Oncol 2011;29: 4373–4380.
32. Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 2009;9:86.
33. Fostira F, Tsitlaidou M, Papadimitriou C, et al. Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group Study. Breast Cancer Res Treat 2012;134:353–362.
34. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and outcome of BRCA mutations in unselected patients with triple receptor-negative breast cancer. Clin Cancer Res 2011;17:1082–1089.
35. Rummel S, Varner E, Shriver CD, et al. Evaluation of BRCA1 mutations in an unselected patient population with triple-negative breast cancer. Breast Cancer Res Treat 2013;137:119–125.
36. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol 2015; 33:304–311.
37. Tung N, Lin NU, Kidd J, et al. Frequency of germline mutations in 25 cancer susceptibility genes in a sequential series of patients with breast cancer. J Clin Oncol 2016;34:1460–1468.
38. Buys SS, Sandbach JF, Gammon A, et al. A study of over 35,000 women with breast cancer tested with a 25-gene panel of hereditary cancer genes. Cancer 2017;123:1721–1730.
39. Shimelis H, LaDuca H, Hu C, et al. Triple-negative breast cancer risk genes identified by multigene hereditary cancer panel testing. J Natl Cancer Inst 2018;110:855–862.
40. Evans DG, Howell A, Ward D, et al. Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. J Med Genet 2011;48: 520–522.
41. Meyer P, Landgraf K, Högel B, et al. BRCA2 mutations and triple-negative breast cancer. PLoS One 2012;7:e38361.
42. Metcalfe K, Lynch HT, Foulkes WD, et al. Oestrogen receptor status and survival in women with BRCA2-associated breast cancer. Br J Cancer 2019;120:398–403.
43. Jonasson JG, Stefansson OA, Johannsson OT, et al. Oestrogen receptor status, treatment and breast cancer prognosis in Icelandic BRCA2 mutation carriers. Br J Cancer 2016;115:776–783.
44. Lee LJ, Alexander B, Schnitt SJ, et al. Clinical outcome of triple negative breast cancer in BRCA1 mutation carriers and noncarriers. Cancer 2011; 117:3093–3100.
45. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004;22:735–742.
46. Basham VM, Lipscombe JM, Ward JM, et al. BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. Breast Cancer Res 2002;4:R2.
47. Couch FJ, Farid LM, DeShano ML, et al. BRCA2 germline mutations in male breast cancer cases and breast cancer families. Nat Genet 1996;13: 123–125.
48. Ding YC, Steele L, Kuan CJ, et al. Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. Breast Cancer Res Treat 2011;126:771–778.
49. Friedman LS, Gayther SA, Kurosaki T, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. Am J Hum Genet 1997; 60:313–319.
50. Evans DG, Susnerwala I, Dawson J, et al. Risk of breast cancer in male BRCA2 carriers. J Med Genet 2010;47:710–711.
51. Tai YC, Domchek S, Parmigiani G, et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2007;99: 1811–1814.
52. What are the key statistics about breast cancer in men? Accessed May 28, 2015. Available at: http://www.cancer.org/cancer/breastcancerin-men/detailedguide/breast-cancer-in-men-key-statistics
53. Levine DA, Argenta PA, Yee CJ, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol 2003;21:4222–4227.
54. Piver MS, Jishi MF, Tsukada Y, et al. Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. A report of the Gilda Radner Familial Ovarian Cancer Registry. Cancer 1993;71:2751–2755.
55. Arts-de Jong M, de Bock GH, van Asperen CJ, et al. Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: a systematic review. Eur J Cancer 2016;61:137–145.
56. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 2005; 104:2807–2816.
57. Schrader KA, Hurlburt J, Kalloger SE, et al. Germline BRCA1 and BRCA2 mutations in ovarian cancer: utility of a histology-based referral strategy. Obstet Gynecol 2012;120:235–240.
58. Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol 2011;121:353–357.
59. Song H, Cicek MS, Dicks E, et al. The contribution of deleterious germline mutations in BRCA1, BRCA2 and the mismatch repair genes to ovarian cancer in the population. Hum Mol Genet 2014;23:4703–4709.
60. Chen J, Bae E, Zhang L, et al. Penetrance of breast and ovarian cancer in women who carry a BRCA1/2 mutation and do not use risk-reducing salpingo-oophorectomy: an updated meta-analysis [published online August 4, 2020]. JNCI Cancer Spectr, doi: 10.1093/jncics/pkaa029
61. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30:2654–2663.
62. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012;307:382–390.
63. Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer 2003;97:2187–2195.
64. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, et al. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol 2008;26:20–25.
65. Tan DS, Rothermundt C, Thomas K, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol 2008;26:5530–5536.
66. Yang D, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA 2011;306:1557–1565.

67. Dong F, Davineni PK, Howitt BE, et al. BRCA1/2 mutational signature and survival in ovarian high-grade serous carcinoma. Cancer Epidemiol Biomarkers Prev 2016;25:1511–1516.
68. Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. JAMA Oncol 2016;2:482–490.
69. Bjørge T, Lie AK, Hovig E, et al. BRCA1 mutations in ovarian cancer and borderline tumours in Norway: a nested case-control study. Br J Cancer 2004;91:1829–1834.
70. Jazaeri AA, Lu K, Schmandt R, et al. Molecular determinants of tumor differentiation in papillary serous ovarian carcinoma. Mol Carcinog 2003; 36:53–59.
71. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res 2004;10:2473–2481.
72. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.
73. Rechsteiner M, Zimmermann AK, Wild PJ, et al. TP53 mutations are common in all subtypes of epithelial ovarian cancer and occur concomitantly with KRAS mutations in the mucinous type. Exp Mol Pathol 2013;95:235–241.
74. Werness BA, Ramus SJ, DiCioccio RA, et al. Histopathology, FIGO stage, and BRCA mutation status of ovarian cancers from the Gilda Radner Familial Ovarian Cancer Registry. Int J Gynecol Pathol 2004;23:29–34.
75. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. J Clin Oncol 2007;25:3985–3990.
76. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol 2006;100:58–64.
77. Powell CB, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. Int J Gynecol Cancer 2011;21:846–851.
78. Rush SK, Swisher EM, Garcia RL, et al. Pathologic findings and clinical outcomes in women undergoing risk-reducing surgery to prevent ovarian and fallopian tube carcinoma: A large prospective single institution experience. Gynecol Oncol 2020;157:514–520.
79. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol 2005;23:127–132.
80. Shaw PA, Rouzbahman M, Pizer ES, et al. Candidate serous cancer precursors in fallopian tube epithelium of BRCA1/2 mutation carriers. Mod Pathol 2009;22:1133–1138.
81. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol 2006;30:230–236.
82. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol 2007;31:161–169.
83. Agalliu I, Gern R, Leanza S, et al. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res 2009;15:1112–1120.
84. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106: 1697–1701.
85. Nicolosi P, Ledet E, Yang S, et al. Prevalence of germline variants in prostate cancer and implications for current genetic testing guidelines. JAMA Oncol 2019;5:523–528.
86. Giri VN, Hegarty SE, Hyatt C, et al. Germline genetic testing for inherited prostate cancer in practice: Implications for genetic testing, precision therapy, and cascade testing. Prostate 2019;79:333–339.
87. Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making [published online May 31, 2017]. JCO Precis Oncol, doi: 10.1200/PO.17.00029
88. Na R, Zheng SL, Han M, et al. Germline mutations in ATM and BRCA1/2 distinguish risk for lethal and indolent prostate cancer and are associated with early age at death. Eur Urol 2017;71:740–747.
89. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016; 375:443–453.
90. Lang SH, Swift SL, White H, et al. A systematic review of the prevalence of DNA damage response gene mutations in prostate cancer. Int J Oncol 2019;55:597–616.
91. Nyberg T, Frost D, Barrowdale D, et al. Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Eur Urol 2020;77:24–35.
92. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748–1757.
93. Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res 2004;10:2918–2921.
94. Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010;16: 2115–2121.
95. Hamel N, Kotar K, Foulkes WD. Founder mutations in BRCA1/2 are not frequent in Canadian Ashkenazi Jewish men with prostate cancer. BMC Med Genet 2003;4:7.
96. Nastiuk KL, Mansukhani M, Terry MB, et al. Common mutations in BRCA1 and BRCA2 do not contribute to early prostate cancer in Jewish men. Prostate 1999;40:172–177.
97. Goggins M, Schutte M, Lu J, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 1996;56:5360–5364.
98. Lal G, Liu G, Schmocker B, et al. Inherited predisposition to pancreatic adenocarcinoma: role of family history and germ-line p16, BRCA1, and BRCA2 mutations. Cancer Res 2000;60:409–416.
99. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res 2002;62:3789–3793.
100. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2007;16:342–346.
101. Ghiorzo P, Fornarini G, Sciallero S, et al. CDKN2A is the main susceptibility gene in Italian pancreatic cancer families. J Med Genet 2012;49: 164–170.
102. Lucas AL, Shakya R, Lipsyc MD, et al. High prevalence of BRCA1 and BRCA2 germline mutations with loss of heterozygosity in a series of resected pancreatic adenocarcinoma and other neoplastic lesions. Clin Cancer Res 2013;19:3396–3403.
103. Holter S, Borgida A, Dodd A, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. J Clin Oncol 2015;33:3124–3129.
104. Zhen DB, Rabe KG, Gallinger S, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study. Genet Med 2015;17:569–577.
105. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer 2015;121: 4382–4388.
106. Mandelker D, Zhang L, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA 2017;318:825–835.
107. Shindo K, Yu J, Suenaga M, et al. Deleterious germline mutations in patients with apparently sporadic pancreatic adenocarcinoma. J Clin Oncol 2017;35:3382–3390.
108. Huang KL, Mashl RJ, Wu Y, et al. Pathogenic germline variants in 10,389 adult cancers. Cell 2018;173:355–370,e314.
109. Chaffee KG, Oberg AL, McWilliams RR, et al. Prevalence of germ-line mutations in cancer genes among pancreatic cancer patients with a positive family history. Genet Med 2018;20:119–127.
110. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA 2018;319:2401–2409.
111. Lowery MA, Wong W, Jordan EJ, et al. Prospective evaluation of germline alterations in patients with exocrine pancreatic neoplasms. J Natl Cancer Inst 2018;110:1067–1074.
112. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol 2009;27: 433–438.
113. de Jonge MM, Mooyaart AL, Vreeswijk MP, et al. Linking uterine serous carcinoma to BRCA1/2-associated cancer syndrome: A meta-analysis and case report. Eur J Cancer 2017;72:215–225.
114. Lavie O, Ben-Arie A, Segev Y, et al. BRCA germline mutations in women with uterine serous carcinoma--still a debate. Int J Gynecol Cancer 2010; 20:1531–1534.
115. Saule C, Mouret-Fourme E, Briaux A, et al. Risk of serous endometrial carcinoma in women with pathogenic BRCA1/2 variant after

risk-reducing salpingo-oophorectomy [published online February 10, 2018]. J Natl Cancer Inst, doi: 10.1093/jnci/djx159

116. Laitman Y, Michaelson-Cohen R, Levi E, et al. Uterine cancer in Jewish Israeli BRCA1/2 mutation carriers. Cancer 2019;125:698–703.
117. Shu CA, Pike MC, Jotwani AR, et al. Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. JAMA Oncol 2016;2:1434–1440.
118. Beiner ME, Finch A, Rosen B, et al.Hereditary Ovarian Cancer Clinical Study Group. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol 2007;104:7–10.
119. Lee YC, Milne RL, Lheureux S, et al. Risk of uterine cancer for BRCA1 and BRCA2 mutation carriers. Eur J Cancer 2017;84:114–120.
120. Gumaste PV, Penn LA, Cymerman RM, et al. Skin cancer risk in BRCA1/2 mutation carriers. Br J Dermatol 2015;172:1498–1506.
121. Iqbal J, Nussenzweig A, Lubinski J, et al. The incidence of leukaemia in women with BRCA1 and BRCA2 mutations: an International Prospective Cohort Study. Br J Cancer 2016;114:1160–1164.
122. Lorenzo Bermejo J, Hemminki K. Risk of cancer at sites other than the breast in Swedish families eligible for BRCA1 or BRCA2 mutation testing. Ann Oncol 2004;15:1834–1841.
123. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310–1316.
124. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 2012;11:235–242.
125. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317–1325.
126. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;351:427–437.
127. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769–1778.
128. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57:75–89.
129. Stoutjesdijk MJ, Boetes C, Jager GJ, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 2001;93:1095–1102.
130. Berg WA. How well does supplemental screening magnetic resonance imaging work in high-risk women? J Clin Oncol 2014;32:2193–2196.
131. Buist DS, Porter PL, Lehman C, et al. Factors contributing to mammography failure in women aged 40-49 years. J Natl Cancer Inst 2004; 96:1432–1440.
132. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 2000;92:1081–1087.
133. Tilanus-Linthorst M, Verhoog L, Obdeijn IM, et al. A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently contribute to a frequent false-negative mammography. Int J Cancer 2002;102:91–95.
134. van Gils CH, Otten JD, Verbeek AL, et al. Effect of mammographic breast density on breast cancer screening performance: a study in Nijmegen, The Netherlands. J Epidemiol Community Health 1998;52:267–271.
135. Gilliland FD, Joste N, Stauber PM, et al. Biologic characteristics of interval and screen-detected breast cancers. J Natl Cancer Inst 2000;92: 743–749.
136. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 2005;23:8469–8476.
137. Riedl CC, Ponhold L, Flöry D, et al. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. Clin Cancer Res 2007;13:6144–6152.
138. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. Radiology 2007;242:698–715.
139. Passaperuma K, Warner E, Causer PA, et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. Br J Cancer 2012;107:24–30.
140. 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: djv349.
141. Phi XA, Saadatmand S, De Bock GH, et al. Contribution of mammography to MRI screening in BRCA mutation carriers by BRCA status and age: individual patient data meta-analysis. Br J Cancer 2016;114: 631–637.
142. Le-Petross HT, Whitman GJ, Atchley DP, et al. Effectiveness of alternating mammography and magnetic resonance imaging for screening women with deleterious BRCA mutations at high risk of breast cancer. Cancer 2011;117:3900–3907.
143. Goldfrank D, Chuai S, Bernstein JL, et al. Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. Cancer Epidemiol Biomarkers Prev 2006;15:2311–2313.
144. Narod SA, Lubinski J, Ghadirian P, et al. Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet Oncol 2006;7:402–406.
145. Pijpe A, Andrieu N, Easton DF, et al.HEBON. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). BMJ 2012;345(sep06 2): e5660.
146. Ciatto S, Houssami N, Bernardi D, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. Lancet Oncol 2013;14:583–589.
147. Skaane P, Bandos AI, Gullien R, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology 2013;267:47–56.
148. Rafferty EA, Park JM, Philpotts LE, et al. Assessing radiologist performance using combined digital mammography and breast tomosynthesis compared with digital mammography alone: results of a multicenter, multireader trial. Radiology 2013;266:104–113.
149. Friedewald SM, Rafferty EA, Conant EF. Breast cancer screening with tomosynthesis and digital mammography-reply. JAMA 2014;312: 1695–1696.
150. Lourenco AP, Barry-Brooks M, Baird GL, et al. Changes in recall type and patient treatment following implementation of screening digital breast tomosynthesis. Radiology 2015;274:337–342.
151. Rose SL, Tidwell AL, Ice MF, et al. A reader study comparing prospective tomosynthesis interpretations with retrospective readings of the corresponding FFDM examinations. Acad Radiol 2014;21:1204–1210.
152. Destounis S, Arieno A, Morgan R. Initial experience with combination digital breast tomosynthesis plus full field digital mammography or full field digital mammography alone in the screening environment. J Clin Imaging Sci 2014;4:9.
153. Margolies L, Cohen A, Sonnenblick E, et al. Digital breast tomosynthesis changes management in patients seen at a tertiary care breast center. ISRN Radiol 2014;2014:658929.
154. Lång K, Andersson I, Rosso A, et al. Performance of one-view breast tomosynthesis as a stand-alone breast cancer screening modality: results from the Malmö Breast Tomosynthesis Screening Trial, a population-based study. Eur Radiol 2016;26:184–190.
155. Gilbert FJ, Tucker L, Gillan MG, et al. Accuracy of digital breast tomosynthesis for depicting breast cancer subgroups in a UK retrospective reading study (TOMMY Trial). Radiology 2015;277:697–706.
156. Zuckerman SP, Conant EF, Keller BM, et al. Implementation of synthesized two-dimensional mammography in a population-based digital breast tomosynthesis screening program. Radiology 2016;281:730–736.
157. Skaane P, Bandos AI, Eben EB, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. Radiology 2014;271:655–663.
158. Lowry KP, Lee JM, Kong CY, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118:2021–2030.
159. Hartmann LC, Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med 2016;374:454–468.
160. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016;387:945–956.
161. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009;10:327–340.
162. Rosenthal AN, Fraser LSM, Philpott S, et al. Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United

Kingdom Familial Ovarian Cancer Screening Study. J Clin Oncol 2017; 35:1411–1420.

163. Skates SJ, Greene MH, Buys SS, et al. Early detection of ovarian cancer using the risk of ovarian cancer algorithm with frequent CA125 testing in women at increased familial risk - combined results from two screening trials. Clin Cancer Res 2017;23:3628–3637.
164. Gao Y, Goldberg JE, Young TK, et al. Breast cancer screening in high-risk men: a 12-year longitudinal observational study of male breast imaging utilization and outcomes. Radiology 2019;293:282–291.
165. Li X, You R, Wang X, et al. Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: a meta-analysis and systematic review. Clin Cancer Res 2016;22:3971–3981.
166. Honold F, Camus M. Prophylactic mastectomy versus surveillance for the prevention of breast cancer in women's BRCA carriers. Medwave 2018; 18:e7161.
167. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77–84.
168. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. J Natl Cancer Inst 2001;93:1633–1637.
169. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:159–164.
170. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2004;22:1055–1062.
171. Carbine NE, Lostumbo L, Wallace J, et al. Risk-reducing mastectomy for the prevention of primary breast cancer. Cochrane Database Syst Rev 2018;4:CD002748.
172. Morrow M, Mehrara B. Prophylactic mastectomy and the timing of breast reconstruction. Br J Surg 2009;96:1–2.
173. Jakub JW, Peled AW, Gray RJ, et al. Oncologic safety of prophylactic nipple-sparing mastectomy in a population with BRCA mutations: a multi-institutional study. JAMA Surg 2018;153:123–129.
174. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res 2002;8: 3776–3781.
175. Finch AP, Lubinski J, Møller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2014;32:1547–1553.
176. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101:80–87.
177. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol 2008;26:1331–1337.
178. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609–1615.
179. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 1999;91:1475–1479.
180. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346: 1616–1622.
181. Harmsen MG, Piek JMJ, Bulten J, et al. Peritoneal carcinomatosis after risk-reducing surgery in BRCA1/2 mutation carriers. Cancer 2018;124: 952–959.
182. Sherman ME, Piedmonte M, Mai PL, et al. Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. J Clin Oncol 2014;32:3275–3283.
183. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 2005;23:7491–7496.
184. Xiao YL, Wang K, Liu Q, et al. Risk reduction and survival benefit of risk-reducing salpingo-oophorectomy in hereditary breast cancer: meta-analysis and systematic review. Clin Breast Cancer 2019;19:e48–e65.
185. Domchek SM, Friebel TM, Singer CF, et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality. JAMA 2010;304:967–975.
186. Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol 2006;7:223–229.
187. Metcalfe K, Lynch HT, Foulkes WD, et al. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. JAMA Oncol 2015;1:306–313.
188. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction [published online March 18, 2015]. J Natl Cancer Inst, doi: 10.1093/jnci/djv033
189. Chai X, Domchek S, Kauff N, et al. RE: Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction [published online August 11, 2015]. J Natl Cancer Inst, doi: 10.1093/jnci/djv217
190. Terry MB, Daly MB, Phillips KA, et al. Risk-reducing oophorectomy and breast cancer risk across the spectrum of familial risk. J Natl Cancer Inst 2019;111:331–334.
191. Kotsopoulos J, Huzarski T, Gronwald J, et al. Bilateral oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers [published online September 6, 2016]. J Natl Cancer Inst, doi: 10.1093/jnci/djw177
192. Stjepanovic N, Villacampa G, Nead KT, et al. Association of pre-menopausal risk-reducing salpingo-oophorectomy with breast cancer risk in BRCA1/2 mutation carriers: maximising bias-reduction. Eur J Cancer 2020;132:53–60.
193. Marchetti C, De Felice F, Boccia S, et al. Hormone replacement therapy after prophylactic risk-reducing salpingo-oophorectomy and breast cancer risk in BRCA1 and BRCA2 mutation carriers: A meta-analysis. Crit Rev Oncol Hematol 2018;132:111–115.
194. Gordhandas S, Norquist BM, Pennington KP, et al. Hormone replacement therapy after risk reducing salpingo-oophorectomy in patients with BRCA1 or BRCA2 mutations; a systematic review of risks and benefits. Gynecol Oncol 2019;153:192–200.
195. Chlebowski RT, Prentice RL. Menopausal hormone therapy in BRCA1 mutation carriers: uncertainty and caution. J Natl Cancer Inst 2008;100: 1341–1343.
196. Garber JE, Hartman AR. Prophylactic oophorectomy and hormone replacement therapy: protection at what price? J Clin Oncol 2004;22: 978–980.
197. McAlpine JN, Hanley GE, Woo MM, et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. Am J Obstet Gynecol 2014;210:471.e1–471.e11.
198. Findley AD, Siedhoff MT, Hobbs KA, et al. Short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve: a pilot randomized controlled trial. Fertil Steril 2013;100:1704–1708.
199. Daly MB, Dresher CW, Yates MS, et al. Salpingectomy as a means to reduce ovarian cancer risk. Cancer Prev Res (Phila) 2015;8:342–348.
200. Chlebowski RT, Rohan TE, Manson JE, et al. Breast cancer after use of estrogen plus progestin and estrogen alone: analyses of data from 2 Women's Health Initiative randomized clinical trials. JAMA Oncol 2015; 1:296–305.
201. College of American Pathologists (CAP). Protocol for the examination of specimens from patients with carcinoma of the ovary. 2009. Available at:. Accessed March 2011. http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/Ovary_09protocol.pdf
202. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. multiple outcomes of raloxifene evaluation. JAMA 1999;281:2189–2197.
203. Cuzick J, Sestak I, Bonanni B, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 2013;381:1827–1834.
204. Lippman ME, Cummings SR, Disch DP, et al. Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. Clin Cancer Res 2006;12: 5242–5247.
205. Martino S, Cauley JA, Barrett-Connor E, et al.CORE Investigators. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004;96:1751–1761.
206. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2727–2741.
207. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and

Raloxifene (STAR) P-2 Trial: preventing breast cancer. Cancer Prev Res (Phila) 2010;3:696–706.

208. Powles TJ, Ashley S, Tidy A, et al. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 2007;99:283–290.
209. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005;97: 1652–1662.
210. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–2335.
211. Gronwald J, Tung N, Foulkes WD, et al. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer 2006;118:2281–2284.
212. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet 2000;356:1876–1881.
213. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 2001;286:2251–2256.
214. Ingle JN, Liu M, Wickerham DL, et al. Selective estrogen receptor modulators and pharmacogenomic variation in ZNF423 regulation of BRCA1 expression: individualized breast cancer prevention. Cancer Discov 2013;3:812–825.
215. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 2011;364: 2381–2391.
216. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 2014;383: 1041–1048.
217. Nemati Shafaee M, Gutierrez-Barrera AM, Lin HY, et al. Aromatase inhibitors and the risk of contralateral breast cancer in BRCA mutation carriers. J Clin Oncol 2015;33(28_suppl):3–3.
218. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol 2007;8:26–34.
219. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 1998;339:424–428.
220. Iodice S, Barile M, Rotmensz N, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 2010;46:2275–2284.
221. Moorman PG, Havrilesky LJ, Gierisch JM, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol 2013;31:4188–4198.
222. Narod SA, Dubé MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94:1773–1779.
223. Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863–1870.
224. Milne RL, Knight JA, John EM, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005;14:350–356.
225. Lee E, Ma H, McKean-Cowdin R, et al. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiol Biomarkers Prev 2008;17:3170–3178.
226. Offit K, Levran O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548–1551.
227. Sawyer SL, Tian L, Kähkönen M, et al. Biallelic mutations in BRCA1 cause a new Fanconi anemia subtype. Cancer Discov 2015;5:135–142.
228. Keupp K, Hampp S, Hübbel A, et al. Biallelic germline BRCA1 mutations in a patient with early onset breast cancer, mild Fanconi anemia-like phenotype, and no chromosome fragility. Mol Genet Genomic Med 2019;7:e863.
229. Domchek SM, Tang J, Stopfer J, et al. Biallelic deleterious BRCA1 mutations in a woman with early-onset ovarian cancer. Cancer Discov 2013;3:399–405.
230. Offit K, Kohut K, Clagett B, et al. Cancer genetic testing and assisted reproduction. J Clin Oncol 2006;24:4775–4782.
231. Offit K, Sagi M, Hurley K. Preimplantation genetic diagnosis for cancer syndromes: a new challenge for preventive medicine. JAMA 2006;296: 2727–2730.
232. Jasper MJ, Liebelt J, Hussey ND. Preimplantation genetic diagnosis for BRCA1 exon 13 duplication mutation using linked polymorphic markers resulting in a live birth. Prenat Diagn 2008;28:292–298.
233. Sagi M, Weinberg N, Eilat A, et al. Preimplantation genetic diagnosis for BRCA1/2--a novel clinical experience. Prenat Diagn 2009;29:508–513.
234. Sidransky D, Tokino T, Helzlsouer K, et al. Inherited p53 gene mutations in breast cancer. Cancer Res 1992;52:2984–2986.
235. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol 2009;27:1250–1256.
236. Lalloo F, Varley J, Ellis D, et al. Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. Lancet 2003; 361:1101–1102.
237. Masciari S, Dewanwala A, Stoffel EM, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med 2011;13:651–657.
238. Lane DP. Cancer. p53, guardian of the genome. Nature 1992;358:15–16.
239. Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997;88:323–331.
240. Garber JE, Goldstein AM, Kantor AF, et al. Follow-up study of twenty-four families with Li-Fraumeni syndrome. Cancer Res 1991;51: 6094–6097.
241. Nichols KE, Malkin D, Garber JE, et al. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. Cancer Epidemiol Biomarkers Prev 2001;10:83–87.
242. Siddiqui R, Onel K, Facio F, et al. The TP53 mutational spectrum and frequency of CHEK2*1100delC in Li-Fraumeni-like kindreds. Fam Cancer 2005;4:177–181.
243. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer 2016;122:3673–3681.
244. Birch JM, Hartley AL, Tricker KJ, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 1994;54:1298–1304.
245. Krutilkova V, Trkova M, Fleitz J, et al. Identification of five new families strengthens the link between childhood choroid plexus carcinoma and germline TP53 mutations. Eur J Cancer 2005;41:1597–1603.
246. Li FP, Fraumeni JF, Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 1969;71:747–752.
247. Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358–5362.
248. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–1238.
249. Varley JM, Evans DG, Birch JM. Li-Fraumeni syndrome--a molecular and clinical review. Br J Cancer 1997;76:1–14.
250. Holmfeldt L, Wei L, Diaz-Flores E, et al. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet 2013;45: 242–252.
251. Kamihara J, Rana HQ, Garber JE. Germline TP53 mutations and the changing landscape of Li-Fraumeni syndrome. Hum Mutat 2014;35: 654–662.
252. Curiel-Lewandrowski C, Speetzen LS, Cranmer L, et al. Multiple primary cutaneous melanomas in Li-Fraumeni syndrome. Arch Dermatol 2011; 147:248–250.
253. Giavedoni P, Ririe M, Carrera C, et al. Familial melanoma associated with Li-Fraumeni Syndrome and Atypical Mole Syndrome: total-body digital photography, dermoscopy and confocal microscopy. Acta Derm Venereol 2017;97:720–723.
254. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, et al. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. Cancer 2012;118:908–913.
255. Wilson JR, Bateman AC, Hanson H, et al. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. J Med Genet 2010;47:771–774.
256. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst 1998;90:606–611.
257. Lustbader ED, Williams WR, Bondy ML, et al. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. Am J Hum Genet 1992;51:344–356.

258. Birch JM, Blair V, Kelsey AM, et al. Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. Oncogene 1998;17:1061–1068.
259. Chompret A. The Li-Fraumeni syndrome. Biochimie 2002;84:75–82.
260. 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.
261. Eeles RA. Germline mutations in the TP53 gene. Cancer Surv 1995;25: 101–124.
262. Bougeard G, Sesboüé R, Baert-Desurmont S, et al. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. J Med Genet 2008;45:535–538.
263. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33: 2345–2352.
264. Tinat J, Bougeard G, Baert-Desurmont S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. J Clin Oncol 2009;27: e108–e109., author reply e110.
265. Ginsburg OM, Akbari MR, Aziz Z, et al. The prevalence of germ-line TP53 mutations in women diagnosed with breast cancer before age 30. Fam Cancer 2009;8:563–567.
266. Lalloo F, Varley J, Moran A, et al. BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. Eur J Cancer 2006;42:1143–1150.
267. Lee DS, Yoon SY, Looi LM, et al. Comparable frequency of BRCA1, BRCA2 and TP53 germline mutations in a multi-ethnic Asian cohort suggests TP53 screening should be offered together with BRCA1/2 screening to early-onset breast cancer patients. Breast Cancer Res 2012;14:R66.
268. Mouchawar J, Korch C, Byers T, et al. Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast cancer: Australian Breast Cancer Family Study. Cancer Res 2010;70: 4795–4800.
269. McCuaig JM, Armel SR, Novokmet A, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? Fam Cancer 2012;11: 607–613.
270. Leroy B, Anderson M, Soussi T. TP53 mutations in human cancer: database reassessment and prospects for the next decade. Hum Mutat 2014;35:672–688.
271. Kandoth C, McLellan MD, Vandin F, et al. Mutational landscape and significance across 12 major cancer types. Nature 2013;502:333–339.
272. Mai PL, Khincha PP, Loud JT, et al. Prevalence of cancer at baseline screening in the National Cancer Institute Li-Fraumeni syndrome cohort. JAMA Oncol 2017;3:1640–1645.
273. Kratz CP, Achatz MI, Brugières L, et al. Cancer screening recommendations for individuals with Li-Fraumeni Syndrome. Clin Cancer Res 2017;23:e38–e45.
274. Greer MC, Voss SD, States LJ. Pediatric cancer predisposition imaging: focus on whole-body MRI. Clin Cancer Res 2017;23:e6–e13.
275. Ballinger ML, Best A, Mai PL, et al. Baseline surveillance in Li-Fraumeni syndrome using whole-body magnetic resonance imaging: a meta-analysis. JAMA Oncol 2017;3:1634–1639.
276. Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol 2011;12:559–567.
277. Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol 2016;17:1295–1305.
278. Asdahl PH, Ojha RP, Hasle H. Cancer Screening in Li-Fraumeni Syndrome. JAMA Oncol 2017;3:1645–1646.
279. Avigad S, Peleg D, Barel D, et al. Prenatal diagnosis in Li-Fraumeni syndrome. J Pediatr Hematol Oncol 2004;26:541–545.
280. Prochazkova K, Foretova L, Sedlacek Z. A rare tumor and an ethical dilemma in a family with a germline TP53 mutation. Cancer Genet Cytogenet 2008;180:65–69.

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

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[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

Jennifer K. Litton, MD: UpToDate, Inc.

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