National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

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

Version 1.2020 — December 4, 2019

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

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NCCN Guidelines Version 1.2020
Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

NCCN Genetic/Familial High-Risk Assessment Panel Members
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To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

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Updates in Version 1.2020 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 3.2019 include:

Global

- The name of the Guidelines has changed to "NCCN Guidelines for Genetic Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic."
- Criteria for Further Genetic Risk Evaluation section was removed from the Guidelines.

Breast, Ovarian and/or Pancreatic Cancer Genetic Assessment

EVAL-1

- Approach to Cancer History page is new.

EVAL-A

- Principles of Cancer Risk Assessment and Counseling section was extensively revised.

Hereditary Cancer Testing Criteria

- All testing criteria have been moved into a new section titled, "Hereditary Cancer Testing Criteria."

CRIT-1 and **CRIT-2**

- *BRCA1/2* Testing Criteria has been revised as, "Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes."
  - The criteria were extensively revised and reorganized into three sections
    - ◊ Testing is clinically indicated in the following scenarios
    - ◊ Testing may be considered in the following scenarios
    - ◊ There is a low probability (<2.5%) that testing will have findings of documented clinical utility in the following scenarios

CRIT-3

- Testing Criteria for Pancreatic Cancer Susceptibility Genes is new.

CRIT-4

- Testing Criteria for Li-Fraumeni Syndrome
  - 4th bullet was added, "Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing" with a corresponding footnote, "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."
  - Footnote was removed, "TP53 testing can be ordered alone, concurrently with BRCA1/2 testing, and/or other gene testing or as a follow-up test after negative BRCA1/2 testing."

CRIT-5

- Testing Criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome
  - 6th bullet was added, "PTEN pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis." with a corresponding footnote, "This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic PTEN pathogenic/likely pathogenic variants are common in many tumor types in absence of germline pathogenic/likely pathogenic variant."

Genetic Testing Process

- A new section titled, "Genetic Testing Process," was created, which includes an algorithm for all hereditary testing criteria for "Testing criteria met" and tables for "Cancer Risk Management Based on Genetic Test Results."

GENE-1

- Testing Criteria Met, Genetic Testing
  - "Multi-gene testing, if appropriate" was removed and replaced with "Consider comprehensive testing of patient *with multi-gene panel* or if unaffected, *attempt, if possible, to* test family member with highest likelihood of a pathogenic/likely pathogenic variant *before testing an unaffected individual.*"
  - Footnote e was added, "Patients meeting Cowden syndrome clinical diagnostic criteria (see COWD-A 1 of 3) should be managed as pathogenic/likely pathogenic variant carriers."

GENE-A

- Cancer Risk Management Based on Genetic Test Results
  - "Female" was added to "breast cancer" as appropriate.
  - Genes associated with pancreatic cancer were added to the table, with links to PANC-A as appropriate.

GENE-A 1 of 5

- ATM
  - Ovarian Cancer Risk and Management was revised by adding, "Evidence insufficient; manage based on family history."
  - Comments section revised, "...~~Insufficient evidence to recommend against radiation therapy~~. *ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.*"
- BARD1, Breast Cancer Risk and Management, "including triple negative" was added.
- BRIP1, Breast Cancer Risk and Management was revised from "Unknown or insufficient evidence" to "Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management."

Continued

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Updates in Version 1.2020 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 3.2019 include:

Genetic Testing Process (continued)

GENE-A 2 of 5
- CDH1, comments section was added.
- CDKN2A was added to the table.
- MSH2, MLH1, MSH6, PMS2, EPCAM, comments section was added.

GENE-A 3 of 5
- NBN
  - Breast Cancer Risk and Management was revised, "Increased risk of female breast cancer *for individuals with 657del5 variant*."
  - Ovarian Cancer Risk and Management was revised from, "Unknown or insufficient evidence for ovarian cancer risk" to "Potential increase in ovarian cancer risk, RRSO: Evidence insufficient; manage based on family history."
  - Comments section was revised.
- PALB2
  - Breast Cancer Risk and Management, RRM was revised from, "Evidence insufficient, manage based on family history" to "Discuss option of risk-reducing mastectomy."
  - Ovarian Cancer Risk and Management was revised from "Unknown or insufficient evidence for ovarian cancer risk" to "Potential increase in ovarian cancer risk, RRSO: Evidence insufficient; manage based on family history."

GENE-A 4 of 5
- RAD51C and RAD51D, Breast cancer risk and management was revised from "Unknown or insufficient evidence for breast cancer risk" to "Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management."

GENE-A 5 of 5
- Footnote f was added, "Screening and risk-reduction management is extrapolated from BRCA1/2 data based on levels of risk."

***BRCA* Pathogenic/Likely Pathogenic Variant-Positive Management**

BRCA-A 1 of 2
- Women
  - 5th bullet, 1st sub-bullet was revised, "... management of menopausal symptoms, ~~possible short-term~~ hormone replacement therapy, and related medical issues."
  - 6th bullet was revised by adding, "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, Rohan T, Manson J, et al. JAMA Oncol 2015;1:296-305)."

BRCA-A 2 of 2
- Men
  - 3rd bullet, starting age for prostate cancer screening was changed from 45 y to 40 y.
- Men and Women
  - 2nd bullet was revised, "No specific screening guidelines exist for ~~pancreatic cancer and~~ melanoma, *but general melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure* ~~but screening may be individualized based on cancers observed in the family.~~
  - 3rd bullet was added, "For pancreatic cancer screening recommendations, see PANC-A."

Pancreatic Cancer Screening

PANC-A
- Pancreatic cancer screening section is new.

Li-Fraumeni Syndrome Management

LIFR-A 2 of 2
- Other Aspects of Managing LFS
  - 9th bullet was added, "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."
- Testing Considerations section is new.

Cowden Syndrome/PTEN Hamartoma Tumor Syndrome Management

COWD-A 2 of 3
- Women
  - 4th bullet was revised by adding, "Discuss option of risk-reducing mastectomy *in women with pathogenic/likely pathogenic variants identified. For those with clinical Cowden syndrome, consideration of risk-reducing surgery should be based on family history*."
  - 5th bullet was revised by adding, "For endometrial cancer screening, *consider starting by age 35 y*."

COWD A 3 of 3
- Men and Women
  - 2nd bullet was revised, "Annual thyroid ultrasound starting *at age 7 y* ~~at time of CS/PHTS diagnosis, including in childhood~~."
  - 5th bullet was revised from, "Dermatologic management may be indicated for some patients" to "There may be an increased risk of melanoma, and the prevalence of other skin characteristics with Cowden syndrome may independently make routine dermatology evaluations of value. Annual dermatology examinations are recommended."

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APPROACH TO CANCER HISTORY (For all patients, see Principles of Cancer Risk Assessment and Counseling [EVAL-A].)

- **Personal or family history**
  - **Breast and/or ovarian cancer** → See Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes (CRIT-1)
  - **Pancreatic cancer** → See Testing Criteria for Pancreatic Cancer Susceptibility Genes (CRIT-3)
  - **Prostate cancer** → See Testing Criteria for High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes (CRIT-1)
  - **Colorectal cancer** → See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- **Specific cancer syndromes**
  - **Li-Fraumeni syndrome** → See Testing Criteria for Li-Fraumeni Syndrome (CRIT-4)
  - **Cowden syndrome/PTEN hamartoma tumor syndrome** → See Testing Criteria for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome (CRIT-5)

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

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **The decision to offer genetic testing involves three related stages: 1) pre-test counseling done prior to ordering testing; 2) consideration of the most appropriate tests to order; and 3) post-test counseling done when results are disclosed.[1-5] It is recommended that a genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible. Testing should be considered in appropriate high-risk individuals where it is likely to impact the risk management and/or treatment of the tested individuals and/or their at-risk family members.**

Pre-test counseling includes the following elements:

- **Evaluation of patient's needs and concerns regarding:**
  - **Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations**
  - **Goals for cancer family risk assessment**
- **Detailed family history including:**
  - **Collection of a comprehensive family history**
    - ◊ **Assessing family history; close blood relatives include first-, second-, and third-degree relatives on each side of the family, particularly around individuals with a diagnosis of cancer (See EVAL-B)**
    - ◊ **Types of cancer, bilaterality, age at diagnosis, subtype, and pathology report confirmation**
    - ◊ **Ethnicity (specifically Ashkenazi Jewish ancestry)**
- **Detailed medical and surgical history including:**
  - **Documentation of prior genetic testing results for patients and their family members**
  - **Personal cancer history (eg, age, histology, laterality)**
  - **Pathology reports of primary cancers and/or benign lesions (eg, breast biopsies)**
  - **Carcinogen exposure (eg, history of radiation therapy)**
  - **Reproductive history**
  - **Hormone or oral contraceptive use**
  - **History of risk-reducing surgeries**
- **Focused physical exam (conducted by qualified clinician):**
  - **Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS) specific: dermatologic,[a] including oral mucosa, head circumference, and thyroid (enlarged or nodular on palpation)**
- **Generation of a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity**
- **Preparation for the possible outcomes of testing, including positive (pathogenic, likely pathogenic), negative, uncertain variants, and mosaic results**
- **Obtaining written informed consent, and documenting the informed consent in the patient's medical record**
- **Discuss possible management options if a mutation is identified (enhanced surveillance, risk-reducing agents, and risk-reducing surgery)**
- **Advise about possible inherited cancer risk to relatives, options for risk assessment, testing, and management.**
- **Cost of genetic testing**
- **Current legislation regarding genetic discrimination and the privacy of genetic information**

References on EVAL-A 6 of 6

[a] For Cowden syndrome dermatologic manifestations, see CRIT-5 and for Peutz-Jeghers syndrome (PJS) dermatologic manifestations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Continued

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Prior to genetic testing, the following should be taken into consideration:

- **The probability of pathogenic/likely pathogenic variant detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial pathogenic/likely pathogenic variant detection. The estimated likelihood of pathogenic/likely pathogenic variant detection may be very low in families with a large number of unaffected female relatives or a large number of male relatives.**
- **Patients who have received an allogeneic bone marrow transplant or with active or recent hematologic malignancies should not have molecular genetic testing via blood or buccal samples (due to unreliable test results from contamination by donor DNA) until other technologies are available. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.**
- **If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider initial testing of a family member with youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient. If there are no available family members with cancer that is a cardinal feature of the syndrome in question, consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question (eg, prostate or pancreas with *BRCA1/2*).**
- **Testing for unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.**
- **In children <18 y, genetic testing is generally not recommended when results would not impact medical management.[6]**
- **Likely pathogenic variants are usually clinically managed similarly to pathogenic variants.**
- **Choice of multi-gene testing, see EVAL-A 3 of 6.**

References on EVAL-A 6 of 6

Continued

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **Choice of multi-gene testing**
  - **The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to hereditary cancer testing of at-risk patients and their families. Based on next-generation sequencing (NGS) technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.**
  - **An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a multi-gene panel test may be more efficient and cost-effective and increase the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or his/her at-risk family members.**
  - **There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.**
  - **Rarely, some individuals may carry pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene; thus, consideration of a multigene panel for individuals already known to carry a single pathogenic/likely pathogenic germline variant from phenotype-directed testing may be considered on a case-by-case basis, based on the degree of suspicion for there being additional variants.**
  - **Because commercially available tests differ in the specific genes analyzed, variant classification, and other factors, it is important to consider the indication for testing and expertise of the laboratory when choosing the specific laboratory and test panel.**
  - **Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes.[b] For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable.**
  - **It may be possible to refine risks associated with both moderate and high penetrance genes, taking into account the influence of gene/gene or gene/environment interactions. In addition, certain pathogenic/likely pathogenic variants in a gene may pose higher or lower risk than other pathogenic/likely pathogenic variants in that same gene. This information should be taken into consideration when assigning risks and management recommendations for individuals and their at-risk relatives.**
  - **In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.**
  - **Pathogenic/likely pathogenic variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring if the partner is also a carrier.**
  - **As more genes are tested, there is an increased likelihood of finding variants of unknown significance (VUS), mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP).**
  - **Multigene panel testing increases the likelihood of finding pathogenic/likely pathogenic variants without clear clinical significance.**
  - **Germline confirmatory testing should be done when a pathogenic variant is found on tumor genomic testing that has clinical implications if also identified in the germline.**

References on EVAL-A 6 of 6

[b] Research is evolving, and gene carriers should be encouraged to participate in clinical trials or genetic registries. Carriers are also encouraged to recontact their genetics providers every few years for updates.

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Evaluating the Source of Genetic Testing Information

- Prior to using any germline findings for medical management, it is important to establish whether the reported findings were obtained from a laboratory that is certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) to issue a report of germline findings directly to ordering health care providers. Some states (eg, New York) may have additional reporting requirements.

- Confirmatory germline testing through an appropriately certified laboratory is recommended when a potential pathogenic/likely pathogenic variant is identified through various data sources as noted below:
  - Commercial entities providing ancestry (and sometimes health) information typically do so through microarray-based single nucleotide polymorphism (SNP) testing that has not been validated for clinical use. Third-party software applications can be used by consumers to obtain an interpretation of the raw data provided by these companies. Raw data and third-party software are not able to provide information that is appropriate for medical management, as these services are not subject to quality-control processes and recent research suggests that the error rate is substantial.[7]
  - Tumor testing can be complementary to germline testing and can assist in interpretation of results. However:
    - ◊ Pathogenic/likely pathogenic variants reported by laboratories providing tumor-only profiling may be of somatic or germline origin. Although germline origin can sometimes be inferred with a high degree of confidence (eg, founder pathogenic/likely pathogenic variants in *BRCA1/2*), confirmatory testing is usually indicated for pathogenic/likely pathogenic variants with a reasonable clinical suspicion of being of germline origin (based on patient/family history or clinical characteristics and in some cases variant frequency).
    - ◊ However, somatic pathogenic/likely pathogenic variants are common in several genes with germline implications (eg, *TP53*, *STK11*, *PTEN*), and will rarely be indicative of a need for germline testing unless clinical/family history features suggest the possibility of a germline pathogenic/likely pathogenic variant.
    - ◊ Interpretation of tumor sequencing results may differ from the interpretation of this same change when present in the germline, for several reasons. Because tumor testing is designed to address treatment actionability, a variant that is interpreted as pathogenic or likely pathogenic in the germline may be interpreted as normal (and not reported) or a VUS in the tumor because it has no clear clinical implications. In addition, the sensitivity of most tumor testing is lower (particularly for intermediate-sized deletions and duplications) than most dedicated germline tests, and the filtering of tumor sequencing data may differ between tumor and germline testing labs. Thus, clinically indicated germline testing is still appropriate for patients meeting testing guidelines, regardless of tumor profiling results.
  - Research: Patients may have participated in research studies that include germline genomic analysis.[8] In such cases, it is recommended to review the patient's findings with a genetics professional and/or the reporting laboratory to establish whether the original report was generated by an appropriately certified laboratory, or whether confirmatory testing is recommended.

References on EVAL-A 6 of 6

Continued

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Post-test counseling includes the following elements:

- **Discussion of results and associated medical risks**
- **Interpretation of results in context of personal and family history of cancer**
- **Discussion of recommended medical management options**

- **Discuss and offer assistance with informing and testing at-risk family members.**
- **Discuss available resources such as high-risk clinics, disease-specific support groups, and research studies.**
- **For patients 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.**
- **Biallelic pathogenic/likely pathogenic variants in some genes, included on gene panels, may be associated with rare autosomal recessive conditions, such as Fanconi anemia or constitutional mismatch repair deficiency (See GENE-A). Thus, for these genes, consideration should be given to carrier testing the partner for pathogenic/likely pathogenic variants in the same gene if it would inform reproductive decision-making and/or risk assessment and management.[9]**
- **Testing family members for a VUS should not be done for clinical purposes. Consider a referral to research studies that aim to define the functional impact of variants such as variant reclassification programs through clinical labs or registries.**

- **When genetic testing for inherited cancer is conducted by providers with limited expertise in genetics and/or without pre-test counseling, referral to a genetics health provider should be considered for the following situations:**
  - **Pathogenic/likely pathogenic variant identified**
  - **Negative results, yet family history remains suggestive of inherited disease**
  - **Any VUS result for which a provider considers using to guide management**
  - **A mosaic or possibly mosaic result**
  - **Discrepant interpretation of variants, including discordant results across laboratories**
  - **Interpretation of polygenic risk scores, particularly in instances in which it may impact patient care**
  - **Interpretation of pathogenic/likely pathogenic variants for patients tested through direct-to-consumer or consumer-initiated models**

References on EVAL-A 6 of 6

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

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[9]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.

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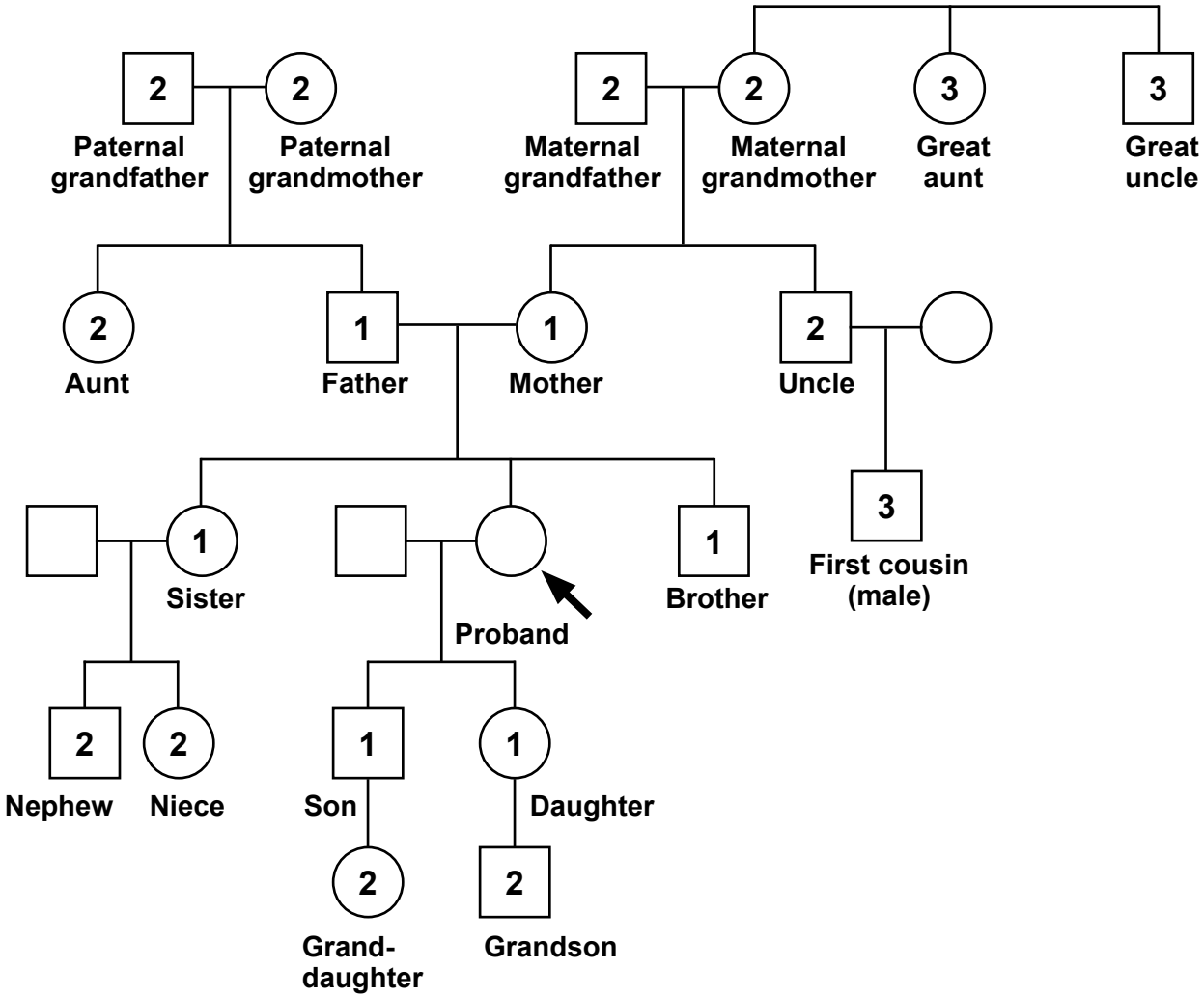
PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[a]



[a]First-degree relatives: parents, siblings, and children;
second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings;
third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, first cousins, and half aunts and uncles.

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

Testing is clinically indicated in the following scenarios:

1. **Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene**
2. **Individuals meeting the criteria below but with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing**
3. ***Personal history of cancer***
   - **Breast cancer with at least one of the following:**
     - **Diagnosed at age ≤45 y; or**
     - **Diagnosed at age 46–50 y with:**
       - ◊ **Unknown or limited family history; or**
       - ◊ **A second breast cancer diagnosed at any age; or**
       - ◊ **≥1 close blood relative[e] with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age**
     - **Diagnosed at age ≤60 y with triple-negative breast cancer;**
     - **Diagnosed at any age with:**
       - ◊ **Ashkenazi Jewish ancestry; or**
       - ◊ **≥1 close blood relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or**
       - ◊ **≥3 total diagnoses of breast cancer in patient and/or close blood relatives[e]**
     - **Diagnosed at any age with male breast cancer**
   - **Epithelial ovarian cancer[f] (including fallopian tube cancer or peritoneal cancer) at any age**
   - **Exocrine pancreatic cancer at any age[g] (See CRIT-3)**
   - **Metastatic or intraductal prostate cancer at any age[h]**
   - **High-grade (Gleason score ≥7) prostate cancer with:**
     - **Ashkenazi Jewish ancestry; or**
     - **≥1 close relative[e] with breast cancer at age ≤50 y or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or**
     - **≥2 close relatives[e] with breast or prostate cancer (any grade) at any age.**
   - **A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline**
   - **To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer[i]**
4. ***Family history of cancer***
   - **An affected or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except individuals who meet criteria only for systemic therapy decision-making)[j]**
   - **An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, PennII)[k]**

Continued on next page

Criteria met → **See GENE-1**

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

Footnotes on CRIT-2

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

(This often includes *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53* among others. See GENE-A for a more complete list.)[a,b,c,d]

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

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

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

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

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

[b] Testing for pathogenic variants in other genes should take into consideration factors such as patient preferences, turnaround time, and insurance restrictions to particular labs (and thus particular panels). The prevalence of VUS increases with testing of additional genes. Individuals should have pre-test education on the challenges in managing pathogenic variants in genes associated with specific syndromes (eg, *CDH1* and *TP53* given their expanding clinical phenotypes) in the absence of a family history typical of such syndromes (does not apply for de novo pathogenic variants). Patients should also have pre-test education regarding the uncertain clinical utility of identifying certain pathogenic variants (eg, monoallelic *MUTYH*).

[c] Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

[d] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[e] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. (See EVAL-B)

[f] *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and PJS or Sertoli-Leydig tumors and DICER1-related disorders.

[g] Approximately 2%–5% of unselected cases of pancreatic adenocarcinoma will have a *BRCA1/2* pathogenic/likely pathogenic variant. However, the disease is highly aggressive and the option to test the affected relative may not be available in the future. Thus, there may be significant benefit to family members in testing these patients near the time of diagnosis. In addition, increasing evidence suggests that identification of a *BRCA1/2* pathogenic/likely pathogenic variant may direct use of targeted therapies for patients with pancreatic cancer (See NCCN Guidelines for Pancreatic Adenocarcinoma). (Holter S, Borgida A, Dodd A, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, Yu J, Suenaga M, et al. J Clin Oncol 2017;35:3382-3390. Golan T, Hammel P, Reni M, et al. N Engl J Med 2019;381:317-327.)

[h] Metastatic prostate cancer is biopsy-proven and/or with radiographic evidence and includes distant metastasis and regional bed or nodes. It is not a biochemical recurrence only. Prostate cancer-specific mortality should be a surrogate for metastatic disease for family history purposes.

[i] Eg, PARP inhibitors for ovarian cancer, prostate cancer, pancreatic cancer, and metastatic HER2-negative breast cancer; platinum therapy for prostate cancer and pancreatic cancer. See the relevant NCCN treatment guidelines for further details.

[j] This may be extended to an affected third-degree relative if related through two male relatives (eg, paternal grandfather's mother or sister). If the affected first-degree relative underwent genetic testing and is negative for detectable mutations and there is no other family history of cancer, there is a low probability that any finding will have documented clinical utility. For probands with pancreatic cancer, only first-degree relatives should be offered testing unless indicated for other relatives based on additional family history.

[k] The approximate 5% threshold for probability of carrying *BRCA1/2* pathogenic variants is utilized because of availability of prior probability models; however, it is recognized that current model estimates vary substantially, and that different thresholds may be appropriate if other genes are included in the model utilized. If genes other than *BRCA1* and *BRCA2* are to be included in models evaluating the threshold for testing, the penetrance, clinical actionability, and phenotypic features of cancers associated with mutations in these genes should be considered. The panel encourages the development of validated models that include these parameters to determine eligibility and appropriateness for gene panel testing for inherited cancer risk. These models are only validated for *BRCA1/2*.

[l] Testing for three founder mutations of *BRCA1/2* may be offered to unaffected men and women as early as age 18–25 years, who have one grandparent identified as of Ashkenazi Jewish ancestry, irrespective of cancer history in the family, as part of longitudinal studies. For those without access to longitudinal research studies, testing may be provided if there is access to pre-test education along with post-test counseling, additional genetic testing if indicated, and high-risk management. Testing should not be offered outside of a medical framework or clinical trial.

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TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES[a]

DIAGNOSIS	TESTING CRITERIA	
Exocrine pancreatic cancers →	Recommend genetic counseling and germline testing[m] for • All individuals diagnosed with exocrine pancreatic cancer[n] • First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[o]	→ See GENE-1
Neuroendocrine pancreatic tumors →	See NCCN Guidelines for Neuroendocrine and Adrenal Tumors	

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[m] Genes that are typically tested for pancreatic cancer risk include *ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, most Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *EPCAM*), *PALB2*, *STK11*, and *TP53*.
[n] Pancreatic cancer risk is higher in individuals of Ashkenazi Jewish descent. Genetic testing of Ashkenazi Jewish patients with pancreatic cancer may have higher yield of mutations than of non-Ashkenazi Jewish patients.
[o] Testing of first-degree relatives should only be done if it is impossible to test the individual who has pancreatic cancer. Some second-degree relatives may meet testing criteria based on additional family history.

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TESTING CRITERIA FOR LI-FRAUMENI SYNDROME[a]

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

FOLLOW-UP

LFS testing criteria met → **See GENE-1**

If LFS testing criteria not met, consider testing for other hereditary syndromes, if appropriate → **Individualized recommendations according to personal and family history**

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

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

[q] To date, there have been no reports of Ewing sarcoma, GIST, desmoid tumor, or angiosarcoma in *TP53* pathogenic/likely pathogenic variant carriers.

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

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

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

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NCCN Guidelines Version 1.2020
Hereditary Cancer Testing Criteria

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TESTING CRITERIA FOR COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)[a,u,v,w]

- Individual from a family with a known *PTEN* pathogenic/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria[x] for CS/PHTS
- Individual not meeting clinical diagnostic criteria[x] for CS/PHTS with a personal history of:
  - Adult Lhermitte-Duclos disease (cerebellar tumors); or
  - Autism spectrum disorder and macrocephaly; or
  - Two or more biopsy-proven trichilemmomas; or
  - Two or more major criteria (one must be macrocephaly); or
  - Three major criteria, without macrocephaly; or
  - One major and ≥3 minor criteria;[y] or
  - ≥4 minor criteria
- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
  - The at-risk individual must have the following:
    - ◊ Any one major criterion or
    - ◊ Two minor criteria
- *PTEN* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline analysis[z]

FOLLOW-UP

- CS/PHTS testing criteria met → See GENE-1
- If CS/PHTS testing criteria not met, consider testing for other hereditary syndromes, if appropriate → Individualized recommendations according to personal and family history

Major criteria:
- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas[aa]
- Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult women, 60 cm in adult men)[bb]
- Macular pigmentation of glans penis
- Mucocutaneous lesions[cc]
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

Minor criteria:[dd]
- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (ie, IQ ≤75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[u] These are testing criteria; clinical diagnostic criteria can be found on COWD-A.
[v] If two criteria involve the same structure/organ/tissue, both may be included as criteria.
[w] Current evidence does not support testing for succinate dehydrogenase (*SDH*) gene pathogenic/likely pathogenic variants in patients with PHTS. (Am J Hum Genet 2011;88:674-675).
[x] Pilarski R, Burt R, Kohlmann W, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616. See COWD-A.
[y] If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.
[z] This should prompt a careful evaluation of personal and family history of the individual to determine the yield of germline sequencing. Somatic PTEN pathogenic/likely pathogenic variants are common in many tumor types in absence of germline pathogenic/likely pathogenic variant.
[aa] Multiple polyp types are often seen in patients with PHTS, and less commonly may include adenomas, hyperplastic polyps, and other histologies.
[bb] Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: Birth to 18 years. Pediatrics 1987;79:706-712.
[cc] The literature available on mucocutaneous lesions is not adequate to accurately specify the number or extent of mucocutaneous lesions required to be a major criterion for CS/PHTS. Clinical judgment should be used.
[dd] Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

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NCCN Guidelines Version 1.2020
Genetic Testing Process

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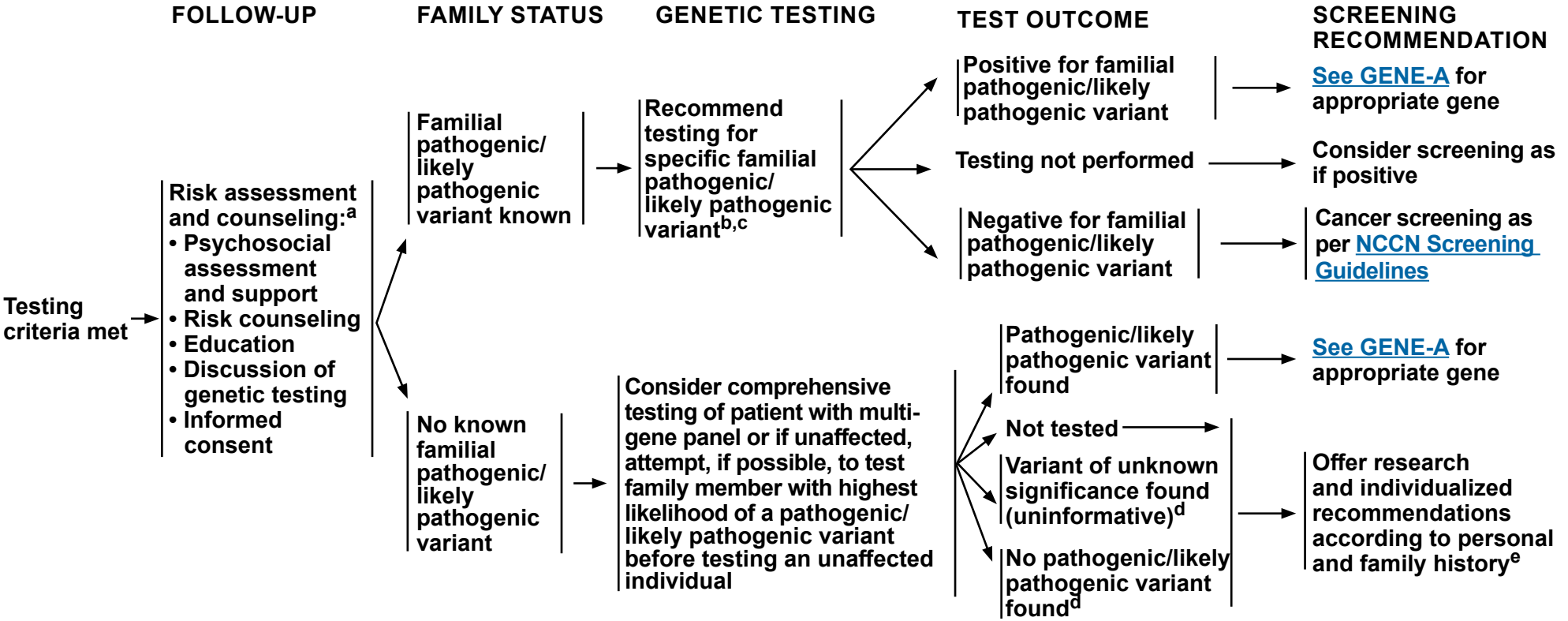

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[b] If of Ashkenazi Jewish descent, in addition to the specific familial pathogenic/likely pathogenic variant, test for all three founder pathogenic/likely pathogenic variants.
[c] Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known pathogenic/likely pathogenic variant.
[d] If no pathogenic/likely pathogenic variant is found, consider testing another family member with next highest likelihood of having a pathogenic/likely pathogenic variant.
[e] Patients meeting Cowden syndrome clinical diagnostic criteria (see COWD-A 1 of 3) should be managed as pathogenic/likely pathogenic variant carriers.

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

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

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for prostate cancer**
	Comments: Counsel for risk of autosomal recessive condition in offspring. ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.		
BARD1	**Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management**	**Unknown or insufficient evidence for ovarian cancer risk**	**Unknown or insufficient evidence for other cancers**
BRCA1	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic, Prostate** • See *BRCA* Pathogenic Variant-Positive Management
BRCA2	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic, Prostate, Melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
BRIP1	**Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	**Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued
Footnotes on GENE-A 5 of 5

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

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

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CDH1	**Increased risk of female lobular breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	**Diffuse gastric cancer** • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer
	Comments: There is controversy over how to manage gastric cancer risk in individuals with pathogenic/likely pathogenic variants in *CDH1* in the absence of a family history of gastric cancer. However, one small study found that >50% of such individuals had gastric cancer identified at the time of risk-reducing total gastrectomy (Jacobs MF, et al. Gastroenterology 2019;157:87-96). Cleft lip with or without cleft palate has been associated with *CDH1* pathogenic/likely pathogenic variants (Frebourg T, et al. J Med Genet 2006;43:138-142).		
CDKN2A	**No increased risk of breast cancer**	**No increased risk of ovarian cancer**	**Increased risk of pancreatic cancer** • See PANC-A
CHEK2	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	**Colon** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		
MSH2, MLH1, MSH6, PMS2, EPCAM[i]	**Unknown or insufficient evidence for breast cancer risk[g]** • Manage based on family history	**Increased risk of ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal **Pancreatic (insufficient evidence for PMS2)** • See PANC-A
	Comment: Counsel for risk of autosomal recessive condition in offspring.		

RRM: Risk-reducing mastectomy

Continued

Footnotes on GENE-A 5 of 5

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

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

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
NBN	**Increased risk of female breast cancer for individuals with 657del5 variant[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk,** • RRSO: Evidence insufficient; manage based on family history	**Unknown or insufficient evidence for other cancers**
	Comments: Current data suggest that breast cancer risks are not increased for pathogenic/likely pathogenic variants other than 657del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	• **Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		
PALB2	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[g,h] • RRM: Discuss option of risk-reducing mastectomy	**Potential increase in ovarian cancer risk** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of female breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued

Footnotes on GENE-A 5 of 5

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

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

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
RAD51C	**Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of female breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian tumors** • See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome	• See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • **Pancreatic**, see PANC-A
TP53	**Increased risk of female breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	• See Li-Fraumeni Syndrome Management • **Pancreatic,** see PANC-A

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Footnotes on GENE-A 5 of 5

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FOOTNOTES/REFERENCES FOR TABLES

[a] Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2017;13:581-588. See Discussion for further details regarding the rationale for different starting ages for breast screening.

[b] Couch FJ, Shimelis H, Hu C, et al. Associations between cancer predisposition testing panel genes and breast cancer. JAMA Oncol 2017;3:1190-1196.

[c] Lilyquist J, LaDuca H, Polley E, et al. Frequency of mutations in a large series of clinically ascertained ovarian cancer cases tested on multi-gene panels compared to reference controls. Gynecol Oncol 2017;147:375-380.

[d] Kurian A, Hughes E, Handorf E, et al. Breast and ovarian cancer penetrance estimates derived from germline multiple-gene sequencing results in women. Precis Oncol 2017;1:1-12.

[e] The following genes and others are found on some of the panels, but there is insufficient evidence to make *any* recommendations for breast MRI, RRSO, or *RRM*; *FANCC*, *MRE11A*, or *MUTYH* heterozygotes; or *RECQL4*, *RAD50*, RINT1, SLX4, *SMARCA4*, or *XRCC2*.

[f] Screening and risk-reduction management is extrapolated from *BRCA1/2* data based on levels of risk.

[g] May be modified based on family history (typically beginning screening 5–10 years earlier than the youngest diagnosis in the family but not later than stated in the table) or specific gene pathogenic/likely pathogenic variant.

[h] For women with pathogenic/likely pathogenic variants who are treated for breast cancer and have not had bilateral mastectomy, screening should continue as described.

[i] Recent data have demonstrated no significant association between pathogenic/likely pathogenic germline *PMS2* variants and risks of Lynch syndrome cancers beyond colorectal and endometrial cancer (Ten Broeke SW, et al. J Clin Oncol;36:2961-2968). This study did not specifically evaluate pancreatic cancer in *PMS2* carriers, but we should note that it is currently unclear if individuals with germline *PMS2* variants have increased risk of pancreatic cancer, even though it is a Lynch syndrome gene. There are no data to quantify the strength of association between *EPCAM* and pancreatic cancer, but *EPCAM* is generally thought to have the same cancer risks/penetrance as *MSH2*, given that pathogenic/likely pathogenic germline alterations in *EPCAM* induce constitutional silencing of *MSH2*.

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN

- Breast awareness[a] starting at age 18 y.
- Clinical breast exam, every 6–12 mo,[b] starting at age 25 y.
- Breast screening[c,d]
  - Age 25–29 y, 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 y, annual mammogram with consideration of tomosynthesis and breast MRI[e] screening with contrast.
  - Age >75 y, 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 y, 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 y 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, Rohan T, Manson J, 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 discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.

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Footnotes on BRCA-A 2 of 2
Continued

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

MEN[h]

- **Breast self-exam training and education starting at age 35 y**
- **Clinical breast exam, every 12 mo, starting at age 35 y**
- **Starting at age 40 y: (See Guidelines for Prostate Cancer Early Detection)**
  - **Recommend prostate cancer screening for *BRCA2* carriers**
  - **Consider prostate cancer screening for *BRCA1* carriers**

MEN AND WOMEN

- **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.**

[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. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. 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 breast imaging in men.

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PANCREATIC CANCER SCREENING

- **Emerging data have examined the efficacy of pancreatic cancer screening in select individuals at increased risk for exocrine pancreatic cancer. To date, most such studies have restricted pancreatic cancer screening to individuals with:**
  1. **A known pathogenic/likely pathogenic germline variant in a pancreatic cancer susceptibility gene (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53*; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline pathogenic/likely pathogenic variant; or**
  2. **A family history of exocrine pancreatic cancer in ≥2 first-degree relatives from the same side of the family, even in the absence of a known pathogenic/likely pathogenic germline variant (many centers would enroll individuals with one affected first-degree relative and one second-degree relative); or**
  3. **A family history of exocrine pancreatic cancer in ≥3 first- and/or second-degree relatives from the same side of the family, even in the absence of a known pathogenic/likely pathogenic germline variant.**
- **These studies have typically started screening with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) in such high-risk individuals.**

- **Potential benefits of pancreatic cancer screening include a suggestion of downstaging, compared to historical data, in that 75%–90% of screen-detected pancreatic cancer has been surgically resectable at diagnosis (which is markedly higher than historical rates of resectability with pancreatic cancers detected due to symptoms).[a,b] There has also been a suggestion of improved mortality compared to historical data, with one study demonstrating an 85% 3-year overall survival rate after screen-detected pancreatic cancer in high-risk individuals,1 and another study demonstrating a 24% 5-year overall survival rate following screen-detected pancreatic cancer in individuals with germline c.67G>C CDKN2A variants.[b] The Canto study also demonstrated 100% overall survival among 10 individuals with screen-detected precursor lesions (intraductal papillary mucinous neoplasms [IPMN] with high-grade dysplasia and/or high-grade pancreatic intraepithelial neoplasia [PanIN]) treated with surgical resection.**

- **Although evidence for downstaging has emerged in recent studies, longer-term studies are needed to determine if this downstaging translates to improved survival. Evidence from patients with sporadic forms of pancreatic ductal adenocarcinoma suggest that long-term survival is common for patients who present with stage I disease. Since many patients who undergo pancreatic surveillance have pancreatic abnormalities, mostly subcentimeter pancreatic cysts (42% of high-risk individuals in one study[c] had at least one pancreatic mass/cyst and/or duct abnormality), there is potential for unnecessary interventions (such as fine-needle aspiration [FNA] and in some cases surgery). Although there is much more experience with evaluating and managing pancreatic cysts and other pancreatic imaging abnormalities, determination of the overall risk/benefits of pancreatic surveillance requires further study. Results of surveillance of high-risk individuals performed in tertiary care/high-volume centers under clinical trial settings may not be the same as those performed in routine clinical practice. Data are beginning to better define which screen-detected lesions in high-risk individuals should be considered to be at particularly high risk for neoplastic progression (eg, those with a solid pancreatic mass, those with pancreatic duct abnormalities, those with growing pancreatic cysts[a]), but further data are needed to better define the threshold for surgical intervention and biopsy in high-risk individuals undergoing pancreatic cancer screening.**

[a] Canto MI, Almario JA, Schulick RD, et al. Gastroenterology 2018;155:740-751.
[b] Vasen H, Ibrahim I, Ponce CG, et al. J Clin Oncol 2016;34:2010-2019.
[c] Canto MI, Hruban RH, Fishman EK, et al. Gastroenterology 2012;142:796-804.

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PANCREATIC CANCER SCREENING

- **For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers, ideally under research conditions. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.**
- **The panel recommends that screening be considered using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals for individuals found to have worrisome abnormalities on screening. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.**

- **For all individuals with pathogenic/likely pathogenic germline variants in *STK11***
  - **Consider pancreatic cancer screening beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).**

- **For all individuals with pathogenic/likely pathogenic germline variants in *CDKN2A***
  - **Consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).**

- **For individuals with pathogenic/likely pathogenic germline variants in one of the other pancreatic cancer susceptibility genes (A*TM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53*), see GENE-A.**
  - **Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified pathogenic/likely pathogenic germline variant.[d]**
  - **The panel does not currently recommend pancreatic cancer screening for carriers of mutations in genes other than *STK11* and *CDKN2A* in the absence of a close family history of exocrine pancreatic cancer.**

Hereditary pancreatitis genes

- **For individuals with pathogenic/likely pathogenic variants in PRSS1 or other hereditary pancreatitis genes AND a clinical phenotype consistent with hereditary pancreatitis[e]**
  - **Consider pancreatic cancer screening 20 years after onset of pancreatitis, or at age 40 years, whichever is earlier.**

[d] Abe T, Blackford A, Tamura K, et al. J Clin Oncol 2019;37:1070-1080.

[e] The panel recognizes that patients with hereditary pancreatitis (sometimes caused by pathogenic germline variants in *PRSS1*, *SPINK1*, and other genes) have increased lifetime risks of pancreatic cancer. The clinical significance of pathogenic germline variants in these genes is unclear, when such variants are identified in individuals lacking a clinical history of pancreatitis. As such, the panel recommends germline testing for *PRSS1*, *SPINK1*, and other pancreatitis genes in individuals with a personal and/or family history of exocrine pancreatic cancer only if there is a personal and/or family history suggestive of hereditary pancreatitis.

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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.

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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 patients 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, Achatz M, Brugières L, et al. Clin Cancer Res 2017;23:e38-e45.

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REVISED CLINICAL DIAGNOSTIC CRITERIA FOR PTEN HAMARTOMA TUMOR SYNDROME[a]

MAJOR CRITERIA:
- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- GI hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97th percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - Multiple trichilemmomas (≥3, at least one biopsy proven)
  - Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - Mucocutaneous neuromas (≥3)
  - Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

MINOR CRITERIA:
- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthoses (≥3)
- Lipomas (≥3)
- Intellectual disability (ie, IQ ≤75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)
- Vascular anomalies/malformations (including multiple intracranial developmental venous anomalies)

Operational diagnosis in an individual (either of the following):
1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or
2. Two major and three minor criteria.

Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* pathogenic/likely pathogenic variant:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

[a] Pilarski R, Burt R, Kohlman W, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616.

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COWDEN SYNDROME/PHTS MANAGEMENT

WOMEN

- **Breast awareness[b] starting at age 18 y.**
- **Clinical breast exam, every 6–12 mo, starting at age 25 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).**
- **Breast screening**
  - **Annual mammography with consideration of tomosynthesis and breast MRI screening with contrast starting at age 30–35 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).[c,d]**
  - **Age >75 y, management should be considered on an individual basis.**
  - **For women with a *PTEN* 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 in women with pathogenic/likely pathogenic variants identified. For those with clinical Cowden syndrome, consideration of risk-reducing surgery should be based on family history.**
  - **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.**
- **For endometrial cancer screening,[e] consider starting by age 35 y.**
  - **Encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Patients are encouraged to keep a calendar in order to identify irregularities in their menstrual cycle.**
  - **Because endometrial cancer can often be detected early based on symptoms, women should be educated regarding the importance of prompt reporting and evaluation of any abnormal uterine bleeding or postmenopausal bleeding. The evaluation of these symptoms should include endometrial biopsy.**
  - **Endometrial cancer screening does not have proven benefit in women with CS/PHTS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1 to 2 years can be considered.**
  - **Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle.**
- **Discuss option of hysterectomy[f] upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.**
- **Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.**

[b] 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.
[c] The appropriateness of imaging modalities and scheduling is still under study.
[d] 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.
[e] There are limited data regarding the lifetime risk of endometrial cancer in CS/PHTS. Surveillance screening and surgical intervention should be on an individual basis.
[f] Oophorectomy is not indicated for CS/PHTS alone but may be indicated for other reasons.

Continued

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COWDEN SYNDROME/PHTS MANAGEMENT

MEN AND WOMEN

- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
- Annual thyroid ultrasound starting at age 7 y.
- Colonoscopy, starting at age 35 y unless symptomatic or if close relative with colon cancer before age 40 y, then start 5–10 y before the earliest known colon cancer in the family. Colonoscopy should be done every 5 y or more frequently if patient is symptomatic or polyps are found.
- Consider renal ultrasound starting at age 40 y, then every 1–2 y.
- There may be an increased risk of melanoma, and the prevalence of other skin characteristics with Cowden syndrome may independently make routine dermatology evaluations of value. Annual dermatology recommendations are recommended.
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

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 women 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.

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

All recommendations are category 2A unless otherwise indicated.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 01/18/19

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Overview

All cancers develop as a result of mutations in certain genes, such as those involved in the regulation of cell growth and/or DNA repair,[1,2] although not all of these mutations are inherited from a parent. For example, sporadic mutations can occur in somatic/tumor cells only, and de novo mutations can occur for the first time in a germ cell (ie, egg or sperm) or in the fertilized egg itself during early embryogenesis. However, family studies have long documented an increased risk for several forms of cancer among first-degree relatives (ie, parents, siblings, children) and second-degree relatives (ie, grandparents, aunts or uncles, grandchildren, nieces or nephews) of affected individuals. These individuals may have an increased susceptibility to cancer as the result of one or more gene mutations present in parental germline cells; cancers developing in these individuals may be classified as hereditary or familial cancers.

Hereditary cancers are often characterized by mutations associated with increased risk for certain cancers (ie, a high-penetrance phenotype) and transmission to offspring through the mother and/or father.[3,4] They often have an early age of onset and exhibit an autosomal dominant inheritance pattern (ie, occur when the individual has a pathogenic or likely pathogenic variant in only one copy of a gene). Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.[5-8]

An individual suspected of being at risk for hereditary cancer should be offered genetic counseling.[9,10] This is consistent with recommendations from the US Preventive Services Task Force.[11] Assessment of an individual's risk for familial or hereditary cancer is based on a thorough evaluation of the personal and family history. With respect to hereditary cancers, advances in molecular genetics have identified a number of genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, *BRCA1/2, TP53, CDH1*) and have provided a means of characterizing the specific gene mutation or mutations present in certain individuals and families exhibiting an increased risk for cancer. The field of cancer genetics has implications for all aspects of cancer management of individuals with hereditary or familial cancers, including prevention, screening, and treatment.[12]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian were developed with an acute awareness of the preliminary nature of much of our knowledge regarding the clinical application of the rapidly emerging field of molecular genetics, and with an appreciation for the need for flexibility when applying these guidelines to individual families. Furthermore, it should be emphasized that these guidelines were not developed as a substitute for professional genetic counseling. Rather, they are intended to: 1) serve as a resource for health care providers to identify individuals who may benefit from cancer risk assessment and genetic counseling; 2) provide genetic counselors with an updated tool for the assessment of individual breast cancer and ovarian cancer risk and to guide decisions related to genetic testing; and 3) facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancer. Although cancers other than breast and ovarian cancers are associated with these hereditary syndromes, the main focus of these NCCN Guidelines® is on the management of breast and ovarian cancer risk in these individuals. During the last few years, a number of additional genetic aberrations that may contribute to increased risks for development of breast and/or ovarian

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cancers have been identified. The current NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian focus primarily on assessment of pathogenic or likely pathogenic variants in *BRCA1/2, TP53,* and phosphatase and tensin homolog (*PTEN*), and recommended approaches to genetic testing/counseling and management strategies in individuals with these pathogenic or likely pathogenic variants. Where possible, pathogenic or likely pathogenic variants in more recently identified genes have been addressed to the extent possible given the limited information available.

A glossary of genetic terms is included in Table 1 for reference.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian, an electronic search of the PubMed database was performed to obtain key literature published between March 14, 2017 and February 28, 2018, using the following search terms: (hereditary breast cancer) or (familial breast cancer) or (hereditary ovarian cancer) or (familial ovarian cancer) or (Li-Fraumeni syndrome) or (Cowden syndrome) or (pten hamartoma tumor syndrome) or (brca breast cancer) or (brca ovarian cancer) or (cancer genetic testing) or (cancer genetic counseling). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[13]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guidelines; Randomized Controlled Trials; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Genetic Risk Assessment and Counseling

For a patient concerned about or suspected of having a hereditary propensity for breast and/or ovarian cancer, an initial risk evaluation should be performed in order to determine if a formal risk assessment should be undertaken (see *Criteria for Further Genetic Risk Evaluation* in the algorithm). The first step in this preliminary assessment is a broad and flexible evaluation of the personal and family history of the individual with respect to breast and/or ovarian cancer, as well as other cancers.[14,15] The magnitude of the risk increases with the number of affected relatives in the family and the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.[16,17] The younger the age at diagnosis, the more likely it is that a genetic component is present. When assessing a family history for a hereditary pattern, the equal likelihood of paternal or maternal transmission of a gene that predisposes to breast cancer must also be kept in mind.

If an individual or a close family member of that individual meets any one of the criteria presented in the NCCN Guidelines (see *Criteria for Further Genetic Risk Evaluation* in the algorithm), that individual may be at increased risk for breast and/or ovarian cancer, and a referral for genetic assessment may be considered. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

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Despite meeting testing criteria, relatively few of these individuals undergo genetic testing.[18]

For individuals potentially meeting established criteria for one or more of the hereditary cancer syndromes, genetic testing should be considered along with appropriate pre-test counseling. A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved in this process.[9] Those not meeting criteria for testing who are still considered at increased risk for familial breast cancer are also likely to benefit from appropriate risk-reduction strategies (eg, a change in the frequency of, or modalities used for, breast cancer screening).[5] The panel recommends that these individuals follow recommendations in the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.NCCN.org).

Formal Risk Assessment

Cancer genetic risk assessment and genetic counseling is a multi-step process of identifying and counseling individuals at risk for familial or hereditary cancer.

Cancer genetic risk assessment involves use of pedigree analysis with available risk assessment models to determine whether a family history is suggestive of sporadic, familial, or hereditary cancer. Risk assessment includes both an evaluation of an individual's absolute risk for breast and/or ovarian cancer as well as an estimation of the likelihood that the individual has a heritable pathogenic or likely pathogenic variant in his/her family. Genetic risk assessment is a dynamic process and can change if additional relatives are diagnosed with cancer.

Statistical models based on personal and family history characteristics have been developed to estimate a person's interval and lifetime risks of developing breast cancer. For example, the Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first- or second-degree female relatives with breast cancer.[19] The Gail model was also developed to assess risk for breast cancer.[20] The modified model is a computer-based, multivariate, logistic regression model that uses age, race, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous breast biopsies, and histology of the breast biopsies to produce actuarial estimates of future breast cancer risk.[21-23] This model considers only family history of breast cancer in first-degree relatives[24] and is heavily weighted by benign breast disease. Therefore, the Gail model may underestimate breast cancer risk for women with a significant family history and should not be used for women suspected of having a hereditary syndrome associated with increased risk for breast cancer.[24]

Decision models developed to estimate the likelihood that a *BRCA1/2* mutation is present include BRCAPRO[25,26] and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).[25] A lifetime risk for breast cancer of 20% to 25% or greater as assessed by models based largely on family history has been used in some guidelines to identify a woman as being at high risk for breast cancer. For example, this risk threshold was used in updates to the American Cancer Society (ACS) guidelines on breast screening, which incorporate MRI.[27,28]

Evaluation of Patient's Needs and Concerns

The first step in evaluating an individual's risk for hereditary breast cancer is to assess her/his concerns and reasons for seeking counseling and to guarantee that her/his personal needs and priorities will be addressed in the counseling process. Several studies have documented a highly exaggerated perception of risk among women with a family history of breast cancer who seek cancer risk counseling.[29] This is a situation that

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can interfere with the adoption of appropriate health behaviors. In addition, the patient's knowledge about the benefits, risks, and limitations of genetic testing should be assessed as well as the patient's goals. A positive, supportive interaction with the counseling team is an important determinant of ultimate satisfaction with the counseling process and of adherence to recommended health behaviors.

Detailed Family History

A detailed family history is the cornerstone of effective genetic counseling. An examination of family history involves development of an expanded pedigree collected beginning with the health of the individual diagnosed with cancer and proceeding outward to include first-, second-, and third-degree relatives on both the maternal and paternal sides. Standardized pedigree nomenclature should be used.[30,31] Unaffected family members, both living and deceased, are also included, as their histories also provide information about the magnitude of genetic risk.

Information collected includes cancer diagnoses by primary site, age at diagnosis, bilaterality (when appropriate), and current age or age at death. Whenever possible, cancer diagnoses in the family are verified by obtaining medical records, pathology reports, or death certificates. This is particularly important in the case of a report of an "abdominal" cancer in a female relative—a situation in which cancers of the cervix, uterus, ovary, and/or colon are often confused. It is also important to know the ancestry/ethnicity of the individual, since members of certain groups (eg, Ashkenazi Jewish) have increased risks of carrying pathogenic or likely pathogenic variants for specific diseases. Any family members who received genetic testing should also be noted, as well as testing results.

Other medical conditions that may be associated with or predispose an individual to breast and/or ovarian cancer should also be noted. Family history data are then graphically represented on a pedigree that follows standard nomenclature to illustrate family relationships and disease information. Factors that limit the informativeness of the pedigree are small family size, a small number of individuals of the susceptible gender for sex-limited cancers, reduced penetrance, early deaths in family members (which precludes the possibility that they will develop adult diseases), prophylactic surgeries that remove an organ from subsequent risk for cancer (eg, hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members (eg, in the case of adoption).[5,32]

A prospective registry study of 306 women diagnosed with breast cancer at <50 years of age, who had no first- or second-degree relatives with breast or ovarian cancer, showed that those individuals with a limited family history (defined as fewer than 2 first- or second-degree female relatives or fewer than 2 female relatives surviving beyond 45 years of age in either lineage) may have an underestimated probability of a *BRCA1/2* mutation based on models dependent on family history.[33]

Medical and Surgical History

The collection of a detailed medical and surgical history from the proband allows the counselor to estimate the contribution of other risk factors that may interact with or modify family history to determine the risk for cancer. Any personal cancer history should include age of diagnosis, histology, and laterality. A history of previous breast biopsies and pathology results, especially those in which the pathology revealed atypical hyperplasia or lobular carcinoma in situ (LCIS), is associated with an increased risk for breast cancer.[34,35] Pathologic verification of these diagnoses is encouraged. History of salpingo-oophorectomy and potential exposure to carcinogens (eg, radiation therapy) should also be included in the patient's assessment. When taking the medical history, the clinician should also be alert to the physical manifestations of Cowden syndrome, especially skin conditions (see section below on *Focused Physical Examination*).

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Reproductive variables are important determinants of risk for both breast and ovarian cancer, suggesting a significant contribution of hormones to the etiology of these cancers. This possible link is supported by the increased breast cancer risk seen among women who have had prolonged exposure to exogenous estrogens and progestins and the reduction in risk for ovarian cancer observed among women who report using oral contraceptives.[36-39]

Focused Physical Examination

A physical examination performed by a qualified clinician (when available) should be part of the risk assessment. Particular attention should be paid to organs/areas of the body known to be affected in individuals with specific hereditary breast and/or ovarian syndromes. For example, certain patterns of mucocutaneous manifestations are associated with Cowden syndrome, as discussed below; a focused physical examination for Cowden syndrome should include a comprehensive dermatologic examination (including oral mucosa), evaluation of head circumference (to determine presence of macrocephaly), and palpation of the thyroid (see section below on *Cowden Syndrome/PTEN Hamartoma Tumor Syndrome*).

Genetic Counseling

Genetic counseling is a critical component of the cancer risk assessment process. Many patients undergoing genetic testing do not receive proper counseling.[40] In the national ABOUT study, patients undergoing genetic testing (N = 3628) completed a survey regarding their experience. About 37% of respondents reported receiving counseling prior to testing.[41] Further, during genetic counseling, many counselors fail to provide a discussion of reproductive risk for autosomal recessive conditions such as Fanconi anemia.[42] See Table 3 for a list of pathogenic/likely pathogenic variants associated with autosomal recessive conditions.

Counseling for hereditary breast and/or ovarian cancer uses a broad approach to place genetic risk in the context of other related risk factors, thereby customizing counseling to the experiences of the individual. The purpose of cancer genetic counseling is to educate individuals about the genetic, biological, and environmental factors related to the individual's cancer diagnosis and/or risk for disease to help them derive personal meaning from cancer genetic information, and to empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. Individuals need to understand the relevant genetic, medical, and psychosocial information and be able to integrate this information before they can make an informed decision. The presentation of testing information is most effective when tailored to the age and education of the person undergoing counseling, and that individual's personal exposure to the disease, level of risk, and social environment.[7] Information could be delivered in person or over the phone.[43]

Pre-test counseling is an essential element of the genetic counseling process in the event that genetic testing for a pathogenic or likely pathogenic variant associated with a hereditary cancer syndrome is under consideration.[7] The foundation of pre-test genetic counseling is based on the principle of informed consent.[9] Pre-test counseling should include a discussion of why the test is being offered and how test results may impact medical management, cancer risks associated with the pathogenic or likely pathogenic variant in question, the significance of possible test results (see *Genetic Testing*, below), the likelihood of a positive result, technical aspects and accuracy of the test, economic considerations, risks of genetic discrimination, psychosocial aspects, confidentiality issues, the potential significance of the test results for family members, and other topics.[7] The patient should be educated regarding inheritance patterns, penetrance, variable expressivity, and the potential for genetic heterogeneity. A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act

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(GINA) enacted in 2008, which prohibits most health insurers and employers from discrimination on the basis of genetic test results.[44]

Post-test counseling must also be performed and includes disclosure of results, a discussion of the significance of the results, an assessment of the impact of the results on the emotional state of the individual, a discussion of the impact of the results on the medical management of the individual, and how and where the patient will be followed.[9] In addition, identification of a pathogenic or likely pathogenic variant associated with a hereditary predisposition to breast and/or ovarian cancer in an individual necessitates a discussion of possible inherited cancer risk to relatives and the importance of informing family members about test results.[7] Results should be interpreted in the context of personal and family history of cancer. It may also be appropriate to offer genetic testing to both parents of an individual who tests positive for one of these pathogenic or likely pathogenic variants to confirm which side of the family carries the variant and is at increased risk. Counseling should also include making the individual aware of any available resources, such as disease-specific support groups, advocacy groups, and research studies.[45] Individuals who have tested positive for a pathogenic or likely pathogenic variant may have greater distress than anticipated, so provisions for supportive interventions should be provided.

Genetic Testing

The selection of appropriate candidates for genetic testing is based on the personal and familial characteristics that determine the individual's prior probability of being a carrier of a pathogenic or likely pathogenic variant, and on the psychosocial degree of readiness of the person to receive genetic test results. The potential benefits, limitations, and risks of genetic testing are also important considerations in the decision-making process. Many women feel that they are already doing everything they can to minimize their risk of developing breast cancer, and others fear the emotional toll of finding out that they are a carrier of a pathogenic or likely pathogenic variant, especially if they have children who would be at risk of inheriting the variant. For those who choose not to proceed with testing, the counseling team tailors recommendations for primary and secondary prevention based on the individual's personal and family history.

In the statement on Genetic and Genomic Testing for Cancer Susceptibility from ASCO updated in 2003, genetic testing is recommended when: 1) there is a personal or family history suggesting genetic cancer susceptibility; 2) the test can be adequately interpreted; and 3) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk for cancer.[46] These recommendations were reiterated in the latest 2010 ASCO update on Genetic and Genomic Testing for Cancer Susceptibility with respect to testing individuals for gene mutations known to cause hereditary breast and/or ovarian cancer(s).[47]

As part of pre-test counseling, the counselor reviews the distinctions between true-positive (ie, pathogenic, likely pathogenic), true-negative, indeterminate (or uninformative), and inconclusive (or variants of unknown significance [VUS]) test results (see Table 2), as well as the technical limitations of the testing process. A clear distinction is made between the probability of being a carrier of a pathogenic or likely pathogenic variant and the probability of developing cancer. The probabilistic nature of genetic test results and the potential implications for other family members must also be discussed.

Individuals who have received allogeneic hematopoietic stem cell transplantation (HSCT) should not have molecular genetic testing performed on blood samples, as these blood cells would represent donor-derived DNA. In such cases, DNA of the individual being tested should be extracted from a fibroblast culture, if available. If this is not possible, buccal cells may be considered as an alternative source for DNA;

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however, a study has reported that over time, buccal epithelial cells are replaced by donor-derived cells in allogeneic HSCT recipients.[48,49] Therefore, genetic testing using buccal swab samples may be limited given this known risk of donor DNA contamination.

The genetic testing strategy is greatly facilitated when a pathogenic or likely pathogenic variant has already been identified in another family member. In that case, the genetic testing laboratory can limit the search for pathogenic or likely pathogenic variants in additional family members to the same location in the gene. In most cases, an individual testing negative for a known familial pathogenic or likely pathogenic variant predisposing to breast cancer can be followed with routine breast screening. Individuals who meet testing criteria but do not undergo gene testing should be followed as if a pathogenic or likely pathogenic variant (ie, *BRCA1/2*, *PTEN*, or *TP53* pathogenic or likely pathogenic variant) is present, if they have a close family member who is a known carrier of the pathogenic or likely pathogenic variant.

For the majority of families in whom presence of a pathogenic or likely pathogenic variant is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood for a positive test result. Unless the affected individual is a member of an ethnic group for which particular founder pathogenic or likely pathogenic variants are known, comprehensive genetic testing (ie, full sequencing of the genes and detection of large gene rearrangements) should be performed by commercial or academic laboratories that are clinically approved or validated.

For individuals with family histories consistent with a pattern of hereditary breast and/or ovarian cancer on both the maternal and paternal sides, the possibility of a second pathogenic or likely pathogenic variant in the family should be considered, and full sequencing may be indicated, even if a variant has already been identified in a relative.

In the situation of an unaffected individual with a significant family history, the testing of the unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. In such cases, the unaffected individual or unaffected close relative with the highest likelihood of testing positive for the pathogenic or likely pathogenic variant should be tested. A negative test result in such cases, however, is considered indeterminate (see Table 2) and does not provide the same level of information as when there is a known pathogenic or likely pathogenic variant in the family. Thus, one should be mindful that when testing unaffected individuals (in the absence of having tested affected family members), significant limitations may exist in interpreting the test results, and testing multiple family members may be indicated.

In the case of *BRCA*-related breast/ovarian cancer, if no family member with breast or ovarian cancer is living, consideration can be given to testing first- or second-degree family members affected with cancers thought to be related to the pathogenic or likely pathogenic variant in question (eg, prostate or pancreatic cancer). Importantly, the significant limitations of interpreting testing results for an unaffected individual should be discussed prior to testing.

Reports regarding germline findings that may impact medical management should come from laboratories that are certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA), with some U.S. states (eg, New York) having additional reporting requirements. Certain large genomic rearrangements are not detectable by a primary sequencing assay, thereby necessitating supplementary testing in some cases.[50-53] For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the

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BRCA1/2 genes that are otherwise not detected by direct sequencing of the *BRCA1/2* genes. Therefore, the NCCN Guidelines Panel emphasizes the need for comprehensive testing, which encompasses full *BRCA1/2* sequencing and detection of large gene rearrangements.

A counseling dilemma is posed by the finding of a VUS (see Table 2), a genetic alteration that may actually represent a benign polymorphism unrelated to an increased breast cancer risk or may indicate an increased breast cancer risk. The individual must be counseled in such a situation, because additional information about that specific pathogenic or likely pathogenic variant will be needed before its significance can be understood. These patients should be considered for referral to research studies that aim to define the functional impact of the gene variant, such as variant reclassification programs through clinical labs or registries. Some examples of these programs and registries include ClinVar (the archival database at the National Center for Biotechnology Information [NCBI]); the NIH-funded Clinical Genome Resource (ClinGen; https://www.clinicalgenome.org/); the Clinical Cancer Genetics Community Research Network of the United States, Mexico, and South America (CCGCRN; https://www.cityofhope.org/research/beckman-research-institute/research-departments-and-divisions/population-sciences/clinical-cancer-genomics/ccg-research-program/ccg-community-research-network); Prospective Registry of Multiplex Testing (PROMPT; https://connect.patientcrossroads.org/); the international Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA; https://enigmaconsortium.org/); and the International Society for Gastrointestinal Hereditary Tumors (InSIGHT; http://insight-group.org/). It is important to note that there may be inconsistencies among how some programs and registries interpret the clinical actionability of some VUS, which may lead to confusion regarding medical management.[54-56] Clinicians and scientists should work together to develop a VUS classification system as more information is discovered in research studies.[57]

Recently, there has been an increase in genetic test results through direct-to-consumer (DTC) services or through tumor profiling. The testing typically used by companies providing ancestry information directly to consumers is microarray-based single nucleotide polymorphism (SNP) testing that has not been validated for clinical use. These companies do not provide comprehensive genetic risk assessment that includes gross deletion or duplication analysis. Third-party services are available to assist patients with interpreting their raw data, but limitations of these services include inadequate informed consent process, clinical validity and utility, and medical oversight.[58] An analysis of concordance between DTC testing results and results from confirmatory testing for 49 patients showed a false-positive rate of 40%, as well as variant classification errors in 8 patients.[59] Given the limitations of the information obtained from DTC services, confirmatory germline testing by a certified laboratory is recommended, and changes to a patient's medical management based solely on DTC testing results are not recommended.[59]

The absence of a pathogenic or likely pathogenic variant for a given gene (eg, *BRCA1/2, TP53*) from tumor profiling does not rule out the possibility of a germline pathogenic or likely pathogenic variant in that gene. If a patient meets testing criteria for germline testing for a given gene, then testing should be considered despite negative or indeterminate tumor profiling results. Incidental germline findings discovered through other sources (eg, participation in a research study) should be reviewed by a genetics professional.[60] Confirmatory testing in these cases may be recommended, especially if the reporting laboratory is not appropriately certified.

Following testing, the proband should be advised regarding possible inherited cancer risk to relatives and his/her options for risk assessment

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and management. The counselor should recommend genetic counseling and testing for at-risk relatives. Since some pathogenic or likely pathogenic variants are associated with rare autosomal recessive conditions (eg, Fanconi anemia is associated with *ATM, BRCA2, BRIP1,* and *PALB2* variants), testing of a partner of a carrier of a pathogenic or likely pathogenic variant may be considered to inform reproductive decision-making.[61] See Table 3 for a list of pathogenic/likely pathogenic variants associated with autosomal recessive conditions.

Multi-Gene Testing

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. Multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes. Multiple studies have shown that this approach may detect pathogenic or likely pathogenic variants not found in single-gene testing.[62-64] A study of 198 women referred for *BRCA1/2* testing who underwent multi-gene testing showed 16 deleterious mutations out of 141 women who tested negative for *BRCA1/2* (11.4%; 95% CI, 7.0–17.7).[63] The discovery of these mutations led to recommendations for further screening. Therefore, findings from multi-gene testing have the potential to alter clinical management.[65]

Multi-gene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available.[66] The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a pathogenic or likely pathogenic variant known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of the variant. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. For example, though ovarian cancer is mainly associated with *BRCA1/2* pathogenic or likely pathogenic variants, it may also be associated with variants in the following genes: *BARD1, BRIP1, MRE11A, MSH2, MSH6, NBN, PALB2, RAD51C, RAD51D,* and *TP53*.[67-70] Genes associated with hereditary breast cancer include the following that could potentially be included in a multi-gene test: *BRCA1/ 2, ATM, BARD1, CHEK2, PALB2, TP53, PTEN, STK11,* and *CDH1*.[10,63,69-75] In these cases where more than one pathogenic or likely pathogenic variant could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective.[66,76,77] Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is suggestive of an inherited susceptibility.[66,78]

There are several issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turnaround time, insurance coverage, and variant reclassification protocol, among others. Tests requiring a longer turnaround time may not be suitable for patients who need rapid results. The specific laboratory and multi-gene test should be chosen carefully.[66] Second, in some cases, next-generation sequencing may miss some pathogenic or likely pathogenic variants that would have been detected with traditional single-gene analysis.[66] Third, pathogenic or likely pathogenic variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.[78] A management plan should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.

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A major dilemma regarding multi-gene testing is that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed in multi-gene testing, and how to communicate and manage risk for carriers of these genes.[73,79-82] This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.[79] Some multi-gene tests may include moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management.[66,73,83-85] Further, it is possible that the risks associated with these genes may not entirely be due to that gene only, but may be influenced by gene/gene or gene/environment interactions. Also, certain variants in a gene may be associated with a different degree of risk than other variants in that gene. For example, the presence of certain *ATM* genetic variants is associated with an increased risk for early-onset breast cancer and frequent bilateral occurrence, but the association between other *ATM* variants and breast cancer susceptibility is less clear.[86-89]

As a result of these dilemmas, risk management following detection of a pathogenic or likely pathogenic variant for a moderate-risk gene, and how best to communicate risk to relatives, is currently unknown.[85,90] Further, the information gained from testing for moderate-penetrance genes may not change risk management recommendations significantly compared to that based on family history only. Multi-gene tests also increase the likelihood of detecting a VUS.[63,64,66,73,74,85,91] Multi-gene analyses of DNA samples from individuals with breast cancer showed that a VUS was found in 33% to 40% of individuals.[74] An analysis of 1191 individuals who underwent testing and were enrolled in PROMPT showed that 37% of variants found were classified as a VUS.[54] The considerable possibility of detecting a VUS adds to the complexity of counseling following multi-gene testing. However, as multi-gene testing is increasingly used, the frequency of a VUS being detected is expected to decrease.

Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when pathogenic or likely pathogenic variants are found for moderate-penetrance genes and when a VUS is found.[92] For this reason, the NCCN Panel recommends that, when multi-gene testing is offered, it is done in the context of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, which issued an updated statement regarding genetic testing in 2015.[93] Given the limited data available in this field, carriers of a pathogenic or likely pathogenic variant should be encouraged to participate in clinical trials or genetic registries.

Hereditary Breast or Breast/Ovarian Cancer Syndromes

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer death in women.[94] The ACS estimates that 255,180 Americans will be diagnosed with invasive breast cancer and 41,070 will die of the disease in the United States in 2017.[95] Up to 10% of breast cancers are due to specific mutations in single genes that are passed down in a family.[6,8,69,75] Specific patterns of hereditary breast/ovarian cancers are linked to pathogenic or likely pathogenic variants in the *BRCA1/2* genes.[96,97] In addition, two very rare hereditary cancer syndromes exhibiting an increased risk for breast cancer are Li-Fraumeni syndrome (LFS) and Cowden syndrome, which are related to germline pathogenic or likely pathogenic variants in the *TP53* and *PTEN* genes, respectively.[98,99] Similar to the *BRCA1/2* genes, the *TP53* and *PTEN* genes encode for proteins involved in processes related to tumor suppression, such as DNA repair and cell cycle regulation.

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

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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 (see Table 1). A database analysis of 35,409 women with breast cancer who underwent multi-gene testing showed that rates of pathogenic variants were highest in women who were diagnosed before 40 years of age and lowest in women diagnosed after 59 years of age.[75] 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, although a subsequent alteration or silencing in the second copy of the gene without the hereditary variant is believed to be necessary for the initiation of cancer development (ie, 2-hit hypothesis).[100,101] 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.

BRCA-Related Breast/Ovarian Cancer Syndrome

Both the *BRCA1* and *BRCA2* genes encode for proteins involved in tumor suppression. The *BRCA1* gene is located on chromosome 17 and is believed to be involved in both DNA repair and the regulation of cell-cycle checkpoints in response to DNA damage. However, the molecular mechanism through which *BRCA1* functions to preserve genomic stability remains unclear.[102] The *BRCA2* gene, located on chromosome 13, is involved in repair of replication-mediated double-strand DNA breaks.[103,104] The overall prevalence of disease-related mutations in *BRCA1/2* genes has been estimated as 1 in 300 and 1 in 800, respectively.[105,106] Currently, hundreds of unique pathogenic or likely pathogenic variants have been identified in both *BRCA1* and *BRCA2* genes. However, a number of founder effects (see Table 1) have been observed in certain populations, wherein the same pathogenic or likely pathogenic variant has been found in multiple, ostensibly unrelated families and can be traced back to a common ancestor. Among the Ashkenazi Jewish population, for example, the frequency of 187delAG and 5385insC variants in *BRCA1* and the 6174delT variant in *BRCA2* approximates 1 in 40.[6,107] Certain founder pathogenic or likely pathogenic variants have also been identified in other populations.[105,108-112]

In a sample of 488 women with non-metastatic breast cancer, 6.1% had a *BRCA1/2* mutation, with mutation prevalence decreasing with age (ie, 12% in women diagnosed at 45 years of age or younger and 3% in women diagnosed at 46 years of age or older).[113] It has been estimated that more than 90% of hereditary families with both breast and ovarian cancers are caused by mutation(s) in the *BRCA1/2* genes.[114] Hence, the degree of clinical suspicion for a *BRCA* pathogenic or likely pathogenic variant in a single individual with both breast and ovarian cancer or someone with a family history of both breast and ovarian cancer should be very high.

BRCA1/2 pathogenic or likely pathogenic variants can be highly penetrant (for definition, see Table 1), 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.[115-117] Estimates of penetrance range from a 41% to 90% lifetime risk for breast cancer, with an increased risk for contralateral breast cancer.[118-125] In addition, female carriers of these genes have an estimated 8% to 62% lifetime risk for ovarian cancer, depending on the population studied.[119-124,126,127] In a 2007 meta-analysis of published data that evaluated *BRCA1/2* penetrance, estimates for mean cumulative risks for breast and ovarian cancer by 70 years of age for *BRCA1* mutation carriers were 57%

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and 40%, respectively.[120] The corresponding estimates for *BRCA2* mutation carriers were 49% and 18%, respectively. In a prospective analysis of risk estimates from individuals with *BRCA1/2* mutations in the United Kingdom (N = 1887), estimates for mean cumulative risks for breast cancer and ovarian cancer by 70 years of age for *BRCA1* mutation carriers were 60% and 59%, respectively.[123] The corresponding estimates for *BRCA2* mutation carriers were 55% and 16.5%, respectively. A prospective cohort study including 9856 unaffected *BRCA1/2* carriers showed that a cumulative risk of breast cancer by 80 years of age was 72% for *BRCA1* mutation carriers and 69% for *BRCA2* mutation carriers.[128] Among the patients diagnosed with unilateral breast cancer (n = 651), the mean cumulative risks for contralateral breast cancer by 70 years of age were estimated to be 83% for *BRCA1* carriers and 62% for *BRCA2* carriers.[123] Other estimates of cumulative risk for contralateral breast cancer 20 years after breast cancer diagnosis are 40% for *BRCA1* mutation carriers and 26% for *BRCA2* mutation carriers.[128] An international study including 19,581 *BRCA1* mutation carriers and 11,900 *BRCA2* mutation carriers showed that 46% of the *BRCA1* mutation carriers and 52% of the *BRCA2* mutation carriers eventually developed breast cancer, and 12% of the *BRCA1* mutation carriers and 6% of the *BRCA2* mutation carriers eventually developed ovarian cancer.[129] 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.

Some of the NCCN treatment guidelines for *BRCA*-related cancers now recommend treatment with PARP (poly ADP-ribose polymerase) inhibitors for patients with germline *BRCA1/2* mutations, as PARP inhibitors have been demonstrated to be active in these patients. These agents include olaparib[130] and talazoparib[131] for HER2-negative metastatic breast cancer, and olaparib[132-134] and rucaparib[135,136] for chemotherapy-refractory ovarian cancer. Though some early studies investigating PARP inhibitors in patients who have germline *BRCA1/2* mutations with metastatic castration-resistant prostate cancer or pancreatic cancer are promising,[137-139] data from larger randomized trials are needed. DNA repair defects (eg, *BRCA1/2* mutations) have been reported to be predictive for sensitivity to platinum agents in breast and ovarian cancers.[140]

Some histopathologic features have been reported to occur more frequently in breast cancers characterized by a *BRCA1/2* pathogenic or likely pathogenic variant. For example, several studies have shown that *BRCA1* breast cancer is more likely to be characterized as ER-/PR-negative and HER2-negative (ie, “triple negative”).[141-146] Studies have reported *BRCA1* mutations in 7% to 28% of patients with triple-negative breast cancer.[75,113,146-153] A meta-analysis examining 12 studies with 2533 patients with breast cancer showed that women with triple-negative breast cancer are more likely to be carriers of a *BRCA1* mutation, relative to women with breast cancer that is not classified as triple-negative (relative risk [RR] = 5.65; 95% CI, 4.15–7.69).[154] Several reports have also suggested the role of *BRCA2* mutations in triple-negative breast cancer. The incidence of *BRCA2* mutations range from 1% to 17% in studies of triple-negative breast cancer cases unselected for age or family history.[113,147,152,153,155] In a sample of 396 women with HER2-positive breast cancer diagnosed at 40 years of age or younger, 4% had a *BRCA1* or *BRCA2* mutation.[156]

An increased incidence of *BRCA1/2* mutations was reported in triple-negative breast cancer cases from at-risk populations. Among Ashkenazi Jewish women with breast cancer unselected for family history (N = 451), triple-negative disease was observed in 14% of patients and *BRCA*

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founder mutations were found in 11% of patients.[157] Among the subgroup with triple-negative breast cancer (n = 65), the incidence of *BRCA* mutations was 39% (*BRCA1* mutation in 30%; *BRCA2* mutation in 9%).[157] Other studies including Ashkenazi Jewish women diagnosed with any breast cancer showed that a *BRCA1/2* mutation was detected in 11% to 18%.[113,158]

Among patients with triple-negative disease, *BRCA* mutation carriers were diagnosed at a younger age compared with non-carriers.[149,159] In a study of a large cohort of patients with triple-negative breast cancer (N = 403), the median age of diagnosis among carriers of *BRCA1* mutations (n = 65) was 39 years.[148] 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). For patients with triple-negative breast cancer with a family history of breast and/or ovarian cancer (n = 105), *BRCA1* mutations were found in 48% of patients.[148]

Male carriers of a *BRCA1/2* mutation also have a greater risk for cancer susceptibility.[160] In one study of 26 high-risk families with at least one case of male breast cancer, 77% demonstrated a *BRCA2* mutation.[114] 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 35.8% of families with at least one case of male breast cancer with at least one other case of either female breast or ovarian cancer.[161] Among male patients with breast cancer who were not selected on the basis of family history, 4% to 14% tested positive for a germline *BRCA2* mutation.[162-165] In a series of male breast cancer cases (N = 115; primarily from cancer registry data), *BRCA2* mutations were detected in 16% of cases; the incidence of *BRCA2* mutations was 40% among patients selected for family history of breast cancer and 13% among those unselected for family history.[164] For males with a *BRCA2* mutation, the cumulative lifetime risk for breast cancer has been estimated at 7% to 8%.[166,167] The cumulative lifetime risk for *BRCA1* mutation carriers is 1.2%.[167] In contrast, for men without a *BRCA1/2* mutation, the lifetime risk for breast cancer has been estimated at approximately 0.1% (1 in 1000).[164,168]

Relatively few studies have examined rates of *BRCA1/2* pathogenic or likely pathogenic variants in black women. An observational study including 396 black women who were diagnosed with invasive breast cancer before 50 years of age showed that 12.4% were carriers of a *BRCA1/2* mutation.[169] Carriers of a *BRCA1/2* mutation were also significantly more likely to have triple-negative disease ($P < .001$), a family history of breast and/or ovarian cancer ($P < .001$), and a diagnosis before 45 years of age ($P < .05$). Based on these findings, study authors suggested that black women diagnosed with invasive breast cancer at a young age (ie, younger than 50 years of age) should be considered for *BRCA* testing.

The evidence that a *BRCA1/2* mutation is associated with poor survival outcomes for breast cancer has been inconsistent.[170,171] A meta-analysis including 13 studies showed that *BRCA1* mutation carriers with breast cancer had worse overall survival (OS) compared to 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.[172] A more recent meta-analysis including 60 studies and 105,220 patients with breast cancer also found that *BRCA1* carriers had worse OS compared to non-carriers (HR, 1.30; 95% CI, 1.11–1.52; $P = .001$).[173] *BRCA2* carriers had worse breast cancer-specific survival compared to non-carriers (HR, 1.29; 95% CI, 1.03–1.62; $P = .03$), though OS was not significantly different. This meta-analysis also showed that, among patients with triple-negative breast cancer, *BRCA1/2* mutations are

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associated with better OS (HR, 0.49; 95% CI, 0.26–0.92; *P* = .03). However, this subgroup analysis only included two 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.[174] An analysis of 119 Swedish women who were diagnosed with early-onset breast cancer showed that not receiving chemotherapy treatment was associated with poor survival in *BRCA1/2* mutation carriers (HR, 3.0; 95% CI, 1.2–7.7; *P* = .014).[175] Carrying a *BRCA1/2* mutation is not significantly associated with nodal metastasis.[176]

BRCA1/2 pathogenic or likely 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.[161] An analysis of 6478 patients who were diagnosed with breast cancer before 50 years of age showed that *BRCA1* mutation carriers had worse OS compared to patients who did not have a *BRCA1/2* mutation (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).[177] *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 those with *BRCA1/2* mutations in that age of disease onset may become lower over time.[178] However, an analysis of 176 families with a known *BRCA1/2* mutation 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.[179] Though inflammatory breast cancer has not been found to be significantly associated with *BRCA1/2* pathogenic or likely pathogenic variants, an analysis of 479 women with breast cancer and a *BRCA1/2* pathogenic or likely pathogenic variant showed that women with inflammatory breast cancer were diagnosed at a younger age than women who had breast cancer that was not inflammatory (*P* = .024).[180]

Increased risks for cancers of the ovary, fallopian tube, and peritoneum are observed in carriers of *BRCA1/2* mutations.[181-183] Germline mutations in *BRCA1/2* are responsible for at least 10% of epithelial ovarian cancers.[184,185] An analysis of 2222 patients with epithelial ovarian cancer showed that 11% carried a *BRCA1/2* mutation when disease was high-grade serous.[186] In the setting of an invasive ovarian cancer diagnosis, as many as 13% to 20% of women have a germline *BRCA1/2* mutation.[124,187-189] In an analysis of families who met German Consortium for Hereditary Breast and Ovarian Cancer testing criteria for *BRCA1/2* mutations (N = 21,401), mutations were detected in 41.9% of families in which there were at least 2 ovarian cancer cases.[161] However, it has been reported that about half of families showing a genetic predisposition to ovarian cancer do not have identifiable *BRCA1/2* mutations.[190] Hence, other gene mutations predisposing a patient to ovarian cancer are likely to exist.[191] A prospective cohort study including 9856 unaffected *BRCA1/2* carriers showed that a cumulative risk of ovarian cancer by 80 years of age was 44% for *BRCA1* mutation carriers and 17% for *BRCA2* mutation carriers.[128]

Several studies have reported more favorable survival outcomes among *BRCA1/2* mutation carrier patients with ovarian cancer compared with non-carrier patients.[192-198] In a case-control study of Ashkenazi Jewish patients with epithelial invasive ovarian cancer (N = 779), patients with a *BRCA1/2* mutation had significantly longer median survival compared with non-carrier patients (54 months vs. 38 months; *P* = .002).[195] Results from

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a pooled analysis from 26 observational studies that included invasive epithelial ovarian cancer cases from *BRCA1/2* mutation carriers (n = 1213) and non-carriers (n = 2666) showed favorable survival outcomes for patients with a *BRCA1/2* mutation.[193] The 5-year survival rate for non-carriers, *BRCA1* carriers, and *BRCA2* carriers was 36%, 44%, and 52%, respectively. The survival advantage compared with non-carriers was significant for both the *BRCA1* carriers (HR, 0.78; 95% CI, 0.68–0.89; *P* < .001) and *BRCA2* mutation carriers (HR, 0.61; 95% CI, 0.50–0.76; *P* < .001).[193] In a population-based case-control study of women with invasive epithelial (nonmucinous) ovarian cancer (N = 1001) from the Australian Ovarian Cancer Study Group, *BRCA1/2* mutation carriers had improved survival outcomes compared with non-carriers in terms of median progression-free survival (20 months vs. 16 months; not statistically significant) and median survival (62 months vs. 55.5 months; *P* = .031).[192] Moreover, *BRCA1/2* mutation carriers appeared to be more responsive to cytotoxic chemotherapy (regardless of class of agent) compared with non-carrier patients.

Survival outcomes appear to be most favorable for *BRCA2* mutation carriers; in a subgroup of patients with *BRCA2* mutations (n = 53), the median survival was 70 months.[192] In an observational study of patients with high-grade serous ovarian cancer (N = 316), patients with *BRCA2* mutations had significantly favorable survival outcomes (HR, 0.33; 95% CI, 0.16–0.69; *P* = .003; 5-year rate: 61% vs. 25%) and progression-free survival (HR, 0.40; 95% CI, 0.22–0.74; *P* = .004; 3-year rate: 44% vs. 16%) compared with non-carrier patients (having wild-type *BRCA*).[197] An observational study including 1345 women with ovarian cancer who participated in clinical trials from the Gynecologic Oncology Group showed that *BRCA2* mutation carriers had significantly longer progression-free survival (HR, 0.60; 95% CI, 0.45–0.79; *P* < .001) and OS (HR, 0.39; 95% CI, 0.25–0.60; *P* < .001) relative to those without mutations.[185] Additionally, *BRCA2* mutations were associated with significantly higher response rates (compared with non-carriers or with *BRCA1* mutation carriers) to primary chemotherapy. In contrast, *BRCA1* mutations were not associated with prognosis or improved chemotherapy response.[197]

The histology of ovarian cancers in carriers of a *BRCA1/2* mutation is more likely to be characterized as serous adenocarcinoma and high grade compared with ovarian cancers in non-mutation carriers, although endometrioid and clear cell ovarian cancers also have been reported in the former population.[183,184,188,199-201] Mutations are also associated with non-mucinous ovarian carcinoma as opposed to mucinous.[187,189] Mucinous epithelial ovarian carcinomas may be associated with other gene mutations, such as *KRAS* and *TP53* mutations.[202] *TP53* pathogenic or likely pathogenic variants are implicated in LFS (see below). Non-epithelial ovarian carcinomas (eg, germ cell and sex cord-stromal tumors) are not significantly associated with a *BRCA1/2* mutation,[203] but they may be associated with other cancer genetic syndromes. For example, sex cord tumors may be associated with Peutz-Jeghers syndrome (see below), while Sertoli-Leydig tumors are associated with both Peutz-Jeghers syndrome and DICER1-related disorders.[204-209] Current data show that ovarian low malignant potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with a *BRCA1/2* mutation.[187] Therefore, the panel does not consider the presence of an ovarian low malignant potential tumor to be a criterion for genetic testing. Interestingly, results from a prospective study suggest that women from families at increased risk for hereditary breast cancer without detectable *BRCA* mutations are not at increased risk for ovarian cancer. However, these results may have been confounded by the ethnic characteristics and size of the study population.[210]

In studies of women with a *BRCA1/2* mutation who underwent risk-reducing salpingo-oophorectomy (RRSO), occult gynecologic carcinomas were identified in 4.5% to 9% of cases based on rigorous pathologic

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examinations of the ovaries and fallopian tubes.[211-213] 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% to 8% of cases from patients with a *BRCA1/2* mutation who underwent RRSO.[211,214,215] The fimbriae or distal tube was reported to be the predominant site of origin for these early malignancies found in patients with *BRCA1/2* mutations.[211,215,216] Although TIC appeared to present more frequently among *BRCA1/2* mutation carriers compared with non-carriers undergoing RRSO,[215,216] TIC has also been documented among patients with serous carcinomas unselected for family history or *BRCA* mutation status.[217] Because TIC was identified in individuals who underwent surgery for risk reduction (for *BRCA1/2* mutation carriers) or other gynecologic indications, the incidence and significance of these early lesions within the general population is unclear. Hence, at the present time, there is no justifiable role for *BRCA* testing for cases based solely on the finding of TIC during pathology evaluation for gynecologic indications.

Germline *BRCA1/2* mutations have been associated with increased risk for prostate cancer,[218-220] with this association being strongest for advanced or metastatic prostate cancer.[221-223] A study of a large cohort of patients from Spain with prostate cancer (N = 2019) showed that patients with *BRCA1/2* mutations had significantly higher rates of aggressive prostate cancer (Gleason score ≥8), nodal involvement, and distant metastasis compared with non-carriers.[224] In a sample of 692 men with metastatic prostate cancer, unselected for family history or age at diagnosis, 5.3% had a *BRCA2* mutation, and 0.9% had a *BRCA1* mutation.[223] In addition, analyses from a treatment center database showed that *BRCA1/2* and *ATM* (see below under *Other Pathogenic/Likely Pathogenic Variants Associated with Breast/Ovarian Cancer*) 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 non-carriers (5 years vs. 16 years, respectively; $P < .001$).[222] This association remained statistically significant when controlling for race, age, PSA, and Gleason score. Ashkenazi Jewish ancestry is also associated with *BRCA1/2* mutations in men with prostate cancer, with rates for *BRCA1* being 0% to 2% and rates for *BRCA2* being 1% to 3%.[218,225-228]

Prior to the increasingly common use of panel testing, studies showed that *BRCA1/2* mutation rates in pancreatic cancer cases ranged from 1% to 11% for *BRCA1* and 0% to 17% for *BRCA2*.[229-237] However, some of these studies included only patients with familial pancreatic cancer[232,233,236] or those of Ashkenazi Jewish ancestry,[234] both of who 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*).[238-242] Given that mortality rates for this cancer are high,[243,244] it may be beneficial to family members to test patients near the time of diagnosis, since the option to test the patient may not be available for very long.

Some studies have suggested an increased risk specifically of serous uterine cancer in *BRCA* mutation carriers.[245-247] Analyses from a multicenter prospective cohort study including 1083 women with a *BRCA1* mutation who underwent RRSO without hysterectomy showed an increased risk for serous and/or serous-like endometrial cancer.[248] 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.[249,250] 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

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in controls (also of Ashkenazi Jewish ancestry) (OR, 5.4; 95% CI, 2.2–13.1).[245]

One study showed that women with a *BRCA2* mutation 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).[251] An analysis of 490 families with *BRCA1/2* mutations showed an increased risk for ocular melanoma in *BRCA2* carriers (RR, 99.4; 95% CI, 11.1–359.8).[252]

NCCN Recommendations

The NCCN Panel recommends that individuals from a family with a known *BRCA1/2* pathogenic or likely pathogenic variant be considered for testing, irrespective of degree of relatedness (see *BRCA1/2 Testing Criteria* in the algorithm). In individuals from a family without a known *BRCA1/2* pathogenic or likely pathogenic variant, testing should be considered for those individuals who meet the testing criteria discussed below. Meeting one or more criteria warrants further personalized risk assessment, genetic counseling, and, often, genetic testing and management. The probability of detection of a pathogenic or likely pathogenic variant will vary based on family structure. In evaluating risks based on family history factors, the maternal and paternal sides should be considered independently. For the testing criteria mentioned below, "close relatives" pertain to first-, second-, or third-degree blood relatives on the same side (either maternal or paternal side) of the family. Individuals with a limited or unknown family history (eg, having fewer than 2 first- or second-degree female relatives surviving beyond 45 years of age on either the maternal or paternal side) may have an underestimated probability of detection of a familial pathogenic or likely pathogenic variant. The likelihood of detection of a pathogenic or likely pathogenic variant may be very low in families with a large number of unaffected female relatives. Clinical judgment should be used to determine the appropriateness of genetic testing.

The panel recommends that patients with a personal history of breast cancer *in addition to* one or more of the following criteria be considered for *BRCA1/2* testing:

- Diagnosed at 45 years of age or younger;
- Diagnosis of at least 2 additional breast cancer primaries (ie, bilateral tumors or 2 or more clearly separate ipsilateral tumors, occurring synchronously or asynchronously) at any age, in the proband and/or in a close relative;
- Diagnosed between 46 and 50 years of age with an unknown or limited family history, or a diagnosis of an additional breast cancer primary at any age, or with 1 or more close relatives with breast cancer at any age, or 1 or more close relatives with high-grade prostate cancer (Gleason score ≥7);
- Diagnosed with triple-negative breast cancer at 60 years of age or younger;
- Diagnosed at any age with 1 or more close relatives with ovarian carcinoma (including fallopian tube and primary peritoneal cancers), metastatic prostate cancer (biopsy-proven and/or with radiographic evidence and including distant metastasis and regional bed or nodes), pancreatic cancer, or breast cancer diagnosed at 50 years of age or younger; and/or
- Having a close male relative with breast cancer at any age.

Germline origin can be inferred with a high degree of confidence in the case of founder variants. In patients with a personal history of breast cancer and Ashkenazi Jewish heritage, no additional family history may be needed to meet testing criteria. In addition, the NCCN Panel recommends

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testing for patients with a personal history of ovarian carcinoma, pancreatic cancer, metastatic prostate cancer (radiographic evidence of or biopsy-proven disease), or male breast cancer, all diagnosed at any age.

Testing is recommended for those with a personal history of high-grade prostate cancer (Gleason score ≥7) diagnosed at any age with any of the following: a family history of at least one relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer at any age (biopsy-proven and/or with radiographic evidence and including distant metastasis and regional bed or nodes), or breast cancer diagnosed at younger than 50 years of age; two relatives with breast or prostate cancer diagnosed at any age; or Ashkenazi Jewish ancestry.

In individuals with a family history only (ie, no personal history of a *BRCA*-related cancer), significant limitations of interpreting test results should be discussed prior to any testing. Moreover, testing of individuals without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing. When evaluating an individual without a cancer diagnosis for his or her likelihood of carrying a *BRCA1/2* pathogenic or likely pathogenic variant, clinical judgment should be made based on factors such as the individual's current age and the age of unaffected female relatives who link the individual with an affected close relative.

For individuals not meeting testing criteria for a *BRCA1/2* pathogenic or likely pathogenic variant, testing should be considered for other hereditary syndromes. If criteria for other hereditary syndromes are not met, then the panel recommends screening as per the NCCN Screening Guidelines (available at www.NCCN.org).

The goal of these Guidelines is to inform primary and secondary prevention of hereditary breast and/or ovarian cancer. Therefore, these Guidelines do not provide specific recommendations regarding targeted therapy options for patients with hereditary breast and/or ovarian cancer. Individuals diagnosed with a *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted therapy (see NCCN Guidelines for Breast Cancer, Ovarian Cancer, and Prostate Cancer, available at www.NCCN.org). If a *BRCA1/2* pathogenic or likely pathogenic variant is detected through tumor profiling on any tumor type in absence of germline subtraction, then *BRCA1/2* genetic testing should be considered.

Risk Assessment, Counseling, and Management

Detailed in the NCCN Guidelines is a set of specific risk assessment criteria that form part of the decision-making process in evaluating whether an individual suspected of being a carrier of a *BRCA1/2* pathogenic or likely pathogenic variant should be considered for genetic testing (see *BRCA1/2 Testing Criteria* in the algorithm). Following risk assessment and counseling, genetic testing should be considered for individuals for whom hereditary breast/ovarian cancer syndrome testing criteria are met. Testing is generally not recommended in children younger than 18 years of age, since conditions associated with *BRCA1/2* pathogenic or likely pathogenic variants generally have an adult onset, and, thus, medical management would not be impacted.[253] Testing for a *BRCA1/2* pathogenic or likely pathogenic variant is recommended in women with early-onset breast cancer (see *BRCA1/2 Testing Criteria* in the algorithm). Testing rates for these women have been increasing in recent years, with one study of women diagnosed with breast cancer earlier than 40 years of age showing an increase in testing rates from 2006 to 2013 (77%–95%, $P < .001$).[254]

Individuals from a family with a known *BRCA1/2* pathogenic or likely pathogenic variant should be tested accordingly. For individuals from a family without a known *BRCA1/2* pathogenic or likely pathogenic variant (and who meet testing criteria), genetic testing should be comprehensive, including full sequencing of *BRCA1/2* and testing for large genomic

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rearrangements. Individuals from a family with a known *BRCA1/2* pathogenic or likely pathogenic variant who test positive for the familial variant, or for whom *BRCA1/2* pathogenic or likely pathogenic variant testing is not performed, should follow the screening recommendations outlined in *BRCA Mutation-Positive Management* in the algorithm (and discussed below).

Somatic *BRCA1/2* pathogenic or likely pathogenic variants are not common. In a sample of 273 unselected breast cancer patients from Sweden, a somatic *BRCA1/2* mutation was detected in 3%.[255] If a pathogenic or likely pathogenic variant is found through tumor profiling, then *BRCA1/2* genetic testing should be considered.[256]

For individuals of Ashkenazi Jewish descent with no known familial *BRCA1/2* pathogenic or likely pathogenic variants, one approach is to first test for the 3 known founder variants; if the tests are negative for founder pathogenic or likely pathogenic variant, and if the individual's ancestry also included non-Ashkenazi ethnicity (or if other *BRCA1/2* testing criteria are met), comprehensive genetic testing should be considered. However, with new panels available, many clinicians are moving away from this stepped approach and are increasingly using comprehensive testing (see *Multi-Gene Testing*). Additional testing may also be considered if there is a significant family history of cancer on the side of the family without the known pathogenic or likely pathogenic variant.

Whenever possible, an affected family member with the highest likelihood of carrying the *BRCA1/2* pathogenic or likely pathogenic variant should be tested first. If more than one family member is affected, members with the following factors should be considered for testing first: youngest age at diagnosis; having bilateral disease or multiple primaries; having other associated cancers (eg, ovarian); and most closely related to the proband. If no living family member with breast or ovarian cancer exists, consider testing first- or second-degree family members affected with cancer thought to be related to *BRCA1/2* pathogenic or likely pathogenic variants (eg, prostate cancer, pancreatic cancer, melanoma). The same principles apply when considering genetic testing for LFS and Cowden syndrome (see below).

As previously discussed, testing of unaffected individuals should only be considered when an appropriate affected family member is not available for testing. Individuals who test positive for a pathogenic or likely pathogenic variant should follow the screening recommendations outlined in *BRCA Mutation-Positive Management* in the algorithm (and discussed below). Alternatively, testing another family member with the next highest likelihood of having a pathogenic or likely pathogenic variant may also be considered. For individuals who have not been tested or for those in whom VUS are found (uninformative testing results), participation in a research program or individualized recommendations based on personal history and family history should be offered.

Counseling issues specific for both female and male carriers of a *BRCA1/2* pathogenic or likely pathogenic variant include the increased incidence of pancreatic cancer and melanoma. In addition, the risks to family members of individuals with a known *BRCA1/2* pathogenic or likely pathogenic variant should also be discussed as well as the importance of genetic counseling for these individuals. Counseling issues pertaining specifically to male breast cancer have also been described, and include an increased risk for prostate cancer and pancreatic cancer in male carriers of a *BRCA1/2* pathogenic or likely pathogenic variant.[257,258]

Recommendations for the medical management of hereditary 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 *BRCA1/2* carriers. An individual with a known *BRCA1/2* pathogenic or likely pathogenic variant in a close family member who does not undergo gene testing should be followed according to the

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same screening/management guidelines as a carrier of a *BRCA1/2* pathogenic or likely pathogenic variant. 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 in the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at www.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.[259] 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 semiannual clinical breast examinations should begin 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 the family history includes a breast diagnosis prior to 30 years of age.[27,259-262] 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 last few decades. There are currently no data indicating that mammography on its own reduces mortality in women with genetically increased risk for breast cancer.[263] 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,[264-267] 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.[264,268] Prospective studies on comparative surveillance modalities in women at high risk for familial breast cancer (ie, confirmed *BRCA1/2* mutation 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%).[259-261,269-271] The sensitivity with ultrasound screening (33%–65%) appeared similar to that of mammography in this high-risk population.[259,269-271] 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 *BRCA1/2* mutation, sensitivity with MRI was significantly higher compared with mammography during the entire study period (86% vs. 19%; $P < .0001$).[272] 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.[272] 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%.[273]

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All of these studies discussed above evaluated a screening strategy that was conducted on an annual basis, and many of the studies included individuals without confirmed *BRCA1/2* mutation status. A study of 1219 *BRCA1* carriers and 732 *BRCA2* carriers showed that the increased sensitivity of mammography over MRI was greater for *BRCA2* carriers (12.6%) than for *BRCA1* carriers (3.9%).[274] In a retrospective study, a different screening interval was evaluated, using alternating mammography and MRI screening every 6 months in women with a confirmed *BRCA1/2* mutation (N = 73).[275] 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.[275]

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 *BRCA1/2* mutation,[276,277] a report from a large cohort study suggested an increased risk in women exposed to radiation at a young age.[278] A retrospective cohort study (from the GENE-RAD-RISK study) showed that exposure to diagnostic radiation (including mammography) prior to 30 years of age was associated with increased risk for breast cancer in women with a *BRCA1/2* mutation (N = 1993).[278] 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 (two-dimensional, 2D) in conjunction with digital breast tomosynthesis (DBT) appears to improve cancer detection and reduce false-positive call-back rates.[279-288] Tomosynthesis allows acquisition of three-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 DBT 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. Food and Drug Administration (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.[280,289,290] 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 *BRCA1/2* mutation carriers, 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.[291] 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.[27]

Post-test 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)

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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.[292]

Studies assessing whether ovarian cancer screening procedures are sufficiently sensitive or specific have yielded mixed results. The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), 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.[293,294] In phase II of the UK Familial Ovarian Cancer Screening Study (UK FOCSS), 4348 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).[295] Thirteen patients were diagnosed with ovarian cancer as a result of the screening protocol, with 5 of the 13 patients 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 3692 women who were at increased familial/genetic risk of ovarian cancer 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.[296] 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 *BRCA1/2* carriers. 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. Regularly scheduled mammography is not recommended by the panel, as there are only limited data to support breast imaging in men, since male breast cancer is rare. Screening for prostate cancer starting at 45 years of age should be recommended for *BRCA2* carriers and considered for *BRCA1* carriers. See the NCCN Guidelines for Prostate Cancer Early Detection (available at www.NCCN.org).

For both men and women testing positive for a *BRCA1/2* pathogenic or likely pathogenic variant, a full body skin and eye exam for melanoma screening and investigational protocols for pancreatic cancer screening should be considered. Individualized screening approaches may be provided according to personal or family history of cancer. The International Cancer of the Pancreas Screening (CAPS) Consortium recommends screening for pancreatic cancer in patients with a *BRCA2* mutation who have a family history of pancreatic cancer.[297] Though endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) were identified as potential screening tools, the Consortium acknowledged that more research is needed on an optimal screening schedule.

Risk Reduction Surgery

Bilateral Total Mastectomy

Discussion Update in Progress

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A meta-analysis including 6 studies (N = 2555) showed that prophylactic bilateral mastectomy reduces the risk for breast cancer (RR, 0.11; 95% CI, 0.04–0.32).[298] However, this risk-reducing surgery was not significantly associated with reduced all-cause mortality. Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that bilateral risk-reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known *BRCA1/2* mutation carriers.[299,300] Results from smaller prospective studies with shorter follow-up periods have provided support for concluding that RRM provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation.[301,302]

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. Since risk of breast cancer remains increased with age in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant,[120] age and life expectancy should be considered during this counseling, as well as family history.

It is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well-studied.[303] Multidisciplinary consultations are recommended prior to surgery and should include the 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.[304] Nipple-sparing mastectomy has been suggested to be a safe and effective risk reduction strategy for patients with a *BRCA1/2* pathogenic or likely pathogenic variant,[305] although more data are needed.

Bilateral Salpingo-oophorectomy

Women with a *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).[181,182] Although the risk for ovarian cancer is generally considered to be lower than the risk for breast cancer in a *BRCA1/2* mutation carrier,[118,119,306] 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 5783 women with a *BRCA1/2* mutation showed that ovarian cancer is more prevalent in individuals with *BRCA1* (4.2%) than *BRCA2* (0.6%) mutations.[307] In *BRCA1* mutation carriers, 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.[307] The highest incidence rate for *BRCA1* mutation carriers was observed between the ages of 50 and 59 years (annual risk, 1.7%); for *BRCA2* mutation carriers, the highest incidence rate was observed between the ages of 60 and 69 years (annual risk, 0.6%). Therefore, the recommended age for RRSO could be younger for women with a *BRCA1* pathogenic or likely pathogenic variant than for women with 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 *BRCA1/2* mutation carriers showed an approximately 80% reduction in the risk for ovarian or fallopian cancer following RRSO.[308] In a large prospective study of women who carried deleterious *BRCA1/2* mutations (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–

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0.56; *P* = .005).[309] An observational study of 5783 women with a *BRCA1/2* mutation 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).[307] RRSO reduces mortality at all ages in *BRCA1* mutation carriers, but among *BRCA2* mutations carriers RRSO is only associated with reduced mortality in those between the ages of 41 and 60 years.[307]

A 1% to 4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.[212,308,310-313] An analysis of 36 carriers of a *BRCA1/2* mutation who developed peritoneal carcinomatosis following RRSO showed that 86% were carriers of a *BRCA1* mutation specifically.[314] When comparing to 113 carriers of a *BRCA1/2* mutation 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 (STIC) 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 with a *BRCA1* mutation who underwent RRSO without hysterectomy.[248]

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 *BRCA1* carriers and 3.5% of *BRCA2* carriers.[315] Presence of a *BRCA1/2* mutation was associated with detection of clinically occult neoplasms during RRSO (*P* = .006).

RRSO is also reported to reduce the risk for breast cancer in carriers of a *BRCA1/2* mutation.[298,308,312,313,316] Reductions in breast cancer risk for carriers of a *BRCA1/2* mutation undergoing RRSO may be associated with decreased hormonal exposure following surgical removal of the ovaries. 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* = 0.11) breast cancer risk reduction (adjusted for oral contraceptive use and parity) was reported following RRSO in carriers of a *BRCA1* and a *BRCA2* mutation, respectively.[316] HRs of 0.47 (95% CI, 0.29–0.77)[313] and 0.30 (95% CI, 0.11–0.84; *P* = .022)[311] were reported in two other studies comparing breast cancer risk in women with a *BRCA1/2* mutation who had undergone RRSO with carriers of these mutations who opted for surveillance only. These studies are further supported by a meta-analysis that found similar reductions in breast cancer risk of approximately 50% for *BRCA1/2* mutation carriers following RRSO.[308]

Results of a prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA2* mutation carriers compared with *BRCA1* mutation carriers.[309] Another retrospective analysis including 676 women with stage I or II breast cancer and a *BRCA1/2* mutation showed that oophorectomy was associated with decreased risk of mortality from breast cancer in *BRCA1* mutation carriers (HR, 0.38; 95% CI, 0.19–0.77, *P* = .007), but not in carriers of a *BRCA2* mutation (*P* = .23).[317] Mortality risk was also significantly impacted in *BRCA1/2* mutation carriers who had ER-negative breast cancer (HR, 0.07; 95% CI, 0.01–0.51, *P* = .009).

A prospective cohort study from the Netherlands (N = 822) did not find a statistically significant difference in breast cancer incidence between *BRCA1/2* mutation carriers who opted for an RRSO and women who did not, regardless of whether the mutation was for *BRCA1* or *BRCA2*.[318] 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

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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 *BRCA1/2* mutation carriers (HR, 0.59; 95% CI, 0.42–0.82, $P < .001$).[319]

Greater reductions in breast cancer risk were observed in women with a *BRCA1* mutation who had an RRSO at 40 years of age or younger (OR, 0.36; 95% CI, 0.20–0.64) relative to *BRCA1* carriers aged 41 to 50 years who had this procedure (OR, 0.50; 95% CI, 0.27–0.92).[316] 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.[316] However, results from Rebbeck et al also suggest that RRSO after 50 years of age is not associated with a substantial decrease in breast cancer risk.[312] A more recent study showed that oophorectomy was not significantly associated with decreased risk of breast cancer in *BRCA1/2* mutation carriers ($N = 3,722$).[320] However, stratified analyses in *BRCA2* carriers 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 *BRCA1* carriers was not statistically significant ($P = .51$). Due to the limited data regarding the impact of RRSO on breast cancer risk when taking into account age and the specific mutation (*BRCA1* vs. *BRCA2*), an optimal age for RRSO is difficult to specify.

It has been reported that short-term hormone replacement therapy (HRT) in women undergoing RRSO does not negate the reduction in breast cancer risk associated with the surgery.[321] In addition, results of a case-control study of *BRCA1* mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.[322] However, caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.[323,324]

Salpingectomy (surgical removal of the fallopian tube with retention of the ovaries) completion rates are increasing, especially in women younger than 50 years of age.[325] Despite some evidence regarding the safety and feasibility of this procedure,[325,326] more data are needed regarding its efficacy in reducing the risk for ovarian cancer.[292,327] Further, *BRCA1/2* carriers who undergo salpingectomy without oophorectomy may not get the 50% reduction in breast cancer risk that *BRCA1/2* carriers who undergo oophorectomy receive. Therefore, at this time, the panel does not recommend risk-reducing salpingectomy alone as the standard of care in *BRCA1/2* carriers. Clinical trials of interval salpingectomy with delayed oophorectomy are ongoing (eg, NCT02321228, NCT01907789).

Some studies suggest a link between *BRCA* 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.[245,246,248] 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 *BRCA* pathogenic/likely pathogenic 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 with 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.[307] RRSO should only be considered upon completion of childbearing. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian

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tubes.[213,214] The protocol published by CAP (2009) can be consulted for details on specimen evaluation.[328] See the NCCN Guidelines for Ovarian Cancer for treatment of findings (available at www.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.[329-334] 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 *BRCA1/2* mutation carriers evaluated, the mean cumulative lifetime risks for contralateral breast cancer were estimated to be 83% for *BRCA1* carriers and 62% for *BRCA2* carriers.[123] Patients with *BRCA1/2* mutations 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.[335] 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 *BRCA1* mutation carriers and 0.42 (95% CI, 0.17–1.02) to 0.63 (95% CI, 0.20–1.50) among *BRCA2* carriers.[336,337] This translates to an approximately 45% to 60% reduction in risk for contralateral tumors among *BRCA1/2* mutation carriers with breast cancer. The data were not consistent in regard to the protective effects of tamoxifen in the subset of *BRCA1/2* mutation carriers 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 individuals with a *BRCA1/2* mutation in the Breast Cancer Prevention Trial revealed that breast cancer risk was reduced by 62% in those with a *BRCA2* mutation receiving tamoxifen relative to placebo (risk ratio, 0.38; 95% CI, 0.06–1.56).[338] 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 those with a *BRCA1* mutation.[338] These findings may be related to the greater likelihood for development of estrogen receptor-negative tumors in *BRCA1* mutation carriers relative to *BRCA2* mutation carriers. However, this analysis was limited by the very small number of individuals with a *BRCA1/2* mutation (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.[339] 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.

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% to 50% in

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BRCA1 mutation carriers and by 60% in *BRCA2* mutation carriers.[340,341] Moreover, risks appeared to decrease with longer duration of oral contraceptive use.[341] In a meta-analysis conducted in a large number of *BRCA1/2* mutation carriers with (n = 1503) and without (n = 6315) ovarian cancer, use of oral contraceptives significantly reduced the risk for ovarian cancer by approximately 50% for both the *BRCA1* mutation carriers (summary relative risk [SRR], 0.51; 95% CI, 0.40–0.65) and *BRCA2* mutation carriers (SRR, 0.52; 95% CI, 0.31–0.87).[342] Another meta-analysis including one cohort study (N = 3,181) and three 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).[343]

Studies on the effect of oral contraceptive use on breast cancer risk among *BRCA1/2* mutation carriers 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 *BRCA1* mutation carriers (OR, 1.20; 95% CI, 1.02–1.40), but not among *BRCA2* mutation carriers.[344] Among *BRCA1* mutation carriers, breast cancer risks with oral contraceptives were significantly 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).[344] In another case-control study, oral contraceptive use for at least 1 year was not significantly associated with breast cancer risk in either *BRCA1/2* mutation carriers.[345] However, among *BRCA2* mutation carriers, use of oral contraceptives for at least 5 years was associated with a significantly increased risk for breast cancer (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.[345] Other case-control studies have reported no significant associations with oral contraceptive use (especially with the use of low-dose formulations after 1975) and risks for breast cancer in *BRCA1/2* mutation carriers.[346,347] In fact, in one study, the use of low-dose oral contraceptives for at least 1 year was associated with significantly decreased risks for breast cancer among *BRCA1* mutation carriers (OR, 0.22; 95% CI, 0.10–0.49; $P < .001$), though not for *BRCA2* mutation carriers.[347] 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 study design might have differed with regard to factors such as the criteria for defining the "control" population for the study (eg, non-*BRCA1/2* mutation carriers vs. mutation 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. Two meta-analyses showed that oral contraceptive use is not significantly associated with breast cancer risk in *BRCA1/2* mutation carriers.[342,343]

Discussion
Update in progress

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. Counseling for reproductive options such as prenatal diagnosis, preimplantation genetic diagnosis (PGD), and assisted reproduction 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.

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

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pregnancy.[348,349] During the past 2 decades, PGD has emerged as an alternative method of genetic testing in early embryos. PGD 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,[348,349] and may therefore offer the advantage of avoiding potential termination of pregnancy. The PGD 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. Lastly, 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 utilize prenatal diagnosis or PGD. 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.[348,349] For example, in cases where both partners carry a *BRCA2* mutation, there may be a high risk for the offspring to develop Fanconi anemia, a rare autosomal recessive condition.[61] A case has been found in which biallelic *BRCA1* mutations caused Fanconi anemia-like disorder.[350] Although the use of prenatal diagnosis or PGD 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 utilize prenatal diagnosis or PGD may include individual ethical beliefs, value systems, cultural and religious beliefs, and social and economic factors. Based on results from surveys administered to women at high risk for hereditary breast or ovarian cancer, 50% to 75% of respondents felt that PGD was an acceptable option for high-risk individuals,[351,352] yet only about 14% to 33% would consider undergoing PGD themselves.[351,353] A survey in high-risk men (N = 228; carriers of a *BRCA* mutation; or having a partner or first-degree relative with a *BRCA* mutation) showed that 80% of these men were unaware of PGD. After being informed of the definition of PGD, 34% indicated that they would consider the option of using PGD.[354] Importantly, these surveys suggested that the majority of high-risk women and men have little or no knowledge of PGD,[352,354,355] highlighting the need for better awareness and education regarding potential reproductive options.

Successful births have been reported with the use of PGD and IVF in *BRCA1/2* mutation carriers,[356,357] but data in the published literature are still very limited. In addition, data pertaining to long-term safety or outcomes of PDG and assisted reproduction in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant are not yet available.

Discussion update in progress

Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* pathogenic or likely pathogenic variants.[99] It has been estimated to be involved in only about 1% of hereditary breast cancer cases,[358] although results from other studies suggest that germline *TP53* gene mutations may be more common than previously believed, with estimates of 1 in 5000 to 1 in 20,000.[359,360] There are only about 300 families reported in an LFS registry maintained by an NCCN Member Institution and the NCI.[361] The tumor suppressor gene, *TP53*, is located on chromosome 17,[362,363] 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.[362-364] 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 *Li-Fraumeni Syndrome Testing Criteria* in the

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algorithm).[99,359,365] Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.[366]

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%.[367] 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.[99,359,361,364,368-373] 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.[359] Hypodiploid acute lymphoblastic leukemia is also associated with LFS,[374,375] and case reports have suggested an association between melanoma and LFS.[376,377]

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.[367] The cumulative incidence rates by age 70 years in men are 22%, 19%, and 11% for soft tissue sarcoma, brain cancer, and osteosarcoma, respectively. Interestingly, two retrospective studies have reported a very high frequency of HER2-positive breast tumors (67%–83% of evaluated breast tumors) among patients with germline *TP53* mutations, which suggests that amplification of HER2 may arise in conjunction with *TP53* mutations.[378,379] This association between HER2-positive breast cancer and germline *TP53* mutations 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,[370] and have an increased risk of developing multiple primary cancers during their lifetimes.[380] 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.[381] 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.[359] 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: 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 (see *Li-Fraumeni Syndrome Testing Criteria* in the algorithm). 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%).[359] Thus, it is

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not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.[373,382] 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 *Li-Fraumeni Syndrome Testing Criteria* in the algorithm).

Other groups have broadened the classic LFS criteria to facilitate identification of individuals with LFS.[368,383-385] One set of these less strict criteria proposed by Birch and colleagues shares many of the features of classic LFS criteria, although a larger range of cancers is included.[359,368] Individuals with de novo germline *TP53* mutations (no mutation in either biological parent) have also been identified.[359,360,369] These cases would not be identified as *TP53* testing candidates based on classic LFS criteria due to requirement of a family history. This issue is circumvented, in part, by the criteria for *TP53* testing proposed by Chompret and colleagues, which 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 (see *Li-Fraumeni Syndrome Testing Criteria* in the algorithm).[384] The Chompret criteria have an estimated positive predictive value of 20% to 35%,[359,384] 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).[359] 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.[359,369,386-388] 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.[386,388]

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.[387] Several studies have investigated the likelihood of a germline *TP53* mutation in this population.[359,386,389-392] In a study of *TP53* mutations evaluated at a single reference laboratory, Gonzalez et al found that 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.[359] In an analysis of patients with early-onset breast cancer (age of diagnosis <30 years) tested for *TP53* mutation at a single institution (N = 28), 6 patients (33%) were found to have *TP53* mutations.[393] Among the patients who were tested, a *TP53* mutation was found in approximately 8% who did not meet traditional LFS criteria for testing. In another study in patients with *BRCA1/2* mutation-negative early-onset breast cancer (age of diagnosis ≤35 years) tested for *TP53* mutation at a single institution (N = 83), approximately 5% were found to have *TP53* mutations.[391] 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.[391] Among women <30 years of age with breast cancer and without a family history, the incidence of *TP53* mutations has been reported at 3% to 8%.[359,390,392,393] Other studies have found an even lower incidence of germline *TP53* gene mutations in this population. For example, Bougeard et al reported that only 0.7% of unselected women with breast cancer before 33 years of age were carriers of a germline *TP53* mutation.[386] Furthermore, Ginsburg and colleagues found no germline *TP53* mutations

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in 95 unselected women with early-onset breast cancer who previously tested negative for *BRCA1/2* mutations.[389]

Finally, 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. *TP53* pathogenic/likely pathogenic variants are common in tumors.[394,395] 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 (see *Li-Fraumeni Syndrome Testing Criteria* in the algorithm). 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.[359,375,380,387] Verification of these sometimes very rare cancers is particularly important.

An individual with a known *TP53* pathogenic or likely pathogenic variant in a close family member who does not undergo testing should be followed according to the same recommendations as a carrier of a *TP53* pathogenic or likely pathogenic variant (see *Li-Fraumeni Syndrome Management in Adults* in the algorithm). In situations where an individual (or family member) from a family with no known familial *TP53* pathogenic or likely pathogenic variant undergoes genetic testing, and no variant is found, testing for other hereditary breast syndromes should be considered if testing criteria are met (see *BRCA1/2 Testing Criteria* and *Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS) Testing Criteria* in the algorithm). Alternatively, testing another family member with the next highest likelihood of having a pathogenic or likely pathogenic variant may be considered. As previously discussed in the *BRCA1/2* testing section above, testing of unaffected individuals should only be considered when an appropriate affected family member is not available for testing. Importantly, the significant limitations of interpreting testing results for an unaffected individual should be discussed prior to testing.

Employment of a screening protocol that includes MRI may improve early cancer detection in individuals with LFS.[396] 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.[397] 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.[397] 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

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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 the algorithm). 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. 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.[398] 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.[399] In a prospective observational study, a clinical surveillance protocol for *TP53* mutation carriers from families affected by LFS was incorporated.[400] The surveillance protocol included biochemical methods and imaging techniques, such as annual brain MRI, annual rapid whole-body MRI, ultrasound of the abdomen and pelvis, and colonoscopy.[401] For surveillance of breast cancers, the protocol was similar to the NCCN Guidelines for LFS Management.[400] Eleven-year follow-up of this study, which included 89 *TP53* mutation carriers, showed that this surveillance protocol may be beneficial, with 84% (16 out of 19) of patients who were diagnosed with cancer and had chosen to undergo surveillance being alive at final follow-up, compared to 49% (21 out of 43) of patients who were diagnosed with cancer and had chosen to not undergo surveillance (P = .012).[401] Five-year OS was greater for patients

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undergoing surveillance (88.8%) compared to patients not undergoing surveillance (59.6%), *P* = .013. The clinical surveillance protocol employed was shown to be feasible, though further evaluation is warranted.[400] 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.[397] 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.[399,402] 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.[403,404] Counseling for reproductive options such as prenatal diagnosis, PGD, 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 the section above on *Reproductive Options* under *Risk Assessment, Counseling, and Management* for *BRCA-Related Breast/Ovarian Cancer Syndrome*.

Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome

The spectrum of disorders resulting from germline pathogenic or likely pathogenic variants in *PTEN*[405] are referred to as the *PTEN* hamartoma tumor syndrome (PHTS). The spectrum of PHTS includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), adult Lhermitte-Duclos disease (LDD), Proteus-like syndrome,[98,406,407] and autism spectrum disorders with macrocephaly.[98,407,408]

The estimated penetrance of *PTEN* mutation is high, at approximately 80%.[409] The incidence of Cowden syndrome has been reported to be 1 in 200,000, although it is likely to be underestimated due to difficulties associated with making a clinical diagnosis of the disease.[410,411] Cowden syndrome is an autosomal dominant disorder, and most cases are associated with germline *PTEN* pathogenic or likely pathogenic variants, though one study found that germline *KILLIN* methylation may also be associated with this syndrome.[412]

Hamartomas (benign tumors resulting from an overgrowth of normal tissue) are a common manifestation of the PHTS syndromes. Cowden syndrome is associated with multiple hamartomatous and/or cancerous lesions in various organs and tissues, including the skin, mucous membranes, breast, thyroid, endometrium, and brain.[98,413] However, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* pathogenic or likely pathogenic variants should be assumed to have Cowden syndrome-associated cancer risks.

The lifetime risk for breast cancer for women diagnosed with Cowden syndrome has been estimated at 25% to 50%, with an average age of 38 to 50 years at diagnosis.[98,413-415] Some studies (as discussed above) have reported a higher cumulative lifetime risk for breast cancer (77%–85%) in individuals with Cowden syndrome or *PTEN* mutations.[416-418] There have been only 2 cases of breast cancer reported in men with Cowden syndrome.[415] Although many women with Cowden syndrome experience benign breast disease,[98] there is no evidence that the rate is higher than in the general population.[415]

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Thyroid disease, including benign multinodular goiter, adenomatous nodules, and follicular adenomas, has been reported to occur in approximately 30% to 68% of adults with *PTEN* mutations,[407,419] and the lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.[98,420] However, data tend to be aggregated, so it is difficult to calculate rates for multinodular goiter versus solitary nodules.[415] A retrospective chart review of 47 children with *PTEN* mutations showed that 26% had abnormal thyroid imaging.[421]

Macrocephaly (defined as head circumference greater than the 97th percentile)[422] is a common finding in patients with Cowden syndrome. It has been estimated that approximately 80% to 100% of individuals with this syndrome will exhibit this clinical finding.[415] Adult LDD and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome.[406,409,417,423] A rare, slow-growing, benign hamartomatous lesion of the brain, LDD, is a dysplastic gangliocytoma of the cerebellum.[98,417] In a multicenter prospective study examining 3042 probands who met clinical criteria for Cowden syndrome, 6% met criteria for LDD.[419] In a study of individuals meeting the diagnostic criteria for Cowden syndrome, the cumulative lifetime risk for LDD was reported to be 32%.[417] The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a *PTEN* gene mutation,[409,424] although exceptions have been reported.[425] In addition, there is a relatively large body of evidence to support that 10% to 20% of individuals with autism spectrum disorder and macrocephaly carry germline *PTEN* mutations.[408,426-429]

As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.[409] Although not well defined, women with Cowden syndrome may have a 5% to 10% risk for endometrial cancer.[98,430 415] While many women with Cowden syndrome may also have uterine fibroids, this risk is not likely to be much greater than in women without Cowden syndrome or *PTEN* mutation.[415]

In addition, brain tumors and vascular malformations affecting any organ are occasionally seen in individuals with Cowden syndrome, although the risks for developing these conditions are not well defined.[98,415] It is important to note, however, that most of the data on the frequencies of the clinical features of Cowden syndrome are from compilations of case reports of relatively young individuals who may have subsequently developed additional signs of the disease (ie, new cancerous lesions), and these data are also likely to be confounded by selection bias.[98] Furthermore, a considerable number of these studies were published prior to the establishment in 1996 of the International Cowden Consortium operational diagnostic criteria for the syndrome, which were based on published data and the expert opinion of individuals representing a group of centers mainly in North America and Europe.[98,431]

Benign skin lesions are experienced by most to all Cowden syndrome patients.[407,413,421] Skin lesions associated with Cowden syndrome include trichilemmomas (ie, benign tumors derived from the outer root sheath epithelium of a hair follicle), oral papillomas, mucocutaneous neuromas (hamartoma of the peripheral nerve sheath), palmoplantar keratoses, penile pigmentation in males, lipomas and vascular anomalies, and fibromas.[415,421,432] Trichilemmomas associated with Cowden syndrome tend to appear on the face, particularly the eyes, mouth, nose, and forehead.[415] Most individuals with Cowden syndrome exhibit characteristic mucocutaneous lesions by their twenties, and such lesions have been reported to occur in 99% of individuals with Cowden syndrome, showing nearly complete penetrance, although this may be a reflection of selection bias in the cases reported.[184,406] The presence of three or more mucocutaneous neuromas is considered a major diagnostic criterion of PHTS,[415] while the presence of 2 or more trichilemmomas has been

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reported to be pathognomonic for Cowden syndrome.[433,434] However, since most of the evidence regarding trichilemmomas is from the older literature, it is possible that the association with Cowden syndrome is somewhat overestimated.[98] There are reports of individuals with a solitary trichilemmoma who do not have Cowden syndrome.[433,434] Nevertheless, due to the strong association between these lesions and Cowden syndrome and the difficulty in clinically distinguishing between a trichilemmoma and another mucocutaneous lesion, it is important that a diagnosis of trichilemmoma is histologically confirmed.

It was previously estimated that about half of individuals with Cowden syndrome have gastrointestinal polyps.[435] However, this was almost certainly an underestimate.[435,436] In an analysis of 67 *PTEN* mutation carriers undergoing colonoscopy, colorectal polyps were found in 92.5% of patients.[435] About half of the patients undergoing colonoscopy had hyperplastic polyps, and about 25% had polyps that were hamartomatous, ganglioneuromatous, or adenomatous.[435] Adenomatous or hyperplastic polyps were associated with development of colorectal cancer in this sample. Out of 39 *PTEN* mutation carriers undergoing esophagogastroduodenoscopy (EGD), upper gastrointestinal polyps were found in 67% of patients.[435] A systematic review of published case series (N = 102) regarding gastrointestinal manifestations in PHTS and component syndromes showed that 92.5% of these patients had polyps, with 64% having 50 or more.[437] Histologies were described as: hyperplastic (44%), adenomatous (40%), hamartomatous (38%), ganglioneuroma (33%), and inflammatory (24.5%). Other studies have also reported ganglioneuromatous polyps (ie, rare, benign peripheral nervous system tumors) in this population.[415,438] A retrospective chart review of 47 children with *PTEN* mutations showed that only 13% had gastrointestinal polyps, but 34% had other gastrointestinal symptoms such as abdominal pain, rectal bleeding, and/or constipation.[421] Early-onset (<50 years of age) colorectal cancer has been reported in 13% of patients with *PTEN* mutation-associated Cowden syndrome, suggesting that routine colonoscopy may be warranted in this population.[435] The lifetime risk for colorectal cancer has been estimated as 9% to 16%.[417,418]

Several studies have projected lifetime estimates of cancer risk that are significantly higher than previously estimated. In a study of patients meeting diagnostic criteria for Cowden syndrome (N = 211; identified from published literature and records from a single institution), the cumulative lifetime risk for any cancer was 89%.[417] *PTEN* mutations had been identified in 97 of 105 patients (92%) who underwent testing. The cumulative lifetime cancer risks for all evaluable patients (n = 210) were 81% for female breast cancer, 21% for thyroid cancer, 19% for endometrial cancer, 15% for renal cancer, and 16% for colorectal cancer.[417] In a prospective study that evaluated genotype-phenotype associations between *PTEN* mutations and cancer risks,[418] deleterious germline mutations in *PTEN* were identified in 368 patients. Calculation of age-adjusted SIRs using cancer incidence data from the SEER database showed elevated SIRs among individuals with *PTEN* mutations for breast cancer (25), thyroid cancer (51), endometrial cancer (43), colorectal cancer (10), renal cancer (31), and melanoma (8.5). The estimated cumulative lifetime cancer risks were 85% for breast, 35% for thyroid, 28% for endometrial, 9% for colorectal, 34% for renal, and 6% for melanoma.[418] In another study in individuals with PHTS found to have deleterious germline *PTEN* mutations (N = 154; detailed information available in n = 146), age- and gender-adjusted SIRs were elevated for female breast cancer (39), endometrial cancer (49), female thyroid cancer (43), male thyroid cancer (199.5), female melanoma (28), and male melanoma (39).[416] The cumulative lifetime risks in these individuals were 77% for female breast cancer and 38% for thyroid cancer. The cumulative lifetime risk for any cancer was 85% overall, and women with PHTS were found to have a 2-fold greater cancer risk compared with men with PHTS.[416] It is important to note, however, that all three of these studies suffer from

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significant ascertainment biases, in that patients were usually selected for *PTEN* testing based on the presence of these malignancies, which would inflate the projected lifetime cancer estimates. An observational study of 180 patients with *PTEN* mutations used Kaplan-Meier methods to estimate that female carriers (n = 99) have an 87% cumulative risk of developing any cancer and/or LDD by 60 years of age, while male carriers have a cumulative risk of 56%.[439]

The BRRS variant of PHTS has been characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay, and, in males, pigmented macules on the glans penis,[440] although formal diagnostic criteria have not been established for this syndrome. *PTEN* gene mutations testing in individuals characterized with BRRS have been reported in approximately 60% of these patients.[441] Further, in another study, 10% of patients with BRRS for whom a *PTEN* gene mutation test was negative were shown to be carriers of large *PTEN* gene deletions.[423]

Risk Assessment, Counseling, and Management

The assessment of individuals suspected of having Cowden syndrome/PHTS incorporates both a history of the benign and malignant conditions associated with the syndrome and a targeted physical examination, including the skin and oral mucosa, breast, and thyroid gland and head circumference (see *Cowden Syndrome/PHTS Testing Criteria* in the algorithm). The NCCN Guidelines Panel has established a list of criteria to help indicate which individuals are candidates for testing for *PTEN* pathogenic or likely pathogenic variants (see *Cowden Syndrome/PHTS Testing Criteria* in the algorithm). These criteria are used to assess the need for further risk assessment and genetic testing, but are not intended to serve as clinical diagnostic criteria.

Testing Criteria

Testing criteria for Cowden syndrome/PHTS are grouped into 3 general categories. A patient is considered for testing for *PTEN* pathogenic or likely pathogenic variants based on whether he/she meets certain criteria or combinations of criteria from these 3 categories. The first criteria category includes individuals meeting diagnostic criteria for Cowden syndrome[442]: a personal history of BRRS, adult LDD, autism spectrum disorder with macrocephaly, or 2 or more biopsy-proven trichilemmomas. Any individual presenting with one or more of these diagnoses warrants *PTEN* testing. Previously, some of the criteria from this group have sometimes been referred to as “pathognomonic,” although it is unlikely that any of these conditions can stand alone as a definitive diagnostic criterion for Cowden syndrome/PHTS. Another criterion that can be considered to be sufficient to warrant testing for *PTEN* pathogenic or likely pathogenic variants is a family history that includes the presence of a known *PTEN* pathogenic or likely pathogenic variant.

The next category of criteria represents “major” features associated with Cowden syndrome/PHTS.[407,411,419,442] The major criteria include the presence of breast cancer, macrocephaly (ie, megalocephaly),[422] endometrial cancer, follicular thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, macular pigmentation of the glans penis, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (ie, one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multiple or extensive oral mucosal papillomatosis, multiple cutaneous facial papules). With respect to decisions related to the presence of mucocutaneous lesions, the panel did not consider the available literature to be adequate to accurately specify the number or extent of these lesions required for the condition to be defined as a major criterion for Cowden syndrome/PHTS, and clinical judgment is needed when evaluating such lesions. An individual exhibiting 2 or more major criteria where one criterion is macrocephaly meets the

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testing threshold. An individual with 3 or more major criteria (without macrocephaly) is also considered to meet the threshold for testing. In addition, individuals exhibiting 1 major criterion with 3 or more minor criteria (discussed below) also meet the testing threshold; if an individual exhibits 2 or more major criteria (eg, breast cancer, follicular thyroid cancer) but does not have macrocephaly, then one of the major criteria may be included as one of the 3 minor criteria to meet the testing threshold.

The final category of criteria represents features with a "minor" association with Cowden syndrome/PHTS.[407,411,419,442] These include autism spectrum disorder (without macrocephaly), colon cancer, esophageal glycogenic acanthosis (3 or more), lipomas, intellectual disability, papillary or follicular variant of papillary thyroid cancer, thyroid structural lesions other than follicular thyroid cancer (eg, adenoma, nodules, goiter), renal cell carcinoma, a single gastrointestinal hamartoma or ganglioneuroma, testicular lipomatosis, or vascular anomalies (including multiple intracranial developmental venous anomalies). The panel felt that evidence from the literature was insufficient to include fibrocystic breast disease, fibromas, or uterine fibroids as part of the testing criteria. An individual would need to exhibit 4 or more minor criteria or, as discussed above, 3 or more minor criteria and one major criterion to meet testing.

Lastly, an at-risk individual (first-degree relative of an affected individual) with one or more major criterion or 2 or more minor criteria, along with a relative diagnosed with Cowden syndrome/PHTS or BRRS (for whom testing has not been performed), would also meet the threshold for *PTEN* testing. Individuals not meeting testing criteria should be followed according to recommendations tailored to his/her personal cancer history and family history. Testing for other hereditary syndromes may also be considered, if appropriate.

Genetic Testing

Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met. The NCCN Guidelines Panel recommends comprehensive testing, which should include full sequencing, gene deletion/duplication analysis, and promoter analysis. A comprehensive clinical test should not include testing for succinate dehydrogenase (*SDH*), as there is no conclusive evidence that this gene is associated with PHTS.[443]

Clinical Diagnostic Criteria

The *PTEN* mutation frequency in individuals meeting International Cowden Consortium diagnostic criteria for Cowden syndrome has previously been estimated at about 80%.[415,441] However, evaluation of data based on samples analyzed at a single academic pathology laboratory (N = 802 evaluable) reported a much lower frequency (34%) of *PTEN* mutations among individuals meeting diagnostic criteria[411] for Cowden syndrome.[407] The authors concluded that the current Consortium diagnostic criteria are not as sensitive in identifying individuals with *PTEN* pathogenic or likely pathogenic variants as previously estimated. Since *PTEN* pathogenic or likely pathogenic variants are relatively rare, recommendations regarding Cowden syndrome diagnostic criteria may be based on studies with a small number of patients. Studies with larger samples have their flaws as well, as patients are selected for testing based on the number and magnitude of clinical features, which may lead to overestimation of the features of Cowden syndrome.[415] A review was conducted examining each consortium diagnostic criterion, and revised criteria were proposed that are more stringent and take into account clinical features that are often seen in PHTS.[415] The criteria were designed by focusing on clinical features associated with *PTEN* pathogenic or likely pathogenic variants. The panel recommends using these criteria for clinical diagnosis of PHTS.

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Like the testing criteria, diagnostic criteria are categorized as major and minor. Major criteria are as follows: breast cancer, epithelial endometrial cancer, follicular thyroid cancer, 3 or more gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplastic polyps), LDD, macroencephaly (regardless of stature, 58 cm for females, 60 cm for males), and macular pigmentation of the glans penis. A final major criterion is multiple mucocutaneous lesions (3 or more multiple trichilemmomas, 3 or more palmoplantar keratotic pits and/or acral hyperkeratotic papules, 3 or more mucocutaneous neuromas, or oral papillomas). Oral papillomas may be included if there are 3 or more, or if there is evidence from a biopsy or from a dermatologist diagnosis.

Minor criteria include the following: autism spectrum disorder, colon cancer, 3 or more esophageal glycogenic acanthosis, 3 or more lipomas, mental retardation (IQ ≤75), renal cell carcinoma, testicular lipomatosis, thyroid cancer (papillary or follicular variant of papillary), thyroid structural lesions, and vascular anomalies (eg, multiple intracranial developmental venous anomalies).

A clinical diagnosis in an individual would include the following: exhibiting 3 or more major criteria where one is macrocephaly, LDD, or gastrointestinal hamartomas; or 2 major and 3 minor criteria. A clinical diagnosis in a family in which one individual meets these PHTS clinical diagnosis criteria or has a *PTEN* pathogenic or likely pathogenic variant would include the following: any 2 major criteria with or without any minor criteria; 1 major and 2 minor criteria; or 3 minor criteria.

An individual with a known *PTEN* pathogenic or likely pathogenic variant in a close family member who does not undergo gene testing should be followed according to the same guideline as a carrier of a *PTEN* variant (see *Cowden Syndrome/PHTS Management* in the algorithm). In situations where an individual (or family member) from a family with no known familial *PTEN* pathogenic or likely pathogenic variant undergoes genetic testing and no variant is found, testing for other hereditary breast syndromes should be considered if testing criteria are met (see *BRCA1/2 Testing Criteria* and *Li-Fraumeni Syndrome Testing Criteria* in the algorithm). Alternatively, testing another family member with the next highest likelihood of having a pathogenic or likely pathogenic variant may be considered. Multi-gene testing may also be considered.

If a *PTEN* pathogenic or likely pathogenic variant is not found, or a VUS was found and Cowden syndrome/PHTS diagnostic criteria are met, then individual management should proceed based on the recommended guidelines (see *Cowden Syndrome/PHTS Management* in the algorithm). If diagnostic criteria are not met, then research and individualized recommendations based on personal and family history should be offered, and testing for other hereditary syndromes may be considered.

Screening Recommendations

Cancer is the major health risk associated with Cowden syndrome/PHTS. Therefore, the NCCN Panel had outlined guidelines for prevention and early detection screening of commonly associated cancers with Cowden syndrome/PHTS. Current medical management recommendations for individuals with Cowden syndrome/PHTS include annual physical examinations, starting at 18 years of age (or 5 years before the youngest age of diagnosis of a component cancer in the family).

The recommendations for *women* with Cowden syndrome/PHTS focus on primary and secondary prevention options for breast cancer since this is the most commonly associated cancer in individuals with Cowden syndrome/PHTS based on the available literature. Women should begin regular monthly breast self-examinations at 18 years of age and have a semiannual clinical breast examination beginning at 25 years of age or 5 to 10 years earlier than the earliest known breast cancer in the family (whichever comes first). Women should also have an annual mammogram and breast MRI screening with contrast starting at 30 to 35 years of age,

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or 5 to 10 years earlier than the earliest known breast cancer in the family (whichever comes first). 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. When mammography is performed, the panel recommends that tomosynthesis be considered.

Although there are no data regarding risk reduction surgery in women with Cowden syndrome, the option of RRM and hysterectomy should be discussed on a case-by-case basis. Oophorectomy is not indicated for Cowden syndrome alone, but may be indicated for other reasons. Counseling for risk-reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, reconstructive options, and reproductive desires. It is also important to address the psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures.

Given that Cowden syndrome is rare, there are no data on screening for endometrial cancer in these patients. The panel recommends patient education regarding the symptoms of endometrial cancer including the necessity of a prompt response to symptoms such as abnormal bleeding. Prompt reporting promotes early detection of endometrial cancer. The evaluation of these symptoms should include an endometrial biopsy. Endometrial cancer screening does not have proven benefit in women with Cowden syndrome. However, endometrial biopsy is highly sensitive and specific as a diagnostic procedure. Therefore, screening through endometrial biopsy every 1 to 2 years may be considered.

Routine transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific to warrant a positive recommendation but may be considered at the clinician's discretion. However, transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial strip thickness throughout the normal menstrual cycle.

Both men and women with Cowden syndrome/PHTS have approximately at least a 3% to 10% lifetime risk of developing thyroid cancer,[98] compared to about 1% in the general population.[444] An annual thyroid ultrasound should be performed, beginning at the time of PHTS diagnosis (including in childhood). In addition, colonoscopy is recommended starting at 35 years of age, or earlier if symptomatic. If a close relative was diagnosed with colon cancer before 40 years of age, then colonoscopy screening should begin 5 to 10 years before the age of the earliest known diagnosis. Colonoscopy should be performed every 5 years or more frequently in cases where the patient is symptomatic or polyps are found. To screen for renal cell carcinoma, renal ultrasound should be considered every 1 to 2 years beginning at 40 years of age. Dermatologic management may be considered for some patients. If there are symptoms in children, then assessment of psychomotor abilities should be considered, as well as a brain MRI. Education regarding the signs and symptoms of cancer is important; patients should also be advised about the risk to relatives, and genetic counseling is recommended for at-risk relatives.

No published data exist on the use of prenatal diagnostics/genetic testing for *PTEN* pathogenic or likely pathogenic variants in families with Cowden syndrome. However, for couples expressing the desire that their offspring not carry a familial *PTEN* pathogenic or likely pathogenic variant, options for prenatal diagnosis, PGD, and assisted reproduction can be discussed. 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 the Discussion section above on *Reproductive*

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Options under *Risk Assessment, Counseling, and Management* for *BRCA-Related Breast/Ovarian Cancer Syndrome*.

Other Pathogenic/Likely Pathogenic Variants Associated with Breast/Ovarian Cancer

In the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the panel primarily focuses on assessment of known high-penetrance pathogenic or likely pathogenic variants (ie, *BRCA1/2, TP53, PTEN*) and recommendations for genetic testing, counseling, and management strategies in individuals with these variants. A retrospective analysis of 337 patients who met NCCN criteria for *BRCA1/2* mutation testing and underwent multigene testing showed that 25 patients (7.4%) had non-*BRCA* mutations.[91] The most common of these mutations were *PALB2* (23%), *CHEK2* (15%), and *ATM* (15%). Below is a description of additional pathogenic or likely pathogenic variants that the panel argues warrants additional screening beyond what is recommended in the general population (ie, those without the specific variant). These include pathogenic or likely pathogenic variants for *ATM, BRIP1, CDH1, CHEK2, NBN, PALB2, RAD51C, RAD51D,* and *STK11.* Risk management for pathogenic or likely pathogenic variants associated with Lynch syndrome and neurofibromatosis type 1 (NF1) are also described.

The investigators of an analysis of breast cancer risk in carriers of moderately penetrant genetic mutations posited that, based on an absolute risk approach, screening with mammography in these carriers should begin when the estimated 5-year risk of developing breast cancer exceeds 1%, consistent with recommendations for the average-risk population.[81] Likewise, breast MRI screening in these carriers should begin when the estimated 5-year risk of developing breast cancer exceeds 2.2%. However, for practical reasons, beginning MRI and mammographic screening at the same time is a reasonable approach. The age at which breast screening is recommended may be impacted by the presence of risk factors such as family history of breast cancer, especially early-onset breast cancer.[81] In those with a family history of early-onset breast cancer, breast screening may begin 5 to 10 years earlier than the youngest breast cancer diagnosis in the family. In women treated for breast cancer who have not had bilateral mastectomy, breast screening should continue as recommended based on age. When mammography is performed, the panel recommends that tomosynthesis be considered. Currently there is insufficient evidence to recommend risk-reducing mastectomy in carriers of moderately penetrant genetic mutations,[81] though this option may be considered and discussed in the presence of a family history of breast cancer.

There is insufficient evidence to recommend a specific age at which RRSO should be considered in carriers of moderately penetrant pathogenic or likely pathogenic variants (ie, *BRIP1, RAD51C, RAD51D*). The decision to carry out RRSO should not be made lightly, given the impact of premature menopause. Therefore, Tung and colleagues,[81] who carried out an analysis of ovarian cancer risk in carriers of moderately penetrant genetic mutations, argued that RRSO should not be considered until a woman's expected lifetime risk of developing ovarian cancer exceeds 2.6%, which is the expected lifetime risk of a woman with a *BRCA*-negative family history of ovarian cancer. See the discussion below in the sections for *BRIP1* and *RAD51C/RAD51D* for more information on the specific age at which RRSO may be discussed.

The pathogenic or likely pathogenic variants described below may be included concurrently in panel testing (see *Multi-Gene Testing* above). Lower penetrance genes that may be included as part of multi-gene testing but for which there is currently insufficient evidence of an association with breast and/or ovarian cancer include: *BARD1*, *FANCC*, *MRE11A*, *MUTYH* heterozygotes, *RECQL4*, *RAD50*, *RINT1, SLX4, SMARCA4*, and *XRCC2*. Risk management recommendations for these

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genes should take into account family history and other clinical factors. A more comprehensive review of these lower-penetrance genes is described in another publication.[445]

ATM

Pathogenic or likely pathogenic variants in the *ATM* (ataxia-telangiectasia mutated) gene may increase risk for breast cancer. A meta-analysis including 19 studies showed that the cumulative lifetime risk for breast cancer in individuals with an *ATM* pathogenic or likely pathogenic variant is 6% by age 50 years and 33% by age 80 years.[446] A meta-analysis of three cohort studies of relatives with ataxia-telangiectasia showed an estimated RR of 2.8 (90% CI, 2.2–3.7; $P < .001$).[447] Other analyses of patients with breast cancer showed that about 1% had an *ATM* mutation.[69,70,113,448] An analysis of 82 Dutch patients with early-onset breast cancer showed that 8.5% (n = 7) of the patients had a detected *ATM* mutation.[449]

The association between specific types of *ATM* genetic variants and breast cancer susceptibility is less clear,[86-89] with some evidence showing that certain missense mutations may act in a dominant-negative fashion to increase cancer risk, relative to truncating mutations.[86,87] A meta-analysis including five studies showed that *ATM* mutation carriers have a 38% lifetime risk of developing breast cancer, with carriers of the c.7271T>G missense mutation having a 69% risk of developing breast cancer by 70 years of age.[450] An analysis from a case-control study (42,671 breast cancer cases and 42,164 controls) showed a significant association between the c.7271T>G variant and breast cancer risk (OR, 11.60; 95% CI, 1.50–89.90; $P = .001$).[451] An analysis of 27 families in which pathogenic *ATM* variants were identified showed an association between the c.7271T>G variant and increased risk for breast cancer (HR, 8.0; 95% CI, 2.3–27.4; $P < .001$).[452]

Results of the case-control WECARE study suggested that radiation exposure may be associated with increased risk for contralateral breast cancer in women who are carriers of very rare *ATM* missense variants predicted to be deleterious.[453] However, a meta-analysis including five studies showed that radiation therapy (with conventional dosing) is not contraindicated in patients with a heterozygous *ATM* mutation.[450] Therefore, there is currently insufficient evidence to recommend against radiation therapy in women who are carriers diagnosed with cancer.

The panel recommends annual mammogram for women with a mutated *ATM* gene beginning at 40 years of age, with consideration of annual breast MRI. There are no data on the benefit of risk-reducing mastectomy for women with *ATM* mutations,[81] but this procedure may be considered based on family history. Large studies of patients with ovarian cancer have shown that there may be a moderately increased risk for ovarian cancer in carriers of an *ATM* mutation,[68,70] but there is currently insufficient evidence to recommend RRSO in these carriers. Given the association between *ATM* and development of the autosomal recessive condition ataxia telangiectasia, counseling for carriers of *ATM* pathogenic or likely pathogenic variants should include a discussion of reproductive options. *ATM* mutations have been found in patients with pancreatic[239,454] and prostate cancers,[222,455] but there is currently insufficient evidence to recommend screening for these cancers in carriers of an *ATM* pathogenic or likely pathogenic variant.

BARD1

An association between breast cancer and mutations in the *BRCA1*-associated RING domain 1 (*BARD1*) gene has been found in two large case-control studies. The first study included 65,057 women with breast cancer who were referred for genetic testing.[69] The prevalence rate for *BARD1* mutations in this sample was 0.18%, which was significantly greater than the prevalence rate for the controls (OR, 2.16; 95% CI, 1.31–

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3.63; *P* < .05). The second case-control analysis (planned as part of a larger study), which included 15,826 patients with breast cancer, showed a prevalence rate of 0.25% (OR, 1.92; 95% CI, 1.36–2.72; *P* < .001).[70] Despite this suggestion of an increased risk for breast cancer in individuals with a *BARD1* mutation, the panel has determined that more evidence is needed to provide recommendations for breast screening for these individuals.

BRIP1

Panel testing of germline DNA in women with ovarian cancer has shown that the prevalence rate of the *BRCA1* interaction protein C-terminal helicase 1 gene (*BRIP1*), a Fanconi anemia gene, is about 1%.[68,70,185] An analysis of 3236 women with epithelial ovarian cancer, 3431 controls, and 2000 unaffected high-risk women from an ovarian cancer screening trial (UKFOCSS) showed that *BRIP1* is associated with an increased risk for ovarian cancer (*P* < .001), with the RR for invasive epithelial ovarian cancer being 11.22 (95% CI, 3.22–34.10; *P* < .001) and 14.09 for high-grade serous disease (95% CI, 4.04–45.02; *P* < .001).[456] An analysis of an Icelandic population (656 ovarian cancer cases, 3913 controls) also showed an association between *BRIP1* and increased risk for ovarian cancer (OR, 8.13; 95% CI, 4.74–13.95; *P* < .001).[457] The cumulative lifetime risk of developing ovarian cancer by 80 years of age in *BRIP1* mutation carriers is estimated to be 5.8% (95% CI, 3.6–9.1).[456]

Tung and colleagues[81] argued that RRSO should not be considered in these mutation carriers until their cumulative risk exceeds that of a woman with a first-degree relative with a non-*BRCA*–related ovarian cancer (approximately 2.64). For carriers of a *BRIP1* pathogenic or likely pathogenic variant, this would be around 50 to 55 years of age. However, some women may have additive risk factors (eg, multiple family members with ovarian cancer, lack of parity),[458] and delaying the discussion of RRSO until 50 years of age may miss some cases of early-onset ovarian cancer. Therefore, the panel recommends that RRSO in carriers of a *BRIP1* pathogenic or likely pathogenic variant be considered beginning at 45 to 50 years of age. A discussion about risk-reducing surgery may be initiated earlier if there is a family history of early-onset ovarian cancer. Ultimately, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in these variant carriers.

There is currently insufficient evidence of an association between increased breast cancer risk and *BRIP1*, and no single truncating variant has been found to be associated with increased risk for breast cancer.[459] *BRIP1* is associated with Fanconi anemia, inherited in an autosomal recessive manner. Therefore, counseling for carriers of *BRIP1* pathogenic or likely pathogenic variants should include a discussion of reproductive options.

CDH1

Germline mutations in *CDH1* are associated with hereditary diffuse gastric cancer and lobular breast cancer, and studies have reported a cumulative lifetime risk for breast cancer of 39% to 52%.[460,461] Given the considerable risk for lobular breast cancer in women with a *CDH1* pathogenic or likely pathogenic variant, the panel recommends screening with annual mammogram (or consideration of breast MRI), beginning at 30 years of age. Screening may be considered earlier in patients with a family history of early-onset breast cancer. Risk-reducing mastectomy may be discussed with these carriers, depending on family history. See the NCCN Guidelines for Gastric Cancer (available at www.NCCN.org) for screening recommendations for gastric cancer for individuals with a *CDH1* pathogenic or likely pathogenic variant.

CHEK2

Another breast cancer susceptibility gene that has been identified is *CHEK2* (cell cycle checkpoint kinase 2). Panel testing of germline DNA in

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large samples of patients with breast cancer has shown that the prevalence rate of a *CHEK2* pathogenic or likely pathogenic variant is about 1%.[69,70,448] Deleterious *CHEK2* mutations have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America.[445,462-464] The cumulative lifetime risk for breast cancer in women with *CHEK2* mutations and familial breast cancer has been estimated to range from approximately 28% to 37%, and is higher in women with stronger family histories of breast cancer than those without.[465,466] The estimated RR for breast cancer, based on data from two large case-control studies, was 3.0 (90% CI, 2.6–3.5).[447]

Studies investigating the association between breast cancer risk and specific *CHEK2* variants have primarily been based on the truncating variant 1100delC. An analysis from the Copenhagen General Population Study (N = 86,975) showed that *CHEK2* 1100delC heterozygotes had an increased risk for breast cancer when analyses were stratified by age and sex (HR, 2.08; 95% CI, 1.51–2.85).[467] A case-control study (10,860 cases and 9,065 controls) carried out by the CHEK2 Breast Cancer Case-Control Consortium of Europe and Australia showed that the 1100delC variant is associated with increased risk for breast cancer, even in women unselected for family history (OR, 2.34; 95% CI, 1.72–3.20; $P < .001$).[468] Another case-control study (44,777 cases and 42,997 controls) showed that heterozygous 1100delC carriers have a significantly increased risk of developing ER-positive breast cancer (OR, 2.55; 95% CI, 2.10–3.10; $P < .001$), but not ER-negative breast cancer (OR, 1.32; 95% CI, 0.93–1.88; $P = 0.12$).[469] Results from a meta-analysis including 18 case-control studies (26,336 cases and 44,219 controls) showed that the missense variant I157T is associated with a modestly increased risk for breast cancer (OR, 1.58; 95% CI, 1.42–1.75; $P < .001$).[470]

The panel recommends annual mammogram for women with a mutated *CHEK2* gene beginning at 40 years of age, with consideration of annual breast MRI. Forty years was chosen by the panel as the age at which to begin breast screening, taking into account the average 5-year risk for breast cancer in carriers of *CHEK2* pathogenic or likely pathogenic variants (see section above on carriers of *ATM* pathogenic or likely pathogenic variants), based on risk data that only take into account frameshift mutations such as 1100delC.[81] There are no data on the benefit of risk-reducing mastectomy for women with *CHEK2* mutations,[81] but this procedure may be considered based on family history.

MLH1, MSH2, MSH6, PMS2, EPCAM

Women with Lynch syndrome are at increased risk for endometrial and ovarian cancers (up to 60% and 24%, respectively).[471-474] Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women who have completed child-bearing and carry an *MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6* mutation.[475-479] There is no clear evidence to support routine screening for gynecologic cancers in these carriers of these pathogenic or likely pathogenic variants. Annual endometrial sampling may be considered, but the benefit is uncertain.[475,480-483] Routine TVUS and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific[475,480-484]; however, there may be circumstances where these tests may be helpful.

Some studies have suggested that some of the mismatch repair genes linked to Lynch syndrome (*MLH1* and *MSH2*) may be associated with increased risk for breast cancer.[485,486] However, there is currently not enough evidence for the panel to recommend breast screening for women with Lynch syndrome beyond that which is recommended for the average-risk population.

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

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NBN

The *NBN* gene is responsible for producing the protein nibrin. Women with heterozygous *NBN* mutations are at increased risk of developing breast cancer (OR, 3.1; 95% CI, 1.4–6.6; *P* = .004).[487] A meta-analysis including 7 studies showed a significant association between the variant 657del5 and breast cancer risk (OR, 2.42; 95% CI, 1.54–3.80).[488] An analysis of women with breast cancer in Poland (N = 562) showed that this founder mutation is associated with early-onset breast cancer (OR, 8.36; 95% CI, 2.57–27.27; *P* < .001).[489] The panel recommends annual mammogram for women with a mutated *NBN* gene beginning at 40 years of age, with consideration of annual breast MRI. Forty years was chosen by the panel as the age at which to begin breast screening, taking into account the average 5-year risk for breast cancer in carriers of these pathogenic or likely pathogenic variants (see above).[81] This recommendation is based primarily on data derived from the Slavic truncating mutation 657del5.[487-490] There are no data on the benefit of risk-reducing mastectomy for women with *NBN* pathogenic or likely pathogenic variants. Therefore, risk-reducing mastectomy is not recommended in carriers of these pathogenic or likely pathogenic variants, but this procedure may be considered based on family history. The *NBN* gene is associated with development of the autosomal recessive condition Nijmegen breakage syndrome. Therefore, counseling for carriers of *NBN* pathogenic or likely pathogenic variants should include a discussion of reproductive options.

NF1

NF1 is an autosomal dominant hereditary cancer syndrome that is caused by an *NF1* pathogenic or likely pathogenic variant. NF1 is associated with increased risk for malignant peripheral nerve sheath tumors, other CNS tumors, and gastrointestinal stromal tumors.[491-494] A population-based study in Finland of 1404 patients with NF1 showed an estimated lifetime cancer risk of 59.6%.[491] This study showed a significant association between NF1 and increased risk for breast cancer (SIR, 3.04; 95% CI, 2.06–4.31; *P* < .001). Among patients with breast cancer, NF1 was associated with poorer survival, with 5-year survival rates for patients with NF1 being 67.9%, compared to 87.8% in patients without NF1. Excess incidence was highest in women younger than 40 years of age (SIR, 11.10; 95% CI, 5.56–19.50; *P* < .001). A population-based study in England of 848 patients with NF1 also showed an increased risk for breast cancer (SIR, 3.5; 95% CI, 1.9–5.9), especially among women younger than 50 years (SIR, 4.9; 95% CI, 2.4–8.8).[495] Cumulative lifetime risk of developing breast cancer by 50 years of age was 8.4% in this sample.

Given the increased risk for early-onset breast cancer in carriers of these pathogenic or likely pathogenic variants, annual breast screening with mammography should begin at 30 years of age.[496] Screening with breast MRI could also be considered. These screening recommendations apply only to individuals with a clinical diagnosis of NF1. The presence of neurofibromas in the breast may lead to false-positive MRI results, but more data are needed to determine the sensitivity and specificity of breast MRI in individuals with NF1. A prospective study of patients with NF1 from the United Kingdom (N = 448) showed that breast cancer risk in these mutation carriers is not significantly increased at 50 years of age and beyond.[494] Case-control analyses of women with NF1 from England showed that RR estimates for women aged 30 to 39 years was 6.5 (95% CI, 2.6–13.5) and 4.4 for women aged 40 to 49 years (95% CI, 2.5–7.0).[497] RR estimates then drop for women aged 50 to 59 years (RR, 2.6; 95% CI, 1.5–4.2) and continue to drop as age increases (RR, 1.9; 95% CI, 1.0–3.3 for women aged 60–69 years and RR, 0.8; 95% CI, 0.2–2.2 for women aged 70–79 years). These studies show that, beginning at age 50, breast cancer risk in women with NF1 may not significantly differ from that of women in the general population. Therefore, breast MRI screening in patients with NF1 may be discontinued at 50 years of age. There are no data regarding the benefit of risk-reducing mastectomy for women with *NF1* pathogenic or likely pathogenic variants. Therefore, risk-reducing

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mastectomy is not recommended in these patients, but this procedure may be considered based on family history. Complications related to NF1 (eg, neurologic complications) may appear early in life, and these have the potential to be severe.[498] Therefore, referral to a neurofibromatosis specialist for management is recommended.

PALB2

PALB2 (partner and localizer of *BRCA2*) is a Fanconi anemia gene. *PALB2* pathogenic or likely pathogenic variants are associated with increased risk for breast cancer, with studies of patients with breast cancer showing that 0.6% to 3% harbor a pathogenic *PALB2* mutation.[69,70,152,448,499-501] A meta-analysis of three studies estimated an RR of 5.3 (90% CI, 3.0–9.4).[447] Breast cancer risk increases with age in women with a *PALB2* mutation, with a 14% lifetime risk by 50 years of age, and a 35% lifetime risk by 70 years of age.[502] The risk also increases with increasing number of relatives affected with breast cancer. Breast cancer risk by 70 years of age for those with no first-degree relatives with breast cancer was 33%, compared to 58% in those with two first-degree relatives.[502] In a study of patients with breast cancer from Poland who underwent genetic testing, contralateral breast cancer was reported in 10% of *PALB2* carriers.[501] This study also showed that 10-year survival among *PALB2* carriers with breast cancer was 48%, compared to 72% in *BRCA1* mutation carriers and 75% in non-carriers ($P < .001$). Further, 10-year survival among those with tumors ≥2 cm was substantially worse (32.4%) than those with tumors <2 cm (82.4%) (HR, 7.04; 95% CI, 2.47–20.07; $P < .001$).

The panel recommends annual mammogram for carriers of a *PALB2* pathogenic or likely pathogenic variant beginning at 30 years of age, as this is the age when the average 5-year risk for breast cancer in these mutation carriers exceeds 1%.[81,502] Breast MRI screening may also be considered. There are no data on the benefit of risk-reducing mastectomy for women with *PALB2* pathogenic or likely pathogenic variants,[81] but this procedure may be considered based on family history. Though some studies suggest that there may be an association between *PALB2* and increased ovarian cancer risk,[185,503] there is currently insufficient evidence to consider RRSO in carriers of these pathogenic or likely pathogenic variants. *PALB2* is associated with Fanconi anemia, inherited in an autosomal recessive manner.[504] Therefore, counseling for carriers of *PALB2* pathogenic or likely pathogenic variants should include a discussion of reproductive options.

RAD51C and RAD51D

Genes in the *RAD51* protein family are involved in homologous recombination and DNA repair. *RAD51C* and *RAD51D* have been shown to be associated with increased risk for ovarian cancer. Panel testing of germline DNA in women with ovarian cancer have shown that the prevalence rate of the *RAD51C* or *RAD51D* pathogenic or likely pathogenic variant is about 1%.[68,70,185] In a comparison of 1132 probands with a family history of ovarian cancer and 1156 controls, *RAD51C* was associated with an increased risk for ovarian cancer (RR, 5.88; 95% CI, 2.91–11.88; $P < .001$).[505] Analyses from the same trial (911 probands and 1060 controls) also showed an association between *RAD51D* and increased risk for ovarian cancer (RR, 6.30; 95% CI, 2.86–13.85; $P < .011$).[506] In a case-control analysis of 3429 women with epithelial ovarian cancer and 2772 controls, both *RAD51C* (OR, 5.2; 95% CI, 1.1–24; $P = .035$) and *RAD51D* (OR, 12.0; 95% CI, 1.5–90; $P = .019$) were associated with an increased risk for ovarian cancer.[507]

The cumulative risk of developing ovarian cancer in carriers of a *RAD51C* mutation does not approach 2.6% (ie, the expected lifetime risk for a woman with a *BRCA*-negative family history of ovarian cancer) until 60 to 64 years of age, with the cumulative risk between the ages of 55 to 59 years being 1.5%.[81,507] In carriers of a *RAD51D* mutation, the cumulative

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risk approaches 2.6% around 50 to 54 years of age. As with carriers of a *BRIP1* pathogenic or likely pathogenic variant, there may be the presence of additive risk factors that may increase the risk for early-onset ovarian cancer. Therefore, the panel recommends that RRSO in carriers of *RAD51C* and *RAD51D* pathogenic or likely pathogenic variants be considered beginning at 45 to 50 years of age. A discussion about risk-reducing surgery may be initiated earlier if there is a family history of early-onset ovarian cancer. As with *BRIP1* pathogenic or likely pathogenic variants, large prospective trials are needed to make a firm age recommendation regarding when a discussion about RRSO should begin in carriers of *RAD51C* and *RAD51D* pathogenic or likely pathogenic variants.

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

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STK11

Germline *STK11* pathogenic or likely pathogenic variants are associated with Peutz-Jeghers syndrome (PJS), an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers as well as breast or non-epithelial ovarian cancers. Breast cancer risk in women with PJS is 8% at 40 years of age, 13% at 50 years of age, 31% at 60 years of age, and 45% at 70 years of age.[508] There are no data on the benefit of risk-reducing mastectomy for women with *STK11* pathogenic or likely pathogenic variants. Therefore, risk-reducing mastectomy is not recommended in these patients, but this procedure may be considered based on family history. Information regarding screening for patients with PJS can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

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Table 1. Glossary of Relevant Genetic Terms (from the National Cancer Institute [NCI])

Autosomal dominant
Autosomal dominant inheritance refers to genetic conditions that occur when a pathogenic or likely pathogenic variant is present in one copy of a given gene (ie, the person is heterozygous).

Autosomal recessive
Autosomal recessive inheritance refers to genetic conditions that occur only when pathogenic or likely pathogenic variants are present in both copies of a given gene (ie, the person is homozygous for a pathogenic or likely pathogenic variant, or carries two different variants of the same gene, a state referred to as compound heterozygosity).

de novo mutation
An alteration in a gene that is present for the first time in one family member as a result of a pathogenic or likely pathogenic variant in a germ cell (egg or sperm) of one of the parents, or a pathogenic or likely pathogenic variant that arises in the fertilized egg itself during early embryogenesis. Also called new mutation.

Familial
A phenotype or trait that occurs with greater frequency in a given family than in the general population; familial traits may have a genetic and/or nongenetic etiology.

Family history
The genetic relationships within a family combined with the medical history of individual family members. When represented in diagram form using standardized symbols and terminology, it is usually referred to as a pedigree or family tree.

Founder effect
A pathogenic or likely pathogenic variant observed with high frequency in a population founded by a small ancestral group that was once geographically or culturally isolated, in which one or more of the founders was a carrier of the mutant gene.

Germline
The cells from which eggs or sperm (ie, gametes) are derived.

Kindred
An extended family.

Pedigree
A graphic illustration of family history.

Penetrance
A characteristic of a genotype; it refers to the likelihood that a clinical condition will occur when a particular genotype is present.

Proband
The individual through whom a family with a genetic disorder is ascertained. In males this is called a propositus, and in females it is called a proposita.

Sporadic cancer
This term has two meanings. It is sometimes used to differentiate cancers occurring in people who do not have a germline pathogenic or likely pathogenic variant that confers increased susceptibility to cancer from cancers occurring in people who are known to carry a variant. Cancer developing in people who do not carry a high-risk pathogenic or likely pathogenic variant is referred to as **sporadic cancer. The distinction is not absolute, because genetic background may influence the likelihood of cancer even in the absence of a specific predisposing variant. Alternatively, sporadic is also sometimes used to describe cancer occurring in individuals without a family history of cancer.**

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Table 2. Genetic Test Results to Determine the Presence of a Cancer-Predisposing Gene

Result	***Description***
True-positive	The person is a carrier of an alteration in a known cancer-predisposing gene.
True-negative	The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member.
Indeterminate (uninformative)	The person is not a carrier of a known cancer-predisposing gene, and the carrier status of other family members is either also negative or unknown.
Inconclusive (variants of unknown significance)	The person is a carrier of an alteration in a gene that currently has no known significance.

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Table 3. Pathogenic/Likely Pathogenic Variants Associated with Autosomal Recessive Condition

Pathogenic/Likely Pathogenic Variants
ATM
BRCA2
BRIP1
NBN
PALB2
RAD51C

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