National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

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

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Continue

¶ Breast surgical oncology
₪ Clinical genetics
Δ Genetic counseling
¤ Gastroenterology
Ω Gynecologic oncology/Gynecology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
§ Radiation oncology
¥ Patient advocacy
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For chemoprevention options, see NCCN Guidelines for Breast Cancer Risk Reduction.

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

Updates in Version 1.2022 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 2.2021 include:

Global

- Statement added throughout as appropriate: NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

Breast, Ovarian and/or Pancreatic Cancer Genetic Assessment

EVAL-A 1 of 7

- Pre-test counseling
  - 8th bullet revised: "Discuss plan for results disclosure when appropriate, including the possibility of the patient consenting to Release of Information of test results to a close relative or spouse when results are released *in case patient is deceased or incapacitated*."
  - 9th bullet revised: "*Discuss* cost of genetic testing."
  - 10th bullet revised: "*Provide overview of* current legislation regarding genetic discrimination and the privacy of genetic information."

EVAL-A 2 of 7

- Prior to genetic testing, 6th bullet revised: "... while patients with variants of ~~unknown~~ *uncertain* significance (VUS)..."

EVAL-A 3 of 7

- Choice of multi-gene testing
  - 2nd sub-bullet revised: "...personal and family history through a *tailored* multi-gene panel test ~~may be~~ *is often* more efficient and cost-effective..." with footnote b, "Tailored is defined as a disease-focused multi-gene panel of clinically actionable cancer susceptibility genes, in contrast to large multi-gene panels of uncertain or unknown clinical relevance."
  - Last bullet revised by adding: "ideally including more diverse populations."

EVAL-A 4 of 7

- Confirmatory germline testing
  - 1st sub-bullet revised by adding: "In addition, the current tests only provide limited founder mutation results without the benefit of family history. More comprehensive genetic counseling and testing for pathogenic variants in other inherited cancer risk genes may be appropriate at the time of confirmation testing."

EVAL-A 5 of 7

- Heading revised: Tumor Testing: *Potential Implications for Germline Testing*

EVAL-A 6 of 7

- Post-test counseling
  - Last bullet added: "Although negative results of genetic testing are generally reassuring, other reasons that a patient can test negative include:..."

Hereditary Cancer Testing Criteria

- Testing criteria for both ovarian cancer and prostate cancer were separated from the Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes and added to cancer specific pages (CRIT-4 and CRIT-5, respectively).

CRIT-1

- General testing criteria, all general criteria were moved to this page.
  - Testing is clinically indicated..., 4th bullet revised: To aid in systemic therapy *and surgical* decision-making~~, such as for HER2-negative metastatic breast cancer.~~
  - Testing may be considered criteria..., bullet revised: An *individual of* Ashkenazi Jewish ~~individual~~ *ancestry without additional risk factors.*
- Added to the page: The following guidelines include content focused on inherited cancer conditions, including general principles of testing and/or criteria for testing and/or cancer risk management based on a genetic test result:...

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 2.2021 include:

Hereditary Cancer Testing Criteria

CRIT-2

- Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes
  - Statement under heading was revised, "~~This can include~~ *Specifically* BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53 ~~among others~~."
  - Testing is clinically indicated
    - ◊ Personal history of breast cancer criteria was reorganized and revised as follows:
      - *By Age at Diagnosis and Family History*
        - ◊ ≤45 y
        - ◊ 46–50 y with ANY:
          - – Unknown or limited family history
          - – ~~A second breast cancer diagnosed at any age~~ *Multiple primary breast cancers (synchronous or metachronous)*
          - – ≥1 close blood relative with breast, ovarian, pancreatic, or prostate cancer at any age
        - ◊ *≥51 y*
          - – ≥1 close blood relative with *ANY*:...
          - – ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
          - – *≥2 close blood relatives with either breast or prostate cancer (any grade) at any age*
        - ◊ *Any Age*
          - – *To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting* (See NCCN Guidelines for Breast Cancer)
          - – *To aid in adjuvant treatment decisions with olaparib for high-risk, HER-2 negative breast cancer*
          - – Triple-negative breast cancer ~~AND ≤60 y~~
          - – *Lobular breast cancer with personal or family history of diffuse gastric cancer.* See NCCN Guidelines for Gastric Cancer
          - – Male breast cancer
          - – *≥1 close blood relative with male breast cancer*
      - *By Ancestry*
        - ◊ Ashkenazi Jewish ancestry
- Family history of cancer *only*
  - 1st sub-bullet revised: "An affected *(not meeting testing criteria listed above)* or unaffected...(except *unaffected* individuals whose *relatives* meet criteria only for systemic therapy decision-making)."
    - ◊ Bullet revised, "If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated ~~for other relatives~~ based on additional family history.

CRIT-2A

- Footnotes added,
  - Footnote j: Robson M, et al, N Engl J Med 2017;377:523-533. Litton JK, et al. N Engl J Med 2018;379:753-763.
  - Footnote k: As indicated in the criteria, testing is recommended for all triple negative breast cancers, and these indications are specifically for PARP inhibitor eligibility.
  - Footnote l: The definition of high-risk disease is that used in the Phase III OlympiA trial which compared adjuvant Olaparib to placebo among BRCA1/BRCA2 carriers with high-risk disease (Tutt ANJ et al., NEJM 2021;384:2394-2405). The definition includes:....See NCCN Guidelines for Breast Cancer for further details.

CRIT-3

- Testing may be considered...
  - Bullet revised: "Multiple primary breast cancers, first diagnosed between the ages of 50 and 65 y" removed and added to Testing is clinically indicated as "Multiple primary breast cancers (synchronous or metachronous)."
    - 2nd bullet added: Personal history of breast cancer <60 y not meeting any of the above criteria may approach a 2.5% probability of having a PV, based on recent data. It is cautioned that the majority of those PVs will be in moderate penetrance genes, which are over-represented in older affected individuals, and for which data on appropriate management are often lacking. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.
- There is a low probability (<2.5%) that testing will have findings of documented ~~clinical utility~~ *high-penetrance genes* in the following scenarios
  - Female diagnosed with breast cancer at age ~~>65~~ *60* y, with no close relative with breast, ovarian, pancreatic, or prostate cancer.

CRIT-7

- Footnote t added: When this gene is included as part of a multi-gene panel, an individual does not need to meet these testing criteria if testing criteria on other testing criteria pages are met. (Also for CRIT-8.)

Continued

Updates in Version 1.2021 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 1.2020 include:

Genetic Testing Process

GENE-1

- **Genetic testing**
  - **Familial pathogenic/likely pathogenic variant known revised, "~~Recommend~~ Genetic testing for specific..."**
  - **No known familial pathogenic/likely pathogenic variant, "~~Consider comprehensive testing of patient with~~ *Germline* multi-gene ~~panel~~ *testing* or..."**

Cancer Risk Management Based on Genetic Test Results

GENE- A all pages

- **Ovarian cancer column clarified as "epithelial."**
- **Evidence for increased risk changed to "Strength of evidence" when data are available.**
- **References were updated accordingly.**

GENE-A 1 of 9

- **BARD1,**
  - **Breast cancer, Absolute risk revised from "Insufficient data to define to "15%–40%"**
  - **Breast cancer, Strength of evidence changed from "Limited, but stronger for triple-negative disease" to "Strong for triple-negative disease."**
  - **Ovarian cancer, Evidence of increased risk changed from "None" to "No established association" Also for CDH1, CDKN2A, CHEK2, NF1, PTEN, STK11, TP53.**

GENE-A 3 of 9

- **CDH1,**
  - **Breast cancer management, 2nd sub-bullet revised from "Evidence insufficient for RRM, manage based on family history" to "Discuss option of RRM."**
- **CDKN2A,**
  - **Melanoma absolute risk added: 28%–76% depending on other risk factors, including family history, geographic location, and other genetic modifier.**
- **CHEK-2**
  - **Colon cancer, "Risk not well-established" added.**

GENE-A 4 of 9

- **MSH6, Ovarian cancer, Absolute risk was changed from >10% to ≤13% and Strength of evidence changed from Strong to Mixed**
- **NBN**
  - **Breast cancer, Evidence for increased risk changed to No established association.**

GENE-A 5 of 9

- **PALB2,**
  - **Breast Cancer, Strength of evidence revised: Strong *(with overrepresentation of triple-negative disease)***
- **PTEN,**
  - **Breast Cancer, Strength of evidence revised: Strong *(with predisposition to luminal subtype)*"**
- **RAD51C and RAD51D:**
  - **Breast Cancer, Strength of evidence revised from "Limited; potential increase in female breast cancer, including triple negative" to "Strong for ER/PR-negative breast cancer."**

GENE-A 6 of 9

- **STK11,**
  - **Non-Epithelial Ovarian Cancer *(Sex cord with annular tubules) moved to Other Cancer Risk column.***
  - **Comment revised from, "The precise risk estimates for pancreatic cancer for STK11 should be interpreted with caution given the relative paucity of data." to "Case-control studies have consistently demonstrated germline STK11 pathogenic variants to be associated with high lifetime risks of pancreatic cancer. However, these variants are rare, and the risk estimates have wide confidence intervals."**
- **TP53,**
  - **Breast cancer, Strength of evidence revised: Strong *(with predisposition to triple-positive disease)***

GENE-B

- **New table added, "Autosomal Recessive Risk in Cancer Genes – Multi-Gene Panel Testing."**

Continued

UPDATES

Updates in Version 1.2021 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic from Version 1.2020 include:

BRCA Pathogenic/Likely Pathogenic Variant-Positive Management

BRCA-A 1 of 3

- All management recommendations reorganized by cancer site.
- Footnote e revised by adding: FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. (Also for LIFR-A and COWD-A)

BRCA-A 3 of 3

- Bullet removed: Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial. (Also for LIFR-A and COWD-A)
- Bullets related to risk to relatives and reproductive options were removed and section is redirected to Principles of Cancer Risk Assessment and Counseling (EVAL-A). (Also for LIFR-A and COWD-A)

Pancreatic Cancer Screening

PANC-A 1 of 2

- Last bullet revised: "...better define the threshold for surgical intervention ~~and biopsy~~ in high-risk individuals undergoing pancreatic cancer screening."

PANC-A 2 of 2

- 1st bullet revised: "For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers, ~~ideally under research conditions~~s. The panel... high incidence of *benign or indeterminate* pancreatic abnormalities,..."
- 2nd bullet revised: "based on clinical judgment, for individuals found to have ~~worrisome~~ *potentially concerning* abnormalities on screening.."

Li-Fraumeni Syndrome Management in Adults

LIFR-A 1 of 2

- Other cancer risks, 2nd bullet revised: "the earliest known colon *or gastric* cancer in the family, ~~(whichever comes first)~~ *respectively*."

Cowden Syndrome Management

COWD-A 2 of 3

- All management recommendations reorganized by cancer site.
- Breast cancer, 3rd bullet, 1st sub-bullet revised: "... starting at age ~~30~~–35 years or ~~5~~–10 years..."

COWD-A 3 of 3

- Footnote f was revised: Oophorectomy is not indicated for CS/PHTS alone ~~but may be indicated for other reasons~~.

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, clinical 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:

- **Evaluate 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) when indicated:**
  - **CS/PHTS specific: dermatologic,[a] including oral mucosa, head circumference, and thyroid (enlarged or nodular on palpation)**
- **Generate a differential diagnosis and educate the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity**
- **Prepare for the possible outcomes of testing, including positive (pathogenic, likely pathogenic), true negative and uninformative negative, uncertain variants, and mosaic results**
- **Obtain written informed consent, and document the informed consent in the patient's medical record**
- **Discuss plan for results disclosure when appropriate, including the possibility of the patient consenting to Release of Information of test results to a close relative or spouse when results are released in case patient is deceased or incapacitated**
- **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**
- **Discuss cost of genetic testing**
- **Provide overview of current legislation regarding genetic discrimination and the privacy of genetic information**

References on EVAL-A 7 of 7

[a] For Cowden syndrome/PTEN hamartoma tumor syndrome (CS/PHTS) dermatologic manifestations, see CRIT-7 and for Peutz-Jeghers syndrome (PJS) dermatologic manifestations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

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 less than 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, while patients with variants of uncertain significance (VUS) and likely benign variants should be managed based on the cancers present in the family.**
- **Choice of multi-gene testing, see EVAL-A 3 of 7.**

References on EVAL-A 7 of 7

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

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 tailored[b] multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or their 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.**
  - **Some individuals may carry pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene; thus, consideration of a multi-gene 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 (eg, methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), 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.[c] 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 VUS, mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP).**
  - **Multi-gene 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.**
  - **There are significant limitations in interpretation of polygenic risk scores (PRSs). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including more diverse populations. See Discussion.**

[b] Tailored is defined as a disease-focused multi-gene panel of clinically actionable cancer susceptibility genes, in contrast to large multi-gene panels of uncertain or unknown clinical relevance.

[c] 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.

References on EVAL-A 7 of 7

Continued

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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.

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] In addition, the current tests only provide limited founder mutation results without the benefit of family history. More comprehensive genetic counseling and testing for pathogenic variants in other inherited cancer risk genes may be appropriate at the time of confirmation testing.**
  - **Research: Patients may have participated in research studies that included 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 7 of 7

Continued

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Tumor Testing: Potential Implications for Germline Testing

- **Testing may provide information suggesting a potential germline finding. Pathogenic/likely pathogenic variants reported in the tumor may be of somatic or germline origin.**
  - **Because tumor testing is designed to address treatment actionability, not germline status, a variant that may be considered as pathogenic or likely pathogenic in the germline may not be reported at all, or reported as normal in the tumor if it lacks clinical implications.**
  - **The filtering of raw sequencing data may differ between tumor and germline testing labs so that variants reported out with one analysis may not be reported with the other.**
  - **Somatic pathogenic/likely pathogenic variants seen in tumor specimens are common in some genes with germline implications (eg, *TP53, STK11, PTEN*) and may not indicate the need for germline testing unless the clinical/family history is consistent with a pathogenic or likely pathogenic variant in the germline.**
  - **Regardless of findings in the tumor, when germline testing is clinically indicated, it should be performed in a CLIA-approved lab with established experience in germline testing because:**
    - ◊ **The germline panel performed by some labs offering paired tumor and germline testing may have incomplete coverage and analyze only a subset of those genes of interest to the clinician.**
    - ◊ **The sensitivity of most tumor testing is lower (particularly for intermediate-sized deletions and duplications) than germline testing.**
    - ◊ **Similarly, circulating tumor DNA (ctDNA) has the potential to identify both somatic and germline variants with germline treatment implications. Some ctDNA assays, but not all, will alert providers that the particular gene variant identified has a high enough variant allele frequency (VAF) that it is suspicious for germline origin. However, most commercially available assays specializing in somatic ctDNA detection are neither intended nor validated for the reporting or interpretation of germline variants. Thus, variants detected by ctDNA that are suspected to be present in the germline should be evaluated via a CLIA-approved assay specializing in detection and interpretation of germline variants.**

References on EVAL-A 7 of 7

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

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 the importance of notifying family members and offer materials/resources for 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 testing. 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, unless there are data to support discrepancy in interpretation of results. 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, if they are being considered for use in clinical management**
  - **Interpretation of pathogenic/likely pathogenic variants for patients tested through direct-to-consumer or consumer-initiated models**

- **Although negative results of genetic testing are generally reassuring, other reasons that a patient can test negative include:**
  1) A gene mutation may exist in the gene that was not recognized due to limitations in technology
  2) Mutations exist in genes that were not evaluated by this testing
  3) Family members may harbor a genetic mutation that the patient may not have inherited

References on EVAL-A 7 of 7

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

References

[1] Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol 2015;33:3660-3667.
[2] Berliner JL, Fay AM, Cummings SA, Burnett B, Tillmanns T. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. J Genet Couns 2013;22:155-163.
[3] American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol 2009;113:957-966.
[4] Lancaster JM, Powell CB, Chen LM, Richardson DL; SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 2015;136:3-7.
[5] Weitzel JN, Blazer KR, Macdonald DJ, Culver JO, Offit K. Genetics, genomics, and cancer risk assessment: State of the art and future directions in the era of personalized medicine. CA Cancer J Clin 2011;61:327-359.
[6] Committee on Bioethics; Committee on Genetics, and American College of Medical Genetics and; Genomic Social; Ethical; Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Pediatrics 2013;131:620-622.
[7] Tandy-Connor S, Guiltinan J, Krempely K, et al. False-positive results released by direct-to-consumer genetic tests highlight the importance of clinical confirmation testing for appropriate patient care. Genet Med 2018;20:1515-1521.
[8] Green R, Berg J, Grody W, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med 2013;15:565-574.
[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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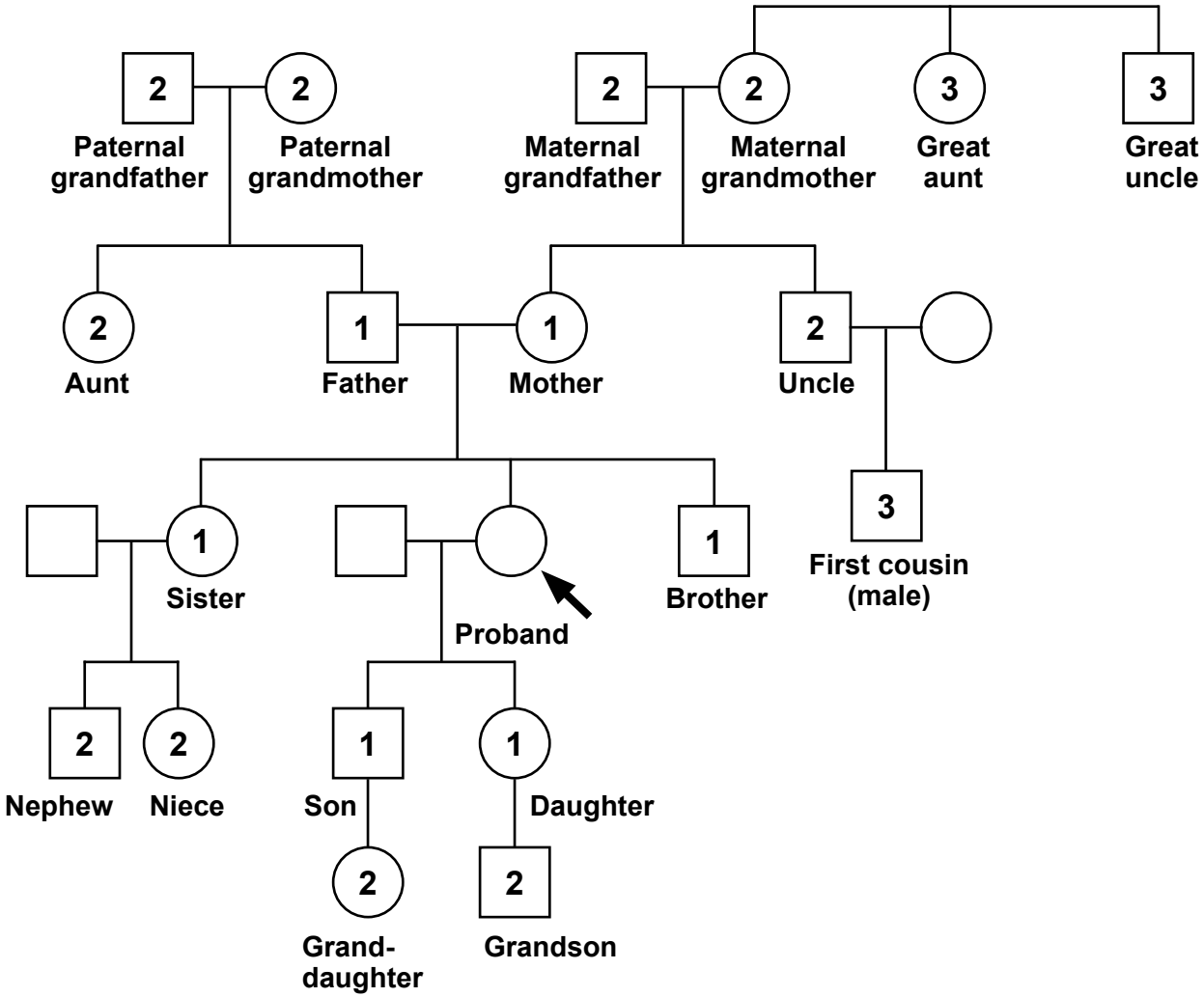
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

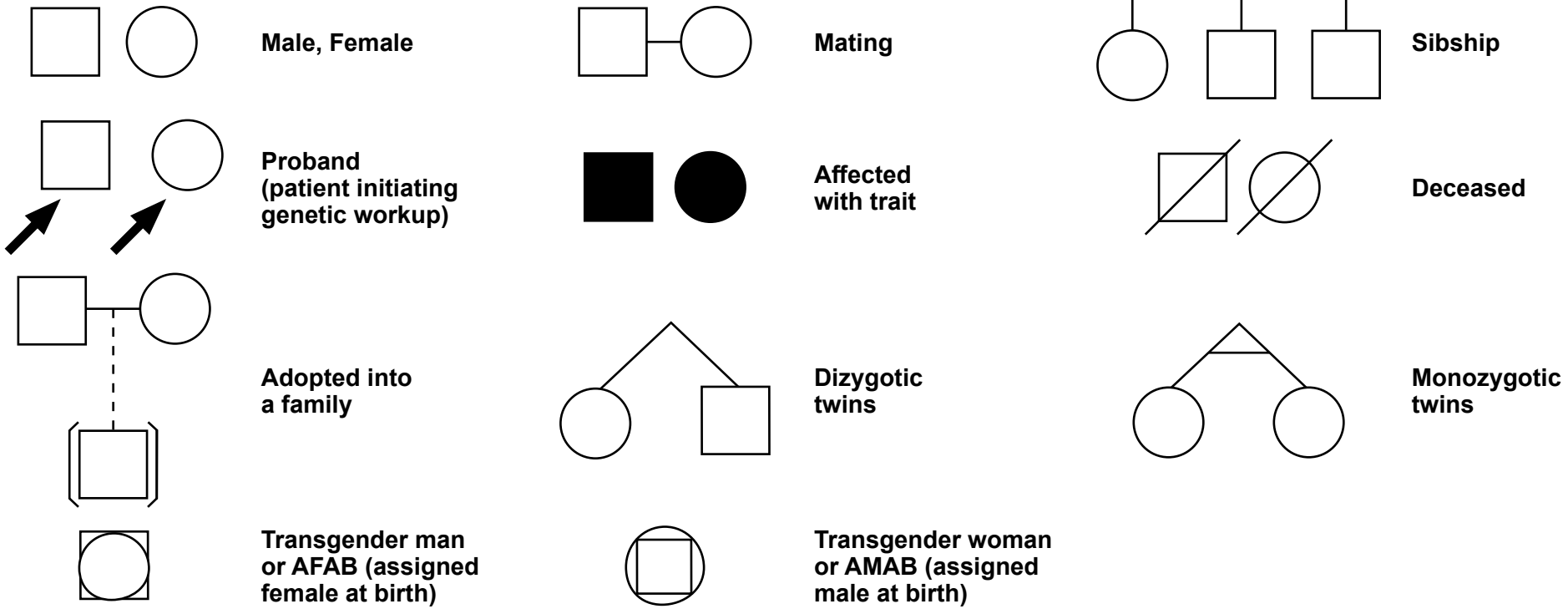
PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[a]



[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.

Note: All recommendations are category 2A unless otherwise indicated.
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.

COMMON PEDIGREE SYMBOLS[b]



[b] Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. Am J Hum Genet 1995;56:745-752.

Note: All recommendations are category 2A unless otherwise indicated.
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.

GENERAL TESTING CRITERIA[a]

Testing is clinically indicated in the following scenarios:
• Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
• Individuals meeting the criteria below but tested negative with previous limited testing (eg, single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing
• A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline
• To aid in systemic therapy and surgical decision-making[b]
• Individual who meets Li-Fraumeni syndrome (LFS) testing criteria (see CRIT-7) or Cowden syndrome/PTEN hamartoma tumor syndrome testing criteria (see CRIT-8) or Lynch syndrome See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
• For personal or family history of ▸ Breast cancer — See Testing Criteria for High-Penetrance Breast Cancer Susceptibility Genes (CRIT-2) ▸ Ovarian cancer — See Testing Criteria for High-Penetrance Ovarian Cancer Susceptibility Genes (CRIT-4) ▸ Pancreatic cancer — See Testing Criteria for Pancreatic Cancer Susceptibility Genes (CRIT-5) ▸ Prostate cancer — See Testing Criteria for Prostate Cancer Susceptibility Genes (CRIT-6) ▸ Colorectal cancer — See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

Testing *may be* considered in the following scenario (with appropriate pre-test education and access to post-test management):
• An individual of Ashkenazi Jewish ancestry[c] without additional risk factors

The following NCCN Guidelines include content focused on inherited cancer conditions, including general principles of testing and/or criteria for testing and/or cancer risk management based on a genetic test result:

- **Treatment Guidelines:**
  - Acute Myeloid Leukemia
  - Basal Cell Skin Cancer
  - Bladder Cancer
  - Breast Cancer
  - Colon Cancer
  - Esophageal and Esophagogastric Junction Cancers
  - Gastric Cancer
  - GIST
  - Hepatobiliary Cancers
  - Kidney Cancer
  - Cutaneous Melanoma
  - Myelodysplastic Syndromes
  - Neuroendocrine and Adrenal Tumors
  - Non-Small Cell Lung Cancer
  - Ovarian Cancer
  - Pancreatic Cancer
  - Prostate Cancer
  - Rectal Cancer
  - Soft Tissue Sarcoma
  - Thyroid Carcinoma
  - Uterine Neoplasms
- **Detection, Prevention, and Risk Reduction Guidelines:**
  - Breast Cancer Screening and Diagnosis
  - Colorectal Cancer Screening
  - Genetic/Familial High-Risk Assessment: Colorectal
  - Prostate Cancer Early Detection
- **Supportive Care Guidelines:**
  - Survivorship

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

[b] 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.

[c] Testing for three founder mutations of *BRCA1/2* may be offered to individuals 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.

Note: All recommendations are category 2A unless otherwise indicated.
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.

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES
(Specifically *BRCA1, BRCA2, CDH1, PALB2, PTEN,* and *TP53*. See GENE-A)[a,d,e,f]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Personal history of breast cancer with specific features:
  - By Age at Diagnosis and Family History
    - ≤45 y
    - 46–50 y with ANY:
      - Unknown or limited family history[g]
      - Multiple primary breast cancers (synchronous or metachronous)
      - ≥1 close blood relative[h] with breast, ovarian, pancreatic, or prostate cancer at any age
    - ≥51 y
      - ≥1 close blood relative[h] with ANY:
        - breast cancer at age ≤50 y or male breast cancer at any age
        - ovarian cancer any age
        - pancreatic cancer any age
        - metastatic,[i] intraductal/cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) prostate cancer any age
      - ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
      - ≥2 close blood relatives[h] with either breast or prostate cancer (any grade) at any age
    - Any Age
      - To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting[j,k] (See NCCN Guidelines for Breast Cancer)
      - To aid in adjuvant treatment decisions with olaparib for high-risk,[l] HER-2 negative breast cancer[j]
      - Triple-negative breast cancer
      - Lobular breast cancer with personal or family history of diffuse gastric cancer. See NCCN Guidelines for Gastric Cancer
      - Male breast cancer
      - ≥1 close blood relative[g] with male breast cancer
  - By Ancestry
    - Ashkenazi Jewish ancestry
- Family history of cancer only
  - An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making).[m]
    - If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
  - An affected or unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[n]

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

Continued on CRIT-3

Footnotes on CRIT-2A

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

Note: All recommendations are category 2A unless otherwise indicated.
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.

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[d] 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*).
[e] Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.
[f] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[g] Weitzel J, et al. JAMA 2007;297:2587-2595.
[h] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family. (See EVAL-B)
[i] 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.
[j] Robson M, et al. N Engl J Med 2017;377:523-533. Litton JK, et al. N Engl J Med 2018;379:753-763.
[k] As indicated in the criteria, testing is recommended for all triple negative breast cancers, and these indications are specifically for PARP inhibitor eligibility.
[l] The definition of high-risk disease is that used in the Phase III OlympiA trial which compared adjuvant Olaparib to placebo among BRCA1/BRCA2 carriers with high-risk disease (Tutt ANJ, et al. NEJM 2021;384:2394-2405). The definition includes:
- Triple negative breast cancer treated with either:
  -- adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor ≥2 cm on pathology analysis
  -- neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes.
- Hormone receptor positive disease treated with either:
  -- adjuvant chemotherapy with ≥4 positive pathologically confirmed lymph nodes
  -- neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+EG score of 3 or higher.
- The CPS+EG scoring system is based on a combination of clinical and pathologic stage, estrogen receptor status and histologic grade. See Neoadjuvant Therapy Outcomes Calculator (Jeruss JS, et al. J Clin Oncol 2008;26:246-252; Mittendorf EA, et al. J Clin Oncol 2011;29:1956-1962). See NCCN Guidelines for Breast Cancer for further details.

[m] 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.
[n] 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*.

Note: All recommendations are category 2A unless otherwise indicated.
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.

TESTING CRITERIA FOR HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES (continued)

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

- **Personal history of breast cancer <60 y not meeting any of the above criteria may approach a 2.5% probability of having a PV, based on recent data.[o] It is cautioned that the majority of those PVs will be in moderate penetrance genes, which are over-represented in older affected individuals, and for which data on appropriate management are often lacking. Access to an experienced genetic counseling team to discuss management options is particularly important in this setting.**
- **An affected or unaffected individual who otherwise does not meet any of the above criteria but with a 2.5%–5% probability of *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[d]**

There is a low probability (<2.5%) that testing will have findings of documented high-penetrance genes in the following scenarios:

- **Female diagnosed with breast cancer at age >60 y, with no close relative[h] with breast, ovarian, pancreatic, or prostate cancer.**
- **Diagnosed with localized prostate cancer with Gleason Score <7 and no close relative[h] with breast, ovarian, pancreatic, or prostate cancer.**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[d] 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*).

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

[o] Kurian A, et al. JAMA 2020;323:995-997.

Note: All recommendations are category 2A unless otherwise indicated.
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.

TESTING CRITERIA FOR OVARIAN CANCER SUSCEPTIBILITY GENES[a] (See GENE-A)

Testing is clinically indicated in the following scenarios:

- **See General Testing Criteria on CRIT-1.**
- **Personal history of epithelial ovarian cancer[p] (including fallopian tube cancer or peritoneal cancer) at any age**
- **Family history of cancer only**
  - **An unaffected individual with a first- or second-degree blood relative with epithelial ovarian cancer[i] (including fallopian tube cancer or peritoneal cancer) at any age[m]**
  - **An unaffected individual who otherwise does not meet the criteria above but has a probability >5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)[n]**

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**

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

[m] 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.

[n] 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*.

[p] *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.

Note: All recommendations are category 2A unless otherwise indicated.
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.

TESTING CRITERIA FOR PANCREATIC CANCER SUSCEPTIBILITY GENES (See GENE-A)[a]

Testing is clinically indicated in the following scenarios:

- **See General Testing Criteria on CRIT-1.**
- **Exocrine pancreatic cancers[q]**
  - **All individuals diagnosed with exocrine pancreatic cancer[r]**
  - **First-degree relatives of individuals diagnosed with exocrine pancreatic cancer[s]**
- **Neuroendocrine pancreatic tumors - See NCCN Guidelines for Neuroendocrine and Adrenal Tumors**

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**

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

[q] 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*.

[r] Pancreatic cancer risk is higher in individuals of Ashkenazi Jewish descent. Genetic testing of Ashkenazi Jewish patients with pancreatic cancer may have a higher yield of mutations than of non-Ashkenazi Jewish patients.

[s] 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. 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, et al. J Clin Oncol 2015;33:3124-3129. Shindo K, et al. J Clin Oncol 2017;35:3382-3390. Golan T, et al. N Engl J Med 2019;381:317-327.) Family history of pancreatic cancer of unknown histology is often assumed to be an exocrine pancreatic cancer.

Note: All recommendations are category 2A unless otherwise indicated.
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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Hereditary Cancer Testing Criteria

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Discussion

TESTING CRITERIA FOR HIGH-PENETRANCE PROSTATE CANCER SUSCEPTIBILITY GENES (See GENE-A)[a]

Testing is clinically indicated in the following scenarios:

- See General Tumor Criteria on CRIT-1.
- Personal history of prostate cancer with specific features:
  - By Tumor Characteristics (any age)
    - ◊ Metastatic[i]
    - ◊ Histology
      - – intraductal/ cribriform
      - – high- or very-high risk group (see NCCN Guidelines for Prostate Cancer)
  - By Family History and Ancestry
    - ◊ ≥1 close blood relative[h] with:
      - – breast cancer at age ≤50 y
      - – ovarian cancer any age
      - – pancreatic cancer any age
      - – metastatic,[i] intraductal/ cribriform histology, or high- or very-high risk group (see NCCN Guidelines for Prostate Cancer) any age
    - ◊ ≥2 close blood relatives[h] with either breast or prostate cancer (any grade) at any age
    - ◊ Ashkenazi Jewish ancestry[c]
- Family history of cancer only
  - An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)[m]

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

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[c] Testing for three founder mutations of *BRCA1/2* may be offered to individuals 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.
[h] Close blood relatives include first-, second-, and third-degree relatives on the same side of the family (See EVAL-B).
[i] 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.
[m] 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.

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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.

TESTING CRITERIA FOR LI-FRAUMENI SYNDROME[a]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.
- Individual from a family with a known *TP53*[t] pathogenic/likely pathogenic variant
- Classic Li-Fraumeni syndrome (LFS) criteria:[u]
  - Combination of an individual diagnosed at age <45 years with a sarcoma[u]
    AND
    A first-degree relative diagnosed at age <45 years with cancer
    AND
    An additional first- or second-degree relative in the same lineage with cancer diagnosed at age <45 years, or a sarcoma at any age
- Chompret criteria:[v]
  - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age
    OR
  - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years
    OR
  - Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history
    OR
  - Breast cancer before 31 years of age
- Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing[w]

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.

[t] When this gene is included as part of a multi-gene panel, an individual does not need to meet these testing criteria if testing criteria on other testing criteria pages are met.

[u] Li FP, et al. Cancer Res 1988;48:5358-5362. To date, there have been no reports of Ewing sarcoma, gastrointestinal stromal tumor (GIST), desmoid tumor, or angiosarcoma in *TP53* pathogenic/likely pathogenic variant carriers.

[v] Chompret A, et al. J Med Genet 2001;38:43-47; Bougeard G, et al. J Clin Oncol 2015;33:2345-2352.

[w] 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.

Note: All recommendations are category 2A unless otherwise indicated.
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.

TESTING CRITERIA FOR COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)[a,x,y,z]

Testing is clinically indicated in the following scenarios:

- See General Testing Criteria on CRIT-1.

- Individual from a family with a known *PTEN*[t] pathogenic/likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria[aa] for CS/PHTS
- Individual not meeting clinical diagnostic criteria[aa] 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;[bb] 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[cc]

See major and minor criteria on CRIT-8A.

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**

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[t] When this gene is included as part of a multi-gene panel, an individual does not need to meet these testing criteria if testing criteria on other testing criteria pages are met.
[x] These are testing criteria; clinical diagnostic criteria can be found on COWD-A.
[y] If two criteria involve the same structure/organ/tissue, both may be included as criteria.
[z] Current evidence does not support testing for succinate dehydrogenase (SDH) gene pathogenic/likely pathogenic variants in patients with PHTS. (Bayley J-P. Am J Hum Genet 2011;88:674-675).
[aa] Pilarski R, et al. J Natl Cancer Inst 2013;105:1607-1616. See COWD-A.
[bb] If an individual has two or more major criteria, such as breast cancer and nonmedullary 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.
[cc] 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.

Note: All recommendations are category 2A unless otherwise indicated.
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TESTING CRITERIA FOR COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)[a]

Major criteria:

- **Breast cancer**
- **Endometrial cancer**
- **Follicular thyroid cancer**
- **Multiple GI hamartomas or ganglioneuromas[dd]**
- **Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult female, 60 cm in adult male)[ee]**
- **Macular pigmentation of glans penis**
- **Mucocutaneous lesions[ff]**
  - **One biopsy-proven trichilemmoma**
  - **Multiple palmoplantar keratoses**
  - **Multifocal or extensive oral mucosal papillomatosis**
  - **Multiple cutaneous facial papules (often verrucous)**

Minor criteria:[gg]

- **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)**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[dd] Multiple polyp types are often seen in patients with PHTS, and less commonly may include adenomas, hyperplastic polyps, and other histologies.
[ee] Roche AF, et al. Pediatrics 1987;79:706-712.
[ff] 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.
[gg] Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

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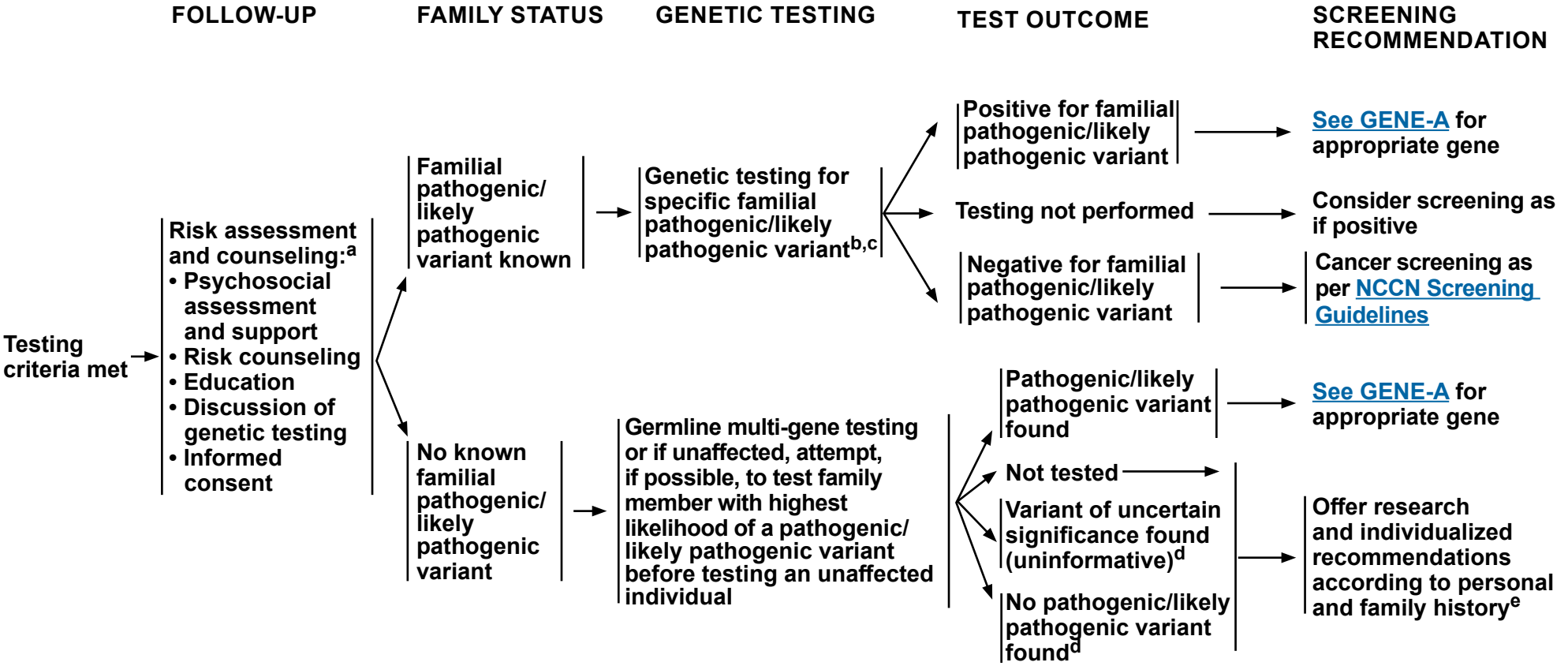

[a] For further details regarding the nuances of genetic counseling and testing, see EVAL-A.
[b] If of Ashkenazi Jewish descent, in addition to the specific familial pathogenic/likely pathogenic variant, test for all three founder pathogenic/likely pathogenic variants.
[c] Additional testing may be indicated 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 CS/PHTS 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,1,2]

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	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
ATM	• **Absolute risk:** 15%–40%[3,4] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence:** Strong	• **Absolute risk:** <3%[5-7] • **Management:**[e] ▸ Risk reduction: Evidence insufficient for RRSO; manage based on family history • **Strength of evidence:** Strong	**Pancreatic cancer** • **Absolute risk:** ~5%–10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence:** Strong **Prostate cancer** • Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring. Heterozygous *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	• **Absolute risk:** 15%–40%[18] • **Management:** ▸ Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence:** Strong for triple-negative disease[18-20]	**Evidence of increased risk:** No established association	**Other cancers** • Unknown or insufficient evidence

Footnotes on GENE-A 7 of 9 **References on GENE-A 8 of 9 and GENE-A 9 of 9**

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
BRCA1	• **Absolute risk:** >60%[21-25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong (with predisposition to triple-negative disease)	• **Absolute risk:** 39%–58%[26] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong	**Pancreatic cancer** • **Absolute risk:** ≤5% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence:** Strong **Prostate cancer** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: There have been a few case reports of Fanconi-like conditions in individuals with two *BRCA1* pathogenic variants.[27,28]		
BRCA2	• **Absolute risk:** >60%[21-25] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong (with predisposition to ER+ disease)	• **Absolute risk:** 13%–29%[26] • **Management:** See *BRCA* Pathogenic Variant-Positive Management • **Strength of evidence:** Very strong	**Pancreatic cancer** • **Absolute risk:** 5%–10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A. • **Strength of evidence:** Very strong **Prostate cancer and melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
BRIP1	• **Absolute risk:** Insufficient data to define • **Management:** Insufficient data; managed based on family history • **Strength of evidence:** Limited; potential increase in female breast cancer (including triple negative)[19]	• **Absolute risk:** >10%[5-7] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y • **Strength of evidence:** Strong	**Other cancers** • Unknown or insufficient evidence
	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.		

Footnotes on GENE-A 7 of 9 **References on GENE-A 8 of 9 and GENE-A 9 of 9**

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
CDH1	• **Absolute risk:** 41%–60%[29-31] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[c,d] ▸ Risk reduction: Discuss option of RRM • **Strength of evidence:** Strong (with predisposition to lobular disease)	**Evidence of increased risk:** No established association	**Hereditary 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	**Evidence of increased risk:** No established association	**Evidence of increased risk:** No established association	**Pancreatic cancer** • **Absolute risk:** >15% • **Management:** Screening, see PANC-A. • **Strength of evidence:** Very strong **Melanoma** • **Absolute risk:** 28%–76% depending on other risk factors, including family history, geographic location, and other genetic modifiers[32,33] • **Strength of evidence:** Strong
	Comments: General melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure.		
CHEK2	• **Absolute risk:** 15%–40%[34,35] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence:** Strong (with predisposition to ER+ disease)[16,36]	**Evidence of increased risk:** No established association	**Colon cancer** • Risk not well-established See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (GENE-1)
	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.		

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Continued

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
MSH2, MLH1, MSH6, PMS2, EPCAM [f]	***MLH1, MSH2, MSH6, PMS2,* and *EPCAM*** • **Absolute risk:** <15%[37,38] • **Management:** Insufficient data; managed based on family history • **Strength of evidence:** Limited	***MLH1, MSH2*** • **Absolute risk:** >10%[39-40] • **Strength of evidence:** Strong ***MSH6*** • **Absolute risk:** ≤13%[41,42] • **Strength of evidence:** Mixed ***PMS2*** • **Absolute risk:** <3%[43-45] • **Strength of evidence:** Limited ***EPCAM*** • **Absolute risk:** <10% • **Strength of evidence:** Limited • **Management for all genes:** See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Pancreatic cancer** • **Absolute risk:** <5%–10% (excluding *PMS2*) • **Management:** Screening mutation carriers with a family history of pancreatic cancer (insufficient evidence for *PMS2*), see PANC-A. • **Strength of evidence:** Strong **Colon, uterine, others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
NBN	• **Evidence for increased risk:** No established association[18,36]	• **Absolute risk:** Insufficient data to define • **Management:** Manage based on family history • **Strength of evidence:** Limited[5-7]	**Other cancers** • Unknown or insufficient evidence
	Comment: Counsel for risk of autosomal recessive condition in children.		
NF1	• **Absolute risk:** 15%–40%[46,47] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[c,d] ▸ Risk reduction: Evidence insufficient for RRM, manage based on family history • **Strength of evidence:** Strong	**Evidence of increased risk:** No established association	**Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: Screening recommendations only apply to individuals with a clinical diagnosis of NF. At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

Footnotes on GENE-A 7 of 9 **References on GENE-A 8 of 9 and GENE-A 9 of 9**

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Continued

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
PALB2	• **Absolute risk:** 41%–60%[17,19,48] • **Management:**[b] ▸ Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[c,d] ▸ Risk reduction: Discuss option of RRM • **Strength of evidence:** Strong (with overrepresentation of triple-negative disease)	• **Absolute risk:** 3%–5%[5-7,17] • **Management:**[e] ▸ Risk reduction: Evidence insufficient; manage based on family history • **Strength of evidence:** Strong	**Pancreatic cancer** • **Absolute risk:** 5%–10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A • **Strength of evidence:** Limited **Other cancers** • Unknown or insufficient evidence
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	• **Absolute risk:** 40%–60% (historical cohort data), >60% (projected estimates)[49-52] • **Management:**[b] See Cowden Syndrome Management • **Strength of evidence:** Strong (with predisposition to luminal subtype[53,54])	**Evidence of increased risk:** No established association	**Thyroid, colon, endometrial cancers** • See Cowden Syndrome Management
RAD51C	• **Absolute risk:** 15%–40%[18,19,20,36,55,56] • **Management:** Insufficient data; managed based on family history • **Strength of evidence:** Strong for ER/PR-negative breast cancer	• **Absolute risk:** >10%[5-7,57] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y • **Strength of evidence:** Strong	**Other cancers** • Unknown or insufficient evidence
	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	• **Absolute risk:** 15%–40%[18,19,20,36,55,56] • **Management:** Insufficient data; managed based on family history • **Strength of evidence:** Strong for ER/PR-negative breast cancer	• **Absolute risk:** >10%[5-7,57] • **Management:** ▸ Risk reduction: Consider RRSO at 45–50 y • **Strength of evidence:** Strong	**Other cancers** • Unknown or insufficient evidence
	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.		

Footnotes on GENE-A 7 of 9 **References on GENE-A 8 of 9 and GENE-A 9 of 9**

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

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	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[8-17] and Other Cancer Risks
STK11	• **Absolute risk:** 40%–60%[58,59] • **Management:** ▸ Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome ▸ Risk reduction: Evidence insufficient RRM, manage based on family history • **Strength of evidence:** Strong	**Evidence of increased risk:** No established association	**Pancreatic cancer** • **Absolute risk:** >15% • **Management:** Screening, see PANC-A • **Strength of evidence:** Strong **Non-Epithelial Ovarian Cancer (Sex cord with annular tubules)** • **Absolute risk:** >10%[58] • **Management:** See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • **Strength of evidence:** Strong **Other cancers** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome
	Comment: Case-control studies have consistently demonstrated germline *STK11* pathogenic variants to be associated with high lifetime risks of pancreatic cancer. However, these variants are rare, and the risk estimates have wide confidence intervals.		
TP53	• **Absolute risk:** >60%[60] • **Management:** See Li-Fraumeni Syndrome Management • **Strength of evidence:** Strong (with predisposition to triple-positive disease[61])	**Evidence of increased risk:** No established association	**Pancreatic cancer** • **Absolute risk:** 5%–10% • **Management:** Screening mutation carriers with a family history of pancreatic cancer, see PANC-A • **Strength of evidence:** Limited **Other cancers** • See Li-Fraumeni Syndrome Management

Footnotes on GENE-A 7 of 9 **References on GENE-A 8 of 9 and GENE-A 9 of 9**

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FOOTNOTES FOR TABLES

[a] 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 for: *FANCC*, *MRE11A*, *MUTYH* heterozygotes, *RAD50, RECQL*, *RINT1*, *SLX4*, *SMARCA4*, or *XRCC2;* or for prostate cancer management for *HOXB13*.

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

[c] 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.

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

[e] Transvaginal ultrasound combined with serum CA-125 for ovarian cancer screening, although of uncertain benefit, may be considered at the clinician's discretion.

[f] 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 S, et al. J Clin Oncol 2018;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*.

Strength of Evidence	Absolute Lifetime Risk Ranges

• **Very strong: Prospective cohort studies in a population-based setting have demonstrated risk.**
• **Strong: Traditional case-control studies or more than three case-control studies including those with cases ascertained by commercial laboratories or those without controls from the same population. Traditional case-control study: A retrospective study that compares patients with a disease or specific outcome (cases) with patients without the disease or outcome (controls).**
• **Limited: Small sample size or case series**
• **None**
	• **Breast cancer: 15%–40%, 41%–60%, >60%**
	• **Ovarian cancer: <3%, 3%–5%, and >5%**
	• **Pancreatic cancer: <5%, 5%–10%, >15%**
	
	• **Population risk (per SEER registry data)**
	  ▸ **Breast cancer: 12%–13%**
	  ▸ **Ovarian cancer: 1%–2%**
	  ▸ **Pancreatic cancer: 1%–2%**

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AUTOSOMAL RECESSIVE RISK IN CANCER GENES – MULTI-GENE PANEL TESTING

GENE and CONDITION	DESCRIPTION
ATM **–** Ataxia-Telangiectasia (AT)	AT is characterized by progressive cerebellar ataxia, telangiectasias, immune defects, and a predisposition to malignancy. Individuals with AT are abnormally sensitive to killing by ionizing radiation and resistant to inhibition of DNA synthesis by ionizing radiation.
BRCA1 **–** Fanconi anemia complementation group S (FANCS)	There are rare reports of compound heterozygous or homozygous *BRCA1* mutations causing FANCS. FANCS is characterized by developmental delay apparent from infancy, short stature, microcephaly, and coarse dysmorphic features. It is associated with defective DNA repair and increased chromosomal breakage.
BRCA2 **–** Fanconi anemia complementation group D1	Fanconi anemia is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life. Biallelic pathogenic variants in *BRCA2* are associated with early-onset acute leukemia and solid tumors with a cumulative probability of any malignancy of 97% by age 6 years.
BRIP1 **–** Fanconi anemia complementation group J (FANCJ)	Fanconi anemia is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life.
MLH1, ***MSH2***, ***MSH6***, ***PMS2***, ***EPCAM*** **–** Constitutional mismatch repair deficiency (CMMRD)	CMMRD is a childhood cancer predisposition syndrome characterized by four main tumor types (hematologic malignancies, brain/central nervous system tumors, colorectal tumors and multiple intestinal polyps, and other malignancies including embryonic tumors and rhabdomyosarcoma).
MSH3 **–** Biallelic MSH3 is associated with increased risk for colonic polyposis	MSH3-related polyposis is characterized by the development of multiple colonic adenomas, with possible progression to colorectal cancer.
NBN **–** Nijmegen breakage syndrome (NBS)	NBS is characterized by microcephaly, growth retardation, immunodeficiency, predisposition to cancer, and premature ovarian failure in females. The highest malignancy risk is for T-cell and B-cell lymphomas. Affected children may experience developmental delays and hyperactivity. Targeted analysis for pathogenic variant c.657_661del5 can be performed first. This pathogenic variant is detected in ~100% of alleles in individuals of Slavic ancestry and in ~70% of alleles in individuals of North American ancestry.
PALB2 **–** Fanconi anemia complementation group N (FANCN)	Fanconi anemia is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and an increased lifetime risk of cancer. Bone marrow failure with pancytopenia often presents in the first decade of life. Pathogenic variants in *PALB2* are associated with solid tumors, such as medulloblastomas and Wilms tumors.
RAD51C **–** Fanconi anemia complementation group O	Fanconi anemia is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure, and a high predisposition to cancer. Bone marrow failure with pancytopenia often presents in the first decade of life.

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NCCN Guidelines Version 1.2022
BRCA-Pathogenic/Likely Pathogenic Variant - Positive Management

NCCN Guidelines Index
Table of Contents
Discussion

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

GENERAL

- **Education regarding signs and symptoms of cancer(s), especially those associated with *BRCA* gene pathogenic/likely pathogenic variants.**

BREAST CANCER

- **Female**
  - **Breast awareness[a] starting at age 18 years.**
  - **Clinical breast exam, every 6–12 months,[b] starting at age 25 years.**
  - **Breast screening[c,d]**
    - ◊ **Age 25–29 years, annual breast MRI[e] screening with contrast[f] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.**
    - ◊ **Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI[e] screening with contrast.**
    - ◊ **Age >75 years, management should be considered on an individual basis.**
    - ◊ **For individuals 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.**
  - **Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.**
- **Consider risk reduction agents as options for breast cancer, including discussion of risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).**
- **Male**
  - **Breast self-exam training and education starting at age 35 years.**
  - **Clinical breast exam, every 12 months, starting at age 35 years.**
  - **Consider annual mammogram screening in men with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family (whichever comes first).[g]**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[a] Females 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 individuals may find BSE most informative when performed at the end of menses.

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

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

[d] Lehman CD, et al. 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 patients. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue.

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

[g] There are only limited data to support screening for male breast cancer. Gao Y, et al Radiology 2019;293:282-291.

Continued

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

OVARIAN/UTERINE CANCER

- **Recommend risk-reducing salpingo-oophorectomy (RRSO),[h] typically between 35 and 40 years, and upon completion of childbearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.**
  - **Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, hormone replacement therapy, and related medical issues.**
  - **Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that individuals are still at risk for developing ovarian cancer. In addition, in premenopausal individuals, 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 individuals 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 individuals with a *BRCA1* pathogenic/likely pathogenic variant prior to surgery.**
- **Individuals who undergo hysterectomy at the time of RRSO are candidates for estrogen-alone hormone replacement therapy, which is associated with a decreased risk of breast cancer compared to combined estrogen and progesterone, which is required when the uterus is left in situ (Chlebowski R, et al. JAMA Oncol 2015;1:296-305).**
- **Address psychosocial and quality-of-life aspects of undergoing RRSO.**
- **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 ovarian cancer, including discussion of risks and benefits (See Discussion for details).**

[h] 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.

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BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

PANCREATIC CANCER
- For pancreatic cancer screening recommendations, see PANC-A.

PROSTATE CANCER
- Starting at age 40 years: (See Guidelines for Prostate Cancer Early Detection)
  - Recommend prostate cancer screening for *BRCA2* carriers.
  - Consider prostate cancer screening for *BRCA1* carriers.

MELANOMA
- 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.

RISK TO RELATIVES
- Principles of Cancer Risk Assessment and Counseling (EVAL-A)

REPRODUCTIVE OPTIONS
- Principles of Cancer Risk Assessment and Counseling (EVAL-A)

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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,[a] 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] One study[a] 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 in high-risk individuals undergoing pancreatic cancer screening.**

[a] Canto MI, et al. Gastroenterology 2018;155:740-751.
[b] Vasen H, et al. J Clin Oncol 2016;34:2010-2019.
[c] Canto MI, 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. 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 benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.**
- **Consider screening using annual contrast-enhanced MRI/MRCP and/or EUS, with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have potentially concerning 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, 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 (female)

- **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 individuals 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 or gastric cancer in the family, respectively.**
- **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.**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[a] Females should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal individuals 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 individuals.

[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. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue.

[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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Continued

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

- Principles of Cancer Risk Assessment and Counseling (EVAL-A).

RISK TO RELATIVES

- Principles of Cancer Risk Assessment and Counseling (EVAL-A).

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.[i] 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.[j]

[h] For additional information on the management of children with LFS, see Kratz C, et al. Clin Cancer Res 2017;23:e38-e45.
[i] Jaiswal S, et al. N Engl J Med 2014;371:2488-2498; Genovese G, et al. N Engl J Med 2014;371:2477-2487.
[j] Weitzel J, et al. Genet Med 2018;20:809-816.

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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.

Continued

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COWDEN SYNDROME/PHTS MANAGEMENT

GENERAL

- **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.**
- **Education regarding the signs and symptoms of cancer.**

BREAST CANCER (female)

- **Breast awareness[b] starting at age 18 years.**
- **Clinical breast exam, every 6–12 months, starting at age 25 years or 5–10 years 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 35 years or 10 years before the earliest known breast cancer in the family (whichever comes first).[c,d]**
  - **Age >75 years, management should be considered on an individual basis.**
  - **For individuals 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 individuals with pathogenic/likely pathogenic variants identified. For those with clinical CS/PTHS 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.**
- **Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.**

COLON

- **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.**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[b] Females should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal individuals 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 females. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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.

COWDEN SYNDROME/PHTS MANAGEMENT

ENDOMETRIAL CANCER

- For endometrial cancer screening,[e] consider starting by age 35 years.
  - 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, individuals 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 individuals 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 individuals 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 individuals 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 hysterectomy.

KIDNEY

- Consider renal ultrasound starting at age 40 y, then every 1–2 y.

NEUROLOGIC

- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.

SKIN

- There may be an increased risk of melanoma, and the prevalence of other skin characteristics with CS/PTHS may independently make routine dermatology evaluations of value. Annual dermatology exams are recommended.

THYROID

- Annual thyroid ultrasound starting at age 7 y. This may also be considered for children at 50% risk of inheriting a known mutation whose parents wish to delay genetic testing until age 18 y.

RISK TO RELATIVES

- Principles of Cancer Risk Assessment and Counseling (EVAL-A).

REPRODUCTIVE OPTIONS

- Principles of Cancer Risk Assessment and Counseling (EVAL-A).

[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.

Note: All recommendations are category 2A unless otherwise indicated.
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.

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.

Note: All recommendations are category 2A unless otherwise indicated.
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.

Discussion

This discussion corresponds to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Last updated: November 20, 2020.

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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 U.S. Preventive Services Task Force (USPSTF).[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, ovarian, and pancreatic 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, Ovarian, and Pancreatic 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, ovarian cancer, and pancreatic 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, ovarian, and pancreatic cancer. The current NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic focus primarily on assessment of pathogenic or likely pathogenic variants associated with increased risk of breast and ovarian cancer, particularly *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. Recommendations regarding pathogenic or likely pathogenic variants associated with pancreatic cancer, and pancreas screening for individuals harboring such variants, has been added to the Guidelines in the 2020 update.

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 Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, an electronic search of the PubMed database was performed to obtain key literature 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 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: 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

Cancer genetic risk assessment and genetic counseling is a multi-step process involving the identification and counseling of individuals at risk for familial or hereditary cancer. The purpose of cancer genetic counseling is to educate individuals about the genetic, biological, and environmental factors related to a cancer diagnosis and/or risk for disease to help derive personal meaning from cancer genetic information, and to empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. Many patients undergoing genetic testing do not receive proper counseling.[14] Further, testing rates are inadequate among some high-risk populations, such as members of racial/ethnic minority groups.[15,16] A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved in every stage of the process.[9]

Testing should be considered in individuals for whom there is a personal or family history suggesting genetic cancer susceptibility and for whom results will aid in risk management and treatment. 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. Genetic risk assessment is a dynamic process and can change if additional relatives are diagnosed with cancer. 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. However, if there is reason to suspect more than one pathogenic or likely pathogenic variant in the family, then broader testing may be considered.

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. 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. This may include the relative closest to the family member with the youngest age at diagnosis, bilateral disease, multiple primary tumors, or other cancers associated with a suspected hereditary syndrome. A negative test result in such cases, however, is considered indeterminate 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 since absence of a mutation in one unaffected relative does not rule out a mutation in others. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer. "Limited" family structure is defined as ≤2 first- or second-degree female relatives who survive past age 45 (on either side of the family) and/or possessing no or inadequate information about one's birth parents.[17]

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; however, a study has reported that over time, buccal epithelial cells are replaced by donor-derived cells in allogeneic HSCT recipients.[18,19] Therefore, genetic testing using buccal swab samples may be limited given this known risk of donor DNA contamination. Fibroblasts are also indicated when testing individuals with active or recent hematologic malignancies.[20]

A counseling dilemma is posed by the finding of a variant of unknown significance (VUS), a genetic alteration that may actually represent a benign polymorphism unrelated to an increased cancer risk or may indicate an increased cancer risk. 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.[21-23] Family members should not be tested for a VUS for the purposes of clinical management unless there are conflicting data between laboratories regarding the classification of a variant. In the event where there are discrepancies in classification, careful consideration must be taken regarding family history, testing family members, and if other functional studies could aid in variant classification. Clinicians and scientists should work together to develop a VUS classification system as more information is discovered in research studies.[24] Carriers of a VUS or likely benign variant should be managed based on family history of cancer.

Carriers of a pathogenic or likely pathogenic variant should be encouraged to participate in clinical trials or genetic registries. Carriers should be encouraged to recontact their genetics providers every few years for updates, as laboratories may issue amended reports as the knowledge base surrounding hereditary cancer risk expands.

Evaluating the Source of Genetic Testing Information

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. 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 analysis that includes gross deletion or duplication analysis. Third-party services are available to assist patients with interpreting their raw data, but these services are not government-regulated. In addition to the errors inherent in working with raw uncurated data from DTC labs, other limitations of these services include inadequate informed consent process, uncertain clinical validity and utility, and lack of medical oversight.[25] 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.[26] 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.[26]

Tumor profiling can be considered complementary to germline testing. However, the absence of a pathogenic or likely pathogenic variant for a given gene from tumor profiling does not rule out the possibility of a germline pathogenic or likely pathogenic variant in that gene. Tumor testing tends to be designed to address treatment actionability and prognosis.[27] Therefore, a variant interpreted as pathogenic or likely pathogenic in the germline may be interpreted as normal or as a VUS in the tumor, if that variant has no clear clinical implications. In addition, the sensitivity of most tumor testing is lower (particularly for intermediate-sized deletions and duplications) than that for most dedicated germline tests, sometimes due to filtering out of germline findings reported in tumor sequencing results. If a patient meets testing criteria for germline testing for a given gene, then confirmatory germline testing should be considered through a CLIA-approved lab despite tumor profiling results. Circulating tumor DNA (ctDNA) assays may be used by some labs. ctDNA has the potential to identify both somatic and germline variants.[28] However, since the primary intent of tumor testing is to inform treatment decision-making, ctDNA assays are not validated for reporting or interpretation of germline variants. If a germline variant that could impact medical management is detected with a ctDNA assay, then confirmatory testing with a CLIA-

approved assay intended for detection and interpretation of germline results is recommended.

Incidental germline findings discovered through other sources (eg, participation in a research study) should be reviewed by a genetics professional.[29] Confirmatory testing in these cases may be recommended, especially if the reporting laboratory is not appropriately certified.

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 can detect pathogenic or likely pathogenic variants not found in single-gene testing.[30-32] Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. In these cases, phenotype-directed testing based on personal and family history through a multi-gene panel test may be more efficient and/or cost-effective.[33-35] Multi-gene testing may also be considered for those who tested negative for one particular syndrome, but whose personal and family history is suggestive of an inherited susceptibility.[33,36] It is has become routine practice at many institutions to now order phenotypically directed multi-gene panel tests to assess for pathogenic changes in multiple relevant genes simultaneously.[37]

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, laboratory expertise, variant reclassification protocol, methods of DNA/RNA analysis, and availability of financial assistance for cascade testing of relatives, among others. Therefore, the specific laboratory and multi-gene test should be chosen carefully.[33] In addition, pathogenic or likely pathogenic variants identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.[36] A management plan based on genetic test results should only be developed for identified pathogenic or likely pathogenic variants that are clinically actionable.

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, and how to communicate and manage risk for carriers of these genes.[38-42] This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.[38] Multi-gene tests often include low to moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management.[16,33,43] 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.[44-47]

Multi-gene tests also increase the likelihood of detecting a VUS.[31-33,39,48-50] However, as multi-gene testing is increasingly used, the frequency of a variant being interpreted as a VUS is expected to decrease. There is also an increase in the chance of finding genotypically distinct cell lines (ie, genetic mosaicism) with next-generation sequencing.[51] Clones of non-cancerous cells (ie, aberrant clonal expansion) containing a pathogenic *TP53* variant have been found in healthy adults undergoing multi-gene testing. This phenomenon can often be attributed to clonal hematopoiesis, a condition in which a hematopoietic stem cell begins making blood cells with the same acquired mutation.[20] When there is no evidence of a hematologic malignancy, then it is referred to as clonal hematopoiesis of indeterminate potential (CHIP). Age-related CHIP is associated with increased risk of hematologic malignancies,[52,53] but may also lead to

unnecessary clinical intervention. Ancillary testing of non-lymphoid non-cancerous tissue can be used to help determine the true presence of a germline variant.[20]

Polygenic risk scores (PRS) are now sometimes included in some genetic test reports. PRS are groups of SNPs associated with a specific disorder or disease, such as hereditary cancer. Some studies evaluating the validity of PRS for identifying those at risk of hereditary cancer to date have been conducted, primarily with breast and prostate cancers. Two studies identified PRS that were strongly associated with ER-negative breast cancer in *BRCA1* mutation carriers, overall breast cancer in *BRCA2* mutation carriers, and high-grade serous ovarian cancer in mutation carriers of both *BRCA1* and *BRCA2* pathogenic variants.[54,55] Another study of male carriers of a *BRCA1/2* pathogenic variant identified PRS associated with breast cancer risk and prostate cancer risk .[56] Studies have also evaluated the potential clinical utility of incorporating PRS into a risk-stratified approach for screening for prostate cancer[57] and for identifying age of onset of aggressive prostate cancer.[58] Studies of PRS have largely been done with those of European ancestry.[59] Studies with larger samples from more diverse populations are needed. Given the lack of validation of PRS, these should not be used to inform medical management at this time.

Pre- and Post-Test Counseling

For individuals potentially meeting established criteria for one or more of the hereditary cancer syndromes, genetic testing should be considered along with appropriate pre- and post-test counseling. 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 Table 2), the likelihood of a positive result, technical aspects and accuracy of the test, cost considerations, risks of genetic discrimination, psychosocial aspects, confidentiality issues, the potential significance of the test results for family members, and other topics.[7] A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act (GINA) enacted in 2008, which prohibits most health insurers and employers from discrimination on the basis of genetic test results.[60] Since some patients with cancer who have a poor prognosis may be unable to receive results directly, a plan for results disclosure should be discussed, such as the patient consenting to Release of Information of test results to a spouse or other close relative. A detailed family history should be collected, which involves development of an expanded pedigree, 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. 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 or divorce).[5,61] 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. Finally, a detailed medical and surgical history from the proband should be collected, and a physical examination should be performed by a qualified clinician when appropriate.

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.[62,63] Telehealth (ie, real-time two-way videoconference) is also increasingly utilized as a feasible alternative for in-person genetic counseling.[63] Remote options (telephone, telehealth) have the potential to help improve genetic testing rates in areas with inadequate access.[63]

Post-test counseling includes disclosure of results, a discussion of the associated medical risks, 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 screened for cancer risk.[9] Counseling should include making the individual aware of any available resources, such as disease-specific support groups, high-risk clinics, advocacy groups, and research studies.[64] The counselor should discuss the importance of 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), the proband should be advised regarding possible inherited cancer risk to relatives and his/her options for risk assessment and management. Testing of a partner of a carrier of a pathogenic or likely pathogenic variant may also be considered to inform reproductive decision-making.[65] See Table 3 for a list of pathogenic/likely pathogenic variants associated with autosomal recessive conditions.

Pre- and post-test genetic counseling with involvement of an expert in cancer genetics is recognized as the gold standard. However, during the meeting for the 2020 update, the panel acknowledged that most genetic testing is conducted by providers with limited expertise in genetics and often without pre-test genetic counseling.[66-68] Shortages in genetics health providers,[69] expansion of testing indications, aggressive marketing, and increased accessibility of testing due to plummeting costs inclusive of DTC models for testing provide the impetus for the panel to identify scenarios in which referral to a genetics health provider should be considered. These scenarios are as follows: identification of a pathogenic or likely pathogenic variant; negative results despite family history suggestive of inherited disease; VUS result for which provider considers altering clinical management; mosaic or possibly mosaic result; discrepant interpretation of variants (eg, discordant results across laboratories); interpretation of PRS; and, detection of pathogenic or likely pathogenic variants from DTC testing.

The full list of elements that should be included in pre- and post-test genetic counseling can be found in the *Principles of Cancer Risk Assessment and Counseling* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org).

High-Penetrance Breast and/or Ovarian Cancer Susceptibility Genes

Specific patterns of hereditary breast and ovarian cancers have been found to be linked to pathogenic or likely pathogenic variants in the *BRCA1/2* genes.[70,71] 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.[72,73] These hereditary syndromes share several features beyond elevation of breast cancer risk. These syndromes arise from germline pathogenic or likely pathogenic variants that are not within sex-linked genes; hence, the variants can be inherited from either parent. The syndromes are associated with breast cancer onset at an early age and development of other types of cancer, and exhibit an autosomal dominant inheritance pattern (see Table 1). Offspring of an individual with one of

these hereditary syndromes have a 50% chance of inheriting the pathogenic or likely pathogenic variant. In addition, individuals with these hereditary syndromes share increased risks for multiple cases of early-onset disease as well as bilateral disease. The pathogenic or likely pathogenic variants associated with these hereditary syndromes are considered to be highly penetrant. In addition, the manifestations (ie, expression) of these hereditary syndromes are often variable in individuals within a single family (eg, age of onset, tumor site, number of primary tumors). The risk of developing cancer in individuals with one of these hereditary syndromes depends on numerous variables including the gender and age of the individual.

Prior to 2020, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian (Breast, Ovarian, and Pancreatic as of 2020) focused largely on testing criteria for *BRCA1/2* and appropriate risk management for carriers of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant. There is now strong evidence that genes beyond *BRCA1/2* confer markedly increased risk of breast and/or ovarian cancers; see the sections below on other pathogenic/likely pathogenic variants associated with breast/ovarian cancer, LFS, and Cowden syndrome/*PTEN* hamartoma tumor syndrome.

BRCA-Related Breast/Ovarian Cancer Syndrome

Both the *BRCA1* and *BRCA2* genes encode for proteins involved in tumor suppression. *BRCA1/2* pathogenic or likely pathogenic variants can be highly penetrant (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.[74-76] 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.

Breast Cancer Risk

Estimates of penetrance range from a 41% to 90% lifetime risk for breast cancer, with an increased risk for contralateral breast cancer.[77-85] 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.[86] 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.[86] A systematic review including 68 papers showed that *BRCA1* (relative risk [RR], 3.7; 95% CI, 2.8–4.9) and *BRCA2* (RR, 2.8; 95% CI, 1.8–4.3) mutations are associated with development of contralateral breast cancer.[87]

The evidence that a *BRCA1/2* mutation is associated with poor survival outcomes for breast cancer has been inconsistent.[88,89] 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.[90] 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).[91] *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 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.[92]

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.[93] 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).[94] *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.[95] 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.[96]

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").[85,97-102] Studies have reported *BRCA1* mutations in 7% to 28% of patients with triple-negative breast cancer.[85,102-111] The incidence of *BRCA2* mutations range from 1% to 17% in studies of triple-negative breast cancer cases unselected for age or family history.[85,103,108,109,111,112] One cohort study showed that hormone receptor-positive disease (ER+ and/or PR+) is associated with *BRCA2* pathogenic or likely pathogenic variants, with an absolute lifetime risk of 40% in *BRCA2* mutation carriers.[85] A case-control study showed that the 20-year survival rate in *BRCA2* mutation carriers with ER-positive tumors was 62.2%, compared to 83.7% in those with ER-negative tumors, though this difference was only statistically significant in those younger than age 50 (n = 199; 68.3% vs. 91.3%, respectively; *P* = .03).[113] A case-control study of carriers of the Icelandic founder *BRCA2* mutation 999del5 showed that ER-positive disease was associated with increased mortality risk, compared to those with ER-negative disease (HR, 1.94; 95% CI, 1.22–3.07; *P* = .005).[114] However, prevalence of ER-negative disease was not significantly greater in *BRCA2* mutation carriers than in non-carriers (75.6% vs. 70.2%, respectively; *P* = .11).

Among patients with triple-negative disease, *BRCA* mutation carriers were diagnosed at a younger age compared with non-carriers.[105,115] 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.[104] 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).

Male carriers of a *BRCA1/2* mutation also have a greater risk for cancer susceptibility.[116] Among male patients with breast cancer unselected for family history, 4% to 14% tested positive for a germline *BRCA2* mutation.[117-120] For males with a *BRCA2* mutation, the cumulative lifetime

risk for breast cancer has been estimated at 7% to 8%.[121,122] The cumulative lifetime risk for *BRCA1* mutation carriers is 1.2%.[122] 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).[119,123]

Ovarian Cancer Risk

Increased risks for cancers of the ovary, fallopian tube, and peritoneum are observed in carriers of *BRCA1/2* mutations.[124-126] Germline mutations in *BRCA1/2* are responsible for at least 10% of epithelial ovarian cancers.[127,128] An analysis of 2222 patients with epithelial ovarian cancer showed that 11% carried a *BRCA1/2* mutation when disease was high-grade serous.[129] In the setting of an invasive ovarian cancer diagnosis, as many as 13% to 20% of women have a germline *BRCA1/2* mutation.[83,130-132] *BRCA1/2* carriers have an estimated 8% to 62% lifetime risk for ovarian cancer, depending on the population studied.[78 54 54 54 54 54 54 54 54,79-83,133,134] 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.[86]

Several studies have reported more favorable survival outcomes among *BRCA1/2* mutation carrier patients with ovarian cancer compared with non-carrier patients.[135-141] Survival outcomes appear to be most favorable for *BRCA2* mutation carriers.[128,135,140] 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.[140]

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.[126,127,131,142-144] Mutations are also associated with non-mucinous ovarian carcinoma as opposed to mucinous.[130,132] Mucinous epithelial ovarian carcinomas may be associated with other gene mutations, such as *TP53* mutations,[145] which 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,[146] but they may be associated with other cancer genetic syndromes. For example, sex cord tumors may be associated with Peutz-Jeghers syndrome (PJS; see below), while Sertoli-Leydig tumors are associated with both PJS and DICER1-related disorders.[147-152] Current data show that ovarian low malignant potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with a *BRCA1/2* mutation.[130]

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 examinations of the ovaries and fallopian tubes.[153-155] 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.[153,156,157] 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.[153,157,158] Although TIC appeared to present more frequently among *BRCA1/2* mutation carriers compared with non-carriers undergoing RRSO,[157,158] TIC has also been documented among patients with serous carcinomas unselected for family history or *BRCA* mutation status.[159] 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.

Prostate Cancer Risk

Germline *BRCA1/2* mutations are associated with increased risk for prostate cancer,[160-163] with this association being strongest for advanced or metastatic prostate cancer.[164-167] 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.[168] 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.[166] In addition, analyses from a treatment center database showed that *BRCA1/2* and *ATM* (see below under *NCCN Genetic Testing Criteria: Testing Criteria Related to Prostate 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; $P < .001$).[165] 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%.[160,169-172]

Pancreatic Cancer Risk

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*.[173-181] However, some of these studies included only patients with familial pancreatic cancer[176,177,180] or those of Ashkenazi Jewish ancestry,[178] 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*).[182-186] Patients with pancreatic cancer and Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, with mutations being more common for *BRCA2*.[178,179,181,187]

More information on genes associated with pancreatic cancer can be found below, under *Hereditary Pancreatic Cancer*.

Other Cancer Risks

Some studies have suggested an increased risk specifically of serous uterine cancer in *BRCA* mutation carriers.[188-191] 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.[192] 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.[193,194] A meta-analysis including five studies of patients with uterine serous cancer and Ashkenazi Jewish ancestry showed that *BRCA1/2* pathogenic/likely pathogenic variant prevalence was greater in women with uterine serous cancer than in controls (also of Ashkenazi Jewish ancestry) (OR, 5.4; 95% CI, 2.2–13.1).[188] In a retrospective case control study including 2627 Jewish Israeli women (88% Ashkenazi Jewish) who were *BRCA1/2* mutation carriers, risk of developing uterine cancer was increased, with an observed-to-expected ratio of 3.98 (95% CI, 2.17–6.67; $P < .001$).[191] This association persisted regardless of uterine cancer histology.

A meta-analysis including 14 studies showed that *BRCA1* is associated with increased risk of colorectal cancer (OR, 1.49; 95% CI, 1.19–1.85; $P < .001$), but *BRCA2* is not (OR, 1.10; 95% CI, 0.77–1.58; $P = .61$).[195] Studies that investigated associations between *BRCA2* mutation and cutaneous melanoma have drawn inconsistent conclusions, though there is some

evidence of an association.[196] 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).[197] Finally, 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).[198]

Risk Management

Recommendations for the medical management of *BRCA*-related breast/ovarian cancer syndrome are based on an appreciation of the early onset of disease, the increased risk for ovarian cancer, and the risk for male breast cancer in *BRCA1/2* carriers. 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.[199] 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.[199-203] 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.[204] 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,[205-208] 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.[205,209] 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%).[199-201,210-212] The sensitivity with ultrasound screening (33%–65%) appeared similar to that of mammography in this high-risk population.[199,210-212] 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).[213] Factors such as age, mutation type, or invasiveness of the tumor did not significantly influence the relative sensitivity of the two screening modalities. Importantly, the large majority (97%) of cancers detected by MRI screening were early-stage tumors.[213] 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%.[214]

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%).[215] 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).[216] 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.[216]

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,[217,218] a report from a large cohort study suggested an increased risk in women exposed to radiation at a young age.[219] 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).[219] 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.[220-229] 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.[221,230,231] 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.[232] 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.[202]

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) 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.[233]

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.[234,235] 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).[236] 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.[237] 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. Data to support breast screening in men are limited. A 12-year longitudinal observational study evaluated the outcomes of mammography screening in 1869 men who were at increased risk of developing breast cancer (ie, personal or family history of breast cancer and/or germline genetic mutation associated with breast cancer, mostly *BRCA1* and *BRCA2*).[238] Node-negative breast cancer was identified in five men (18 per 1000 examinations), which is greater than the cancer detection rates in both average-risk and high-risk women who undergo breast screening. Harboring a genetic mutation (n = 47) was associated with breast cancer (OR, 7; 95% CI, 2–29; *P* = .006). Annual mammogram screening in men

with gynecomastia may be considered, beginning at age 50 or 10 years before the earliest known breast cancer in the family (whichever comes first).

Screening for prostate cancer starting at 40 years of age should be recommended for *BRCA2* carriers and considered for *BRCA1* carriers.[163] 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, general melanoma risk management is indicated, such as annual full body skin exam and minimizing UV exposure. There are no specific screening guidelines for melanoma, though more information can be found at the website for the Skin Cancer Foundation (www.skincancer.org). Information on pancreas screening can be found below under *Hereditary Pancreatic Cancer.*

Risk Reduction Surgery

Bilateral Total Mastectomy

Two meta-analyses show that prophylactic bilateral mastectomy reduces the risk for breast cancer.[239,240] Only one of these analyses showed that risk-reducing surgery is significantly associated with reduced mortality.[240] Retrospective studies and small prospective studies provide support for concluding that RRM provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation.[241-244]

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,[79] 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.[245] RRM is also associated with physical symptoms, such as lower sensitivity to touch, pain, tingling, infection, edema, bruising, and thrombosis.[240] 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.[246] 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,[247] 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).[124,125] Although the risk for ovarian cancer is generally considered to be lower than the risk for breast cancer in a *BRCA1/2* mutation carrier,[77,78,248] 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.[249] 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.[249] 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.[250] 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, 0.04–0.56; *P* = .005).[251] 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).[249] 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.[249]

A 1% to 4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.[154,250,252-255] 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.[256] 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.[192]

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.[257] Presence of a *BRCA1/2* mutation was associated with detection of clinically occult neoplasms during RRSO (*P* = .006).

In early studies, RRSO was reported to reduce the risk for breast cancer in carriers of a *BRCA1/2* mutation.[239,250,254,255,258,259] 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) were reported following RRSO in carriers of a *BRCA1* and a *BRCA2* mutation, respectively.[258] HRs of 0.47 (95% CI, 0.29–0.77)[255] and 0.30 (95% CI, 0.11–0.84; *P* = .022)[253] 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 were further supported by a meta-analysis that found similar reductions in breast cancer risk of approximately 50% for *BRCA1/2* mutation carriers following RRSO.[250]

Results of a prospective cohort study suggested that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA2* mutation carriers compared with *BRCA1* mutation carriers.[251] 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).[260]

The reduction in breast cancer risk following RRSO was questioned in a prospective cohort study from the Netherlands (N = 822), which did not find a statistically significant difference in breast cancer incidence between *BRCA1/2* mutation carriers who opted for an RRSO and women who did not, regardless of whether the mutation was for *BRCA1* or *BRCA2*.[261] Study investigators argued that previous study findings showing a 50% decrease in breast cancer risk may have been influenced by bias, specifically inclusion of patients with a history of breast or ovarian cancer in the comparison group and immortal person-time bias. One study that corrected for immortal person-time bias as a result of this analysis continued to find a protective effect of RRSO on breast cancer incidence in *BRCA1/2* mutation carriers (HR, 0.59; 95% CI, 0.42–0.82, *P* < .001).[262] Another prospective cohort analysis including 1,289 *BRCA1/2* carriers unaffected with breast cancer (196 eventually being diagnosed) also showed that, when RRSO was treated as a time-dependent variable, it was no longer associated with breast cancer risk.[263] A meta-analysis including 19 studies of the association between RRSO and breast cancer risk and mortality showed a protective effect in studies published earlier than 2016, but not in studies published in 2016 or later (*n* = 3).[259]

Results from one of the earlier studies showed that 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).[258] 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.[258] However, results from another early study also suggested that RRSO after 50 years of age is not associated with a substantial decrease in breast cancer risk.[254] 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).[264] 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).

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

Two systematic reviews showed that hormone replacement therapy (HRT) does not negate the reduction in breast cancer risk associated with the surgery.[265,266] One of these reviews showed that breast cancer risk tended to be lower in women who received estrogen only, compared to estrogen plus progesterone (OR, 0.62; 95% CI, 0.29–1.31).[265] Caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.[267,268]

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.[269] Despite some evidence regarding the safety and feasibility of this procedure,[269,270] more data are needed regarding its efficacy in reducing the risk for ovarian cancer.[233,271] 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.[188,189,192] Women who undergo hysterectomy at the time of RRSO are candidates for estrogen-alone HRT, which is associated with a decreased risk of breast cancer, compared to combined estrogen and progesterone, which is required when the uterus is left in situ.[272] 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.[249] 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 tubes.[155,156] The protocol published by CAP (2009) can be consulted for details on specimen evaluation.[273] 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, especially ER-positive disease.[274-281] 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.[82] 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.[282] 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.[283,284] 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).[285] 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.[285] 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.[286] These gene variants were associated with alterations in breast cancer risk during treatment with selective estrogen receptor modulators, and may eventually pave the way for predicting the likelihood of benefit with these chemopreventive approaches in individual patients.

The aromatase inhibitors (AIs) exemestane and anastrozole have been demonstrated to be effective in preventing breast cancer in postmenopausal women considered to be high risk of developing breast cancer.[287,288] However, to date, there is little evidence supporting the use of AIs as an effective chemopreventive approach for individuals with a *BRCA1/2* pathogenic or likely pathogenic variant. A retrospective study showed that AIs may reduce the risk of contralateral breast cancer in women with a *BRCA1/2* pathogenic or likely pathogenic variant and ER-positive breast cancer who take AIs as adjuvant therapy, but these data are currently published in abstract form only.[289]

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 *BRCA1* mutation carriers and by 60% in *BRCA2* mutation carriers.[290,291] Moreover, risks appeared to decrease with longer duration of oral contraceptive use.[291] 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).[292] 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).[293]

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), with breast cancer risk in these carriers being associated with ≥5 years of oral contraceptive use (OR, 1.33; 95% CI, 1.11–1.60), breast cancer diagnosed before 40 years of age (OR, 1.38; 95% CI, 1.11–1.72), and use of oral contraceptives before 1975 (OR, 1.42; 95% CI, 1.17–1.75).[294] Oral contraceptive use was not significantly associated with breast cancer in *BRCA2* mutation carriers in this study. In another case-control study, use of oral contraceptives for at least 5 years was associated with a significantly increased risk for breast cancer in *BRCA2* mutation carriers (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.[295] Oral

contraceptive use for at least 1 year was not significantly associated with breast cancer risk in *BRCA1* or *BRCA2* mutation carriers in this study. In a third case-control study, the use of low-dose oral contraceptives for at least 1 year was associated with significantly decreased risks for breast cancer among *BRCA1* mutation carriers (OR, 0.22; 95% CI, 0.10–0.49; $P < .001$), though not for *BRCA2* mutation carriers.[296] Two meta-analyses[292,293] and another case-control study[297] showed that oral contraceptive use is not significantly associated with breast cancer risk in *BRCA1/2* mutation carriers.

Differences in the study design employed by these case-control studies make it difficult to compare outcomes between studies, and likely account for the conflicting results. The design of these studies might have differed with regard to factors such as the criteria for defining the "control" population for the study (eg, non-*BRCA1/2* 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. Larger prospective trials are needed to elucidate the impact of oral contraceptives on breast cancer risk in carriers of a *BRCA1/2* pathogenic or likely pathogenic variant.

Reproductive Options

The outcomes of genetic testing can have a profound impact on family planning decisions for individuals of reproductive age who are found to be carriers of a *BRCA1/2* pathogenic or likely pathogenic variant. Counseling for reproductive options such as prenatal diagnosis and assisted reproduction using preimplantation genetic diagnosis (PGD) 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 pregnancy.[298,299] 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,[298,299] 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.[298,299] 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.[65] Some case reports have also identified biallelic *BRCA1* mutations causing Fanconi anemia-like disorder.[300-302] 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. Successful births have been reported with the use of PGD and IVF in *BRCA1/2* mutation carriers,[303,304] 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.

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

Prior to 2020, the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic focused largely on testing criteria for *BRCA1/2* and appropriate risk management for carriers of a *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant. There is now strong evidence that genes beyond *BRCA1/2* confer markedly increased risk of breast and/or ovarian cancers. These genes include *ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, RAD51C, RAD51D, STK11,* and *TP53.* Pathogenic or likely pathogenic variants associated with Lynch syndrome and neurofibromatosis type 1 (NF1) are also associated with breast and/or ovarian cancers. The panel's recommendations for cancer risk management intervention for carriers of pathogenic variants associated with breast and/or ovarian cancer risk are based on absolute lifetime risk estimates. Cancer risk management intervention may be recommended when a carrier's absolute risk exceeds that of the average-risk population (ie, 12%–13% for breast cancer and 1%–2% for ovarian cancer, based on SEER registry data[305,306]).[41,307] Quality of the evidence supporting risk estimates should also be evaluated when determining appropriate risk management for carriers of a pathogenic or likely pathogenic variant. For example, prospective cohort studies in a population-based setting can be considered very strong evidence, while limited conclusions can be drawn from case series or studies with small samples.[307]

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.[41] 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.[41] 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,[41] though this option may be considered and discussed in the presence of a family history of breast cancer.

Discussion of RRSO may be considered when risk of developing ovarian cancer exceeds that of the average-risk population (ie, a threshold of about 3%). The decision to carry out RRSO should not be made lightly, given the impact of premature menopause.[41] RRSO is the standard of care for ovarian cancer risk management in carriers of a pathogenic or likely pathogenic variant in an ovarian cancer susceptibility gene. However, some women may choose to not receive an RRSO. TVUS and

serum CA-125 may be considered for these women at the clinician's discretion, though the benefit of these screening methods is unknown (see *BRCA-Related Breast/Ovarian Cancer Syndrome: Risk Management,* above).

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: *FANCC*, *MRE11A*, *MUTYH* heterozygotes, *RECQL4*, *RAD50*, *RINT1, SLX4, SMARCA4*, and *XRCC2*. Risk management recommendations for these 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.[308]

Information regarding testing criteria and risk management for LFS (associated with germline *TP53* pathogenic or likely pathogenic variant) and Cowden syndrome/*PTEN* hamartoma tumor syndrome (associated with germline *PTEN* pathogenic or likely pathogenic variant) can be found in their respective sections, below.

ATM

Pathogenic or likely pathogenic variantss 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.[309] 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; $P < .001$).[310] Other analyses of patients with breast cancer showed that about 1% had an *ATM* mutation.[85,109,311-314] 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.[315]

The association between specific types of *ATM* genetic variants and breast cancer susceptibility is less clear,[44-47] with some evidence showing that certain missense mutations may act in a dominant-negative fashion to increase cancer risk, relative to truncating mutations.[44,45] 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.[316] 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; $P = .001$).[317] 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; $P < .001$).[318]

The panel recommends annual mammogram for carriers with a pathogenic or likely pathogenic *ATM* variant beginning at 40 years of age, with consideration of annual breast MRI. There are no data on the benefit of risk-reducing mastectomy for carriers of a pathogenic *ATM* variant,[41] but this procedure may be considered based on family history. 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.[319] However, a meta-analysis including five studies showed that radiation therapy (with conventional dosing) is not contraindicated in patients with a heterozygous *ATM* mutation.[316] Therefore, radiation therapy does not need to be avoided in these carriers who are diagnosed with cancer.

Large studies of patients with ovarian cancer have shown that there may be a slightly increased risk for ovarian cancer in carriers of an *ATM* mutation,[128,312,320,321] but there is currently insufficient evidence to recommend RRSO in these carriers.[307] 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 cancer (see *Hereditary Pancreatic Cancer*, below).[183,322]

BARD1

A modest association between breast cancer and mutations in the *BRCA1*-associated RING domain 1 (*BARD1*) gene has been found in case-control studies with a prevalence rate of 0.1% to 0.51% in patients with breast cancer.[85,311,312,323-325] Two studies showed that *BARD1* was prevalent in 0.67% to 0.90% of patients with triple-negative breast cancer.[85,111] The panel recommends annual mammogram for carriers of a pathogenic or likely pathogenic *BARD1* variant beginning at 40 years of age, with consideration of annual breast MRI. Risk-reducing mastectomy is not recommended in carriers of a *BARD1* mutation, but this procedure may be considered based on family history.

BRIP1

Panel testing of germline DNA in women with ovarian cancer has shown that the prevalence rate of mutations in the *BRCA1* interaction protein C-terminal helicase 1 gene (*BRIP1*), a Fanconi anemia gene, is about 1%.[128,312,320,321,326] 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; $P < .001$).[327] 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; $P < .001$).[328] 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),[327] though lifetime risk of developing ovarian cancer may also be as high as 12%.[307] 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.

Regarding breast cancer, a case-control study including 10,901 patients with triple-negative breast cancer showed that *BRIP1* was prevalent in 0.43% of cases.[111] The panel has determined that more evidence is needed to provide breast screening recommendations in these carriers. *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%.[329-332] Given the considerable risk for lobular breast cancer in carriers of 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. Alternatively, screening may begin 5 to 10 years earlier than the

youngest breast cancer diagnosis in the family. Risk-reducing mastectomy may be discussed with these carriers, depending on family history.

There is controversy over how best to manage gastric cancer risk in individuals harboring a *CDH1* pathogenic or likely pathogenic variant in the absence of a family history of gastric cancer. A small study found that more than half of the individuals with a *CDH1* pathogenic or likely pathogenic variant who lacked a family history of gastric cancer had early-stage signet ring cell adenocarcinoma identified at the time of risk-reducing gastrectomy.[333] 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. A report of two cases showed that *CDH1* pathogenic or likely pathogenic variant may also be associated with cleft lip with or without cleft palate.[334]

CHEK2

Another breast cancer susceptibility gene that has been identified is *CHEK2* (cell cycle checkpoint kinase 2). Panel testing of germline DNA in large samples of patients with breast cancer has shown that the prevalence rate of a *CHEK2* pathogenic or likely pathogenic variant is about 1% to 2%.[311-314,321] Deleterious *CHEK2* mutations have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America.[308,335-337] 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.[338,339] The estimated RR for breast cancer, based on data from two large case-control studies, was 3.0 (90% CI, 2.6–3.5).[310]

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).[340] 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; $P < .001$).[341] 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; $P = 0.12$).[342] 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; $P < .001$).[343]

The panel recommends annual mammogram for carriers of a pathogenic or likely pathogenic *CHEK2* variant beginning at 40 years of age, with consideration of annual breast MRI. There are no data on the benefit of risk-reducing mastectomy for carriers of a pathogenic *CHEK2* variant, 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).[344-347] However, there is less evidence of increased risk for ovarian cancer in carriers of a pathogenic or likely pathogenic *PMS2* variant.[348-350] Total abdominal hysterectomy and/or bilateral salpingo-oophorectomy are options that may be considered for risk reduction in women who have completed childbearing and carry a mismatch repair gene linked to Lynch syndrome.[351-355] 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.[351,356-359] Routine TVUS and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific[351,356-360]; 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.[361,362] However, there is currently not enough evidence for the panel to recommend breast screening for individuals with Lynch syndrome beyond that which is recommended for the average-risk population.

Patients of reproductive age should be advised regarding their options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis. This discussion should include known risks, limitations, and benefits of these technologies. If both partners are a carrier of a mutation(s) in the same MMR gene or *EPCAM* (eg, if both partners carry a mutation in the *PMS2* gene), then they should also be advised about the risk for constitutional MMR deficiency (CMMRD) syndrome, a rare recessive syndrome.[363] More information regarding Lynch syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

NBN

The *NBN* gene is responsible for producing the protein nibrin. An association between the *NBN* gene and breast cancer risk has been suggested.[311,312,321,364] Two meta-analyses showed a significant association between the variant 657del5 and breast cancer risk, with ORs ranging from 2.42 to 2.66.[365,366] Given the limited evidence, the panel does not recommend breast cancer risk management for carriers of an *NBN* gene mutation beyond what is recommended for the general population, including carriers of a 657del5 pathogenic or likely pathogenic variant.

Some studies have shown a potential increase in ovarian cancer risk in carriers of an *NBN* gene mutation, with ORs ranging from 1.85 to 2.30.[128,312,367] A recent study including 6001 patients with ovarian cancer found an *NBN* gene mutation in 0.35%.[321] There is currently insufficient evidence to recommend RRSO in these carriers at this time. 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.[368-372] A population-based study in Finland of 1404 patients with NF1 showed an estimated lifetime cancer risk of 59.6%.[368] 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).[373]

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.[372,374] 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.[371] 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).[375] 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 carriers of *NF1* 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. Complications related to NF1 (eg, neurologic complications) may appear early in life, and these have the potential to be severe.[376] Therefore, referral to a neurofibromatosis specialist for management is recommended.[372]

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 0.4% to 3% harbor a pathogenic *PALB2* mutation.[85,108,311-314,321,323,377,378] A meta-analysis of three studies estimated an RR of 5.3 (90% CI, 3.0–9.4),[310] while an analysis including 764 families with a known pathogenic or likely pathogenic *PALB2* variant estimated an RR of 7.18 (95% CI, 5.82–8.85) for female breast cancer.[379] *PALB2* pathogenic or likely pathogenic variant is associated with a 33% to 53% lifetime risk of breast cancer.[85,379,380] The risk 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.[380] In a study of patients with breast cancer from Poland who underwent genetic testing, contralateral breast cancer was reported in 10% of *PALB2* carriers.[378] 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 women who are carriers of a *PALB2* pathogenic or likely pathogenic variant beginning at 30 years of age. Breast MRI screening may also be considered. Risk-reducing mastectomy for carriers of a *PALB2* pathogenic or likely pathogenic variant may be considered based on family history. Some studies suggest an association between *PALB2* and increased ovarian cancer risk,[128,367,379] so RRSO in carriers of these pathogenic or likely pathogenic variants may be considered after menopause or earlier if there is a family history of ovarian cancer. *PALB2* is associated with Fanconi anemia, inherited in an autosomal recessive manner.[381] 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 has shown that the prevalence rate of the *RAD51C* or *RAD51D* pathogenic or likely

pathogenic variant is about 1%.[128,312,320,326] 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; $P < .001$).[382] 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; $P < .011$).[383] 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.[384] A study including 6178 and 6690 families with a known pathogenic *RAD51C* and *RAD51D* variant, respectively, showed that the cumulative risk of developing ovarian cancer by age 80 was 11% for carriers of a *RAD51C* pathogenic variant and 13% for carriers of a *RAD51D* pathogenic variant.[385]

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, and 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.[307]

Regarding breast cancer, studies have shown prevalence rates of 0.23% to 0.45% for *RAD51C* and 0.29% to 0.38% for *RAD51D* in patients with triple-negative breast cancer.[108,111,386] Case-control analyses from a large study including 56,480 breast tumors showed that both *RAD51C* and *RAD51D* mutations ($n = 68$ and $n = 29$, respectively) were significantly associated with triple-negative disease (OR, 4.56, 95% CI, 2.61–7.50 for *RAD51C* and OR, 4.14, 95% CI, 1.80–7.04 for *RAD51D*).[85] The panel asserts that there is currently insufficient evidence to recommend breast cancer screening in carriers of these variants. *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.

STK11

Germline *STK11* pathogenic or likely pathogenic variants are associated with 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, such as Sertoli-Leydig tumors. 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.[387] There are no data on the benefit of risk-reducing mastectomy for carriers of *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. Absolute risk of developing ovarian cancer is 18% to 21%.[387,388] 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).

NCCN Genetic Testing Criteria

The testing criteria for high-penetrance breast and/or ovarian cancer are organized into three sections: 1) testing is clinically indicated; 2) testing may be considered; and 3) there is a low probability of testing results having documented clinical utility. The testing criteria listed are for breast and/or ovarian cancer susceptibility genes with strong or moderate evidence of actionability (ie, *BRCA1/2, CDH1,* and *PALB2*; testing criteria for Li-Fraumeni syndrome and Cowden syndrome continue to be contained in their own dedicated sections; see below). Included genes may change with emerging clinical data. Further, the personal and/or

family history criteria included may suggest the possibility of additional syndromes and would necessitate additional unlisted genes to be evaluated.

The NCCN Panel recommends that individuals from a family with a known pathogenic or likely pathogenic variant in a breast and/or ovarian cancer susceptibility gene be considered for testing. In individuals from a family without a known pathogenic or likely pathogenic variant, testing should be considered for those individuals who meet the testing criteria described in the *Testing Criteria for High-Penetrance Breast and Ovarian Cancer Susceptibility Genes* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org). Multi-gene testing may be considered for individuals who meet these criteria and who previously underwent single-gene and/or absent deletion duplication analysis but tested negative. Both first- and second-degree relatives of individuals who meet these testing criteria are also eligible for testing, except for second-degree relatives of individuals with pancreatic cancer or prostate cancer (metastatic, intraductal/cribriform, high- or very high-risk as defined in the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org), for whom prior probability of a high-penetrance cancer susceptibility gene is low in the absence of additional family history of cancer; only first-degree relatives of these affected individuals should be offered testing, unless indicated for other relatives based on additional family history.

Testing Criteria Related to Prostate Cancer

Approximately 11% of patients with prostate cancer and at least 1 additional primary cancer carry germline mutations associated with increased cancer risk.[389] As described above, germline *BRCA1/2* pathogenic and likely pathogenic variants are associated with increased risk for prostate cancer (see *BRCA-Related Breast/Ovarian Cancer Syndrome*, above).[160-163] *ATM* mutations have been found in patients with prostate cancer,[162,163,165,167,389] but there is currently insufficient evidence to recommend prostate screening for these cancers in carriers of an *ATM* pathogenic or likely pathogenic variant.[163] *HOXB13* mutations have also been found in 1.4% to 4.5% of men with prostate cancer.[162,389,390] Prostate tumors with intraductal or cribriform histology may be more likely to harbor somatic and/or germline MMR gene alterations than those with adenocarcinoma histology.[391,392] Intraductal histology specifically is common in germline *BRCA2* mutation carriers with prostate cancer.[393] By definition, intraductal carcinoma includes cribriform proliferation of malignant cells, as long as they remain confined to a preexisting gland that is surrounded by basal cells. These features are seen frequently with an adjacent invasive cribriform component and would be missed without the use of basal cell markers.

For the 2021 Guidelines update, the panel expanded testing criteria related to prostate cancer. Specifically, cribriform histology is now a testing criterion, and any patient in the high- or very high-risk stratification group as defined in the NCCN Guidelines for Prostate Cancer (available at www.NCCN.org) is eligible for testing without any additional testing criteria. References to high-grade (Gleason score ≥7) prostate cancer have been removed, and patients with any prostate cancer diagnosis (including very-low- and low-risk disease as defined in the NCCN Guidelines for Prostate Cancer, available at www.NCCN.org) meet testing criteria if additional family history criteria are met or if the patient is of Ashkenazi Jewish descent. A diagnosis of metastatic prostate cancer without additional personal or family history of cancer continues to be a testing criterion.

Systemic Therapy Decision-Making

Some of the NCCN treatment guidelines for *BRCA*-related cancers (Breast, Ovarian, Prostate, Pancreatic Adenocarcinoma; available at www.NCCN.org) now recommend treatment with PARP (poly ADP-ribose

polymerase) inhibitors for patients with germline or somatic *BRCA1/2* mutations, as PARP inhibitors have been demonstrated to be active in these patients. These agents include olaparib[394] and talazoparib[395] for HER2-negative metastatic breast cancer; niraparib,[396] olaparib,[397] and rucaparib[398] for chemotherapy-refractory ovarian cancer; olaparib[399] and rucaparib[400] for metastatic castration-resistant prostate cancer that has progressed following previous treatment; and olaparib as a maintenance therapy option for metastatic pancreatic cancer.[401] Even though the focus of these Guidelines continues to be on management of breast, ovarian, and/or pancreatic cancer risk in individuals with associated hereditary syndromes, the Guidelines now identify intent to aid in systemic therapy decision-making as a scenario in which germline testing is clinically indicated. If a mutation is detected through tumor profiling that has clinical implications if identified in the germline, then germline testing for this variant is indicated.

Ashkenazi Jewish Ancestry

The rate of the three founder pathogenic variants in those of Ashkenazi Jewish ancestry is 2.2% to 2.5%.[402-404] Studies have shown that genetic testing based on clinical guidelines emphasizing family history of breast, ovarian, prostate, or other cancers missed about 38% to 56% of mutation carriers in those of Ashkenazi ancestry.[402,403,405,406] Therefore, there is some evidence to support population-based genetic testing for individuals with Ashkenazi Jewish ancestry. However, there are concerns about the demand on genetic counseling resources, the preparedness of health care professionals to provide cancer genetic counseling and management, and participants' fears and concerns about testing, including those regarding privacy, stigmatization, and the need for appropriate medical and or surgical management in patients and family members found to have a founder mutation. Thus, universal testing for founder *BRCA1/2* mutations in individuals of Ashkenazi Jewish ancestry, regardless of personal or family history, should be offered primarily in the setting of longitudinal research studies. If there is no access to longitudinal studies, then testing may be offered when pre- and post-test genetic counseling are available (see below). There remains a vital need for longitudinal data from research studies exploring various methods of providing population based genetic testing of individuals with Ashkenazi Jewish ancestry in the United States.

Breast Cancer Population Testing

In 2019, the American Society of Breast Surgeons published a consensus statement recommending genetic testing for all patients with breast cancer.[407] This recommendation is based on studies showing that criteria in testing guidelines miss some patients with breast cancer who harbor a pathogenic or likely pathogenic variant[408,409] and that population-based multi-gene testing is more cost-effective than testing based on personal and family history criteria.[35,410] Analyses from studies of postmenopausal women with breast cancer showed rates of 3.6% to 5.6% harboring a pathogenic or likely pathogenic variant, supporting possible population testing for this group of patients.[411,412] Further analyses of this population have suggested universal testing for those age 65 or younger, as two studies showed that about 7% of these patients harbor a pathogenic or likely pathogenic variant associated with breast cancer.[411,413]

The panel does not endorse universal testing of all patients with breast cancer due to limitations of this approach, such as low specificity, shortages in trained genetics health professionals to provide appropriate pre- and post-test genetic counseling, and lack of evidence to support risk management for genes included in many multi-gene panels. Though all patients with breast cancer should be evaluated to determine the appropriateness of germline genetic testing, testing should ultimately be based on patient characteristics, such as those specified in the *Testing Criteria for High-Penetrance Breast and Ovarian Cancer Susceptibility Genes* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at

www.NCCN.org).[16] Though the panel does not endorse genetic testing for all patients with breast cancer, revisions in the 2020 version of the Guidelines address limitations that may have led to patients harboring a pathogenic or likely pathogenic variant being "missed" by previous versions of testing criteria. These revisions include incorporation of a risk stratification approach in which testing criteria have been expanded beyond *BRCA1/2* (eg, "*BRCA1/2* Testing Criteria" page was revised as "Testing Criteria for High-Penetrance Breast and Ovarian Cancer Susceptibility Genes") and reorganized (see description of the testing criteria categorization under *NCCN Genetic Testing Criteria*, above), as well as clarification of testing indication for the purpose of systemic therapy decision-making (see *Systemic Therapy Decision-Making*, above).

Probability Models

Decision models developed to estimate the likelihood that a *BRCA1/2* mutation is present include BRCAPRO,[414,415] Penn II,[416] and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).[414] 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.[202,417] Penn II has been validated in families with two or more cases of breast and/or ovarian cancer.[416,418] Therefore, caution should be taken in applying this model to individuals with only one case of breast or ovarian cancer. In addition, this model was developed specifically to evaluate the likelihood of a *BRCA1/2* mutation, and not the appropriateness of multi-gene testing.

If an individual does not meet the criteria for testing for high-penetrance breast and/or ovarian cancer susceptibility genes that are described above, then testing may be considered in those who are determined to have a 2.5% to 5% probability of harboring a *BRCA1/2* pathogenic or likely pathogenic variant, based on probability models validated for *BRCA1/2* (eg, Tyrer-Cuzick, BRCAPro, BOADICEA). However, the panel cautions that model estimates vary substantially, and different thresholds may be applied if other genes are utilized in a specific model. If genes other than *BRCA1/2* are to be included in models that evaluate the threshold for testing, then penetrance, clinical actionability, and phenotypic features of cancers associated with these genes should be taken into account. Models that take these parameters into account to determine eligibility and appropriateness of multi-gene testing should be developed and validated. Subgroup analyses of 1075 *BRCA1/2* mutation carriers from the Breast Cancer Prospective Family Study Cohort showed that BRCAPRO underpredicted breast cancer risk, but BOADICEA was well-validated.[419] In 2020, the web-based CanRisk tool was developed to apply BOADICEA for clinical use and is now available, though further development and testing is needed to increase acceptability of the tool by clinicians.[420]

Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* pathogenic or likely pathogenic variants.[73] It has been estimated to be involved in only about 1% of hereditary breast cancer cases,[421] 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.[422,423] There are only about 300 families reported in an LFS registry maintained by an NCCN Member Institution and the NCI.[424] The tumor suppressor gene, *TP53*, is located on chromosome 17,[425,426] 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.[425-427] Germline mutations in the *TP53* gene have been observed in greater than 50% (and in >70% in some studies) of families meeting the classic definition of LFS (see *Li-Fraumeni Syndrome Testing Criteria* in the

algorithm).[73,422,428] Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.[429]

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%.[430] LFS is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (although Ewing sarcoma is less likely to be associated with LFS), premenopausal breast cancer, colon cancer, gastric cancer, adrenocortical carcinoma, and brain tumors.[73,422,424,427,431-436] 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.[422] Hypodiploid acute lymphoblastic leukemia is also associated with LFS,[437,438] and case reports have suggested an association between melanoma and LFS.[439,440]

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.[430] The cumulative incidence rates by age 70 years in men are 22%, 19%, and 11% for soft tissue sarcoma, brain cancer, and osteosarcoma, respectively. Case-control analyses from a large study including 56,480 breast tumors showed that *TP53* mutations (*n* = 82) were significantly associated with HER2-positive disease, regardless of whether disease was ER-positive (OR, 11.95, 95% CI, 5.84–23.0) or negative (OR, 22.71, 95% CI, 10.45–45.49).[85] These results are supported by two earlier retrospective studies that reported a very high frequency of HER2-positive breast tumors (67%–83% of evaluated breast tumors) among patients with germline *TP53* mutations.[441,442] Taken together, results suggest that amplification of HER2 may arise in conjunction with germline *TP53* mutations. This association warrants further investigation, as such patients may potentially benefit from chemoprevention therapies that incorporate HER2-targeted agents.

Individuals with LFS often present with certain cancers (eg, soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood,[433] and have an increased risk of developing multiple primary cancers during their lifetimes.[443] 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.[444] 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.[422] 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, two 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:[434] 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%).[422] Thus, it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.[436,445] 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.[446-448] For example, criteria for *TP53* testing proposed by Chompret and colleagues recommend testing for patients with multiple primary tumors of at least two "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).[447] The Chompret criteria have an estimated positive predictive value of 20% to 35%,[422,447] 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).[422] 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.[422,432,449-451] 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.[449,451]

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.[450] Several studies have investigated the likelihood of a germline *TP53* mutation in this population.[422,449,452-455] 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%.[422,453,455,456] 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.[449] Furthermore, Ginsburg and colleagues found no germline *TP53* mutations in 95 unselected women with early-onset breast cancer who previously tested negative for *BRCA1/2* mutations.[452] When taking into account family history of LFS-associated tumors, the *TP53* germline mutation prevalence increases. For example, in a study including 83 patients with *BRCA1/2* mutation-negative early-onset breast cancer (age of diagnosis ≤35 years), deleterious *TP53* mutations were identified in 3 of 4 patients (75%) with a family history of at least 2 LFS-associated tumors (breast cancer, bone or soft tissue sarcoma, brain tumors, or adrenocortical carcinoma) and in 1 of 17 patients (6%) with a family history of breast cancer only.[454] In another study, all women younger than 30 years of age with breast cancer who had a first- or second-degree relative with at least one of the core cancer types (n = 5) had germline *TP53* mutations.[422]

A member of a family with a known *TP53* pathogenic or likely pathogenic variant is considered to be at sufficient risk to warrant variant testing, even in the absence of any other risk factors. Individuals not meeting testing criteria should be followed according to recommendations tailored to

his/her personal cancer history and family history, and testing for other hereditary syndromes may be considered. If a *TP53* mutation is detected through tumor profiling, and there are clinical implications if a *TP53* mutation is identified in the germline, then germline testing for a *TP53* variant may be considered, depending on a careful examination of the individual's personal and family history. *TP53* pathogenic/likely pathogenic variants are common in tumors.[457,458] 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.[422,438,443,450] Verification of these sometimes very rare cancers is particularly important.

Employment of a screening protocol that includes MRI may improve early cancer detection in individuals with LFS.[459] 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.[460] 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.[460] It is also important to address the psychosocial and quality-of-life aspects of this syndrome. Given the complexity of LFS management, individuals with LFS should be followed at centers with expertise in management of this syndrome.

For those at risk for breast cancer, training and education in breast self-examination should start at 18 years of age, with the patient performing regular self-examination on a monthly basis. For members of families with LFS, breast cancer surveillance by clinical breast examination is recommended every 6 to 12 months, beginning at 20 years of age (or at the age of the earliest known breast cancer in the family, if younger than 20 years of age) because of the very early age of breast cancer onset seen in these families. Recommendations for breast screening in LFS are similar to those for *BRCA*-related breast and ovarian cancer syndrome management, although screening is begun at an earlier age. They include annual breast MRI screening with contrast (preferred) or mammogram if MRI is not available for women aged 20 to 29 years; annual mammogram and breast MRI screening with contrast in women aged 30 to 75 years; and management on an individual basis for women older than 75 years. For women with a family history of breast cancer diagnosed earlier than 20 years of age, breast MRI screening with contrast may begin at the earliest age of diagnosis. In women treated for breast cancer who have not had bilateral mastectomy, mammography and breast MRI screening with contrast should continue as recommended based on age. When mammography is performed, the panel recommends that tomosynthesis be considered. As with carriers of a *BRCA1/2* pathogenic or likely pathogenic variant, breast MRI screening in women who are younger than 30 years of age is preferred over mammography due to the potential radiation exposure risk and less sensitivity for detection of tumors.

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

Many of the other cancers associated with germline *TP53* pathogenic or likely pathogenic variants do not lend themselves to early detection. Thus, additional recommendations are general and include comprehensive physical examinations (including neurologic examination) every 6 to 12 months, especially when there is a high index of suspicion for second malignancies in cancer survivors and rare cancers (see *Li-Fraumeni Syndrome Testing Criteria* 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.[461] 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.[462] In a prospective observational study, a clinical surveillance protocol for *TP53* mutation carriers from families affected by LFS was incorporated.[463] The surveillance protocol included biochemical methods (ie, bloodwork to evaluate hormone levels, CBC, erythrocyte sedimentation rate, and lactate dehydrogenase; and 24-hour urine cortisol) and imaging techniques, such as annual brain MRI, annual rapid whole-body MRI, ultrasound of the abdomen and pelvis, and colonoscopy.[464] For surveillance of breast cancers, the protocol was similar to the NCCN Guidelines for LFS Management.[463] 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 ($P = .012$).[464] Five-year OS was greater for patients 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.[463] 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.[460] 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.[462,465] 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 multi-gene 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.[466,467] 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*[468] are referred to as *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,[72,469,470] and autism spectrum disorders with macrocephaly.[72,470,471] Cowden syndrome is rare, with an incidence of 1 in 200,000, although it is likely to be underestimated due to difficulties associated with making a clinical diagnosis of the disease.[472,473] 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.[474] The frequency of germline *PTEN* mutation in Cowden syndrome cases is high, at approximately 80%.[475]

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.[72,476] 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/PHTS has been estimated at 25% to 50%, with an average age of 38 to 50 years at diagnosis.[72,476-478] Some studies (as discussed above) have reported a higher cumulative lifetime risk for breast cancer (77%–85%) in individuals with Cowden syndrome/PHTS or *PTEN* mutations.[479-481] There have been only two cases of breast cancer reported in men with Cowden syndrome/PHTS.[478] Although many women with Cowden syndrome/PHTS experience benign breast disease,[72] there is no evidence that the rate is higher than in the general population.[478]

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,[470,482] and the lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.[72,483] However, data tend to be aggregated, so it is difficult to calculate rates for multinodular goiter versus solitary nodules.[478] A retrospective chart review of 47 children with *PTEN* mutations showed that 26% had abnormal thyroid imaging.[484] The youngest reported case of thyroid cancer in a child with Cowden syndrome/PHTS was at age 7.[485]

Macrocephaly (defined as head circumference greater than the 97th percentile)[486] is a common finding in patients with Cowden syndrome/PHTS. It has been estimated that approximately 80% to 100% of individuals with this syndrome will exhibit this clinical finding.[478] Adult LDD and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome/PHTS.[469,475,480,487] A rare, slow-growing, benign hamartomatous lesion of the brain, LDD, is a dysplastic gangliocytoma of the cerebellum.[72,480] In a multicenter prospective study examining 3042 probands who met clinical criteria for Cowden syndrome/PHTS, 6% met criteria for LDD.[482] In a study of

individuals meeting the diagnostic criteria for Cowden syndrome/PHTS, the cumulative lifetime risk for LDD was reported to be 32%.[480] The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a *PTEN* gene mutation,[475,488] although exceptions have been reported.[489] 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.[471,490-493]

As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.[475] Although not well defined, women with Cowden syndrome/PHTS may have a 5% to 10% risk for endometrial cancer.[72,494 478] While many women with Cowden syndrome/PHTS may also have uterine fibroids, this risk is not likely to be much greater than in women without Cowden syndrome/PHTS or *PTEN* mutation.[478]

In addition, brain tumors and vascular malformations affecting any organ are occasionally seen in individuals with Cowden syndrome/PHTS, although the risks for developing these conditions are not well defined.[72,478] It is important to note, however, that most of the data on the frequencies of the clinical features of Cowden syndrome/PHTS 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.[72] 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.[72,495]

Benign skin lesions are experienced by most to all Cowden syndrome/PHTS patients.[470,476,484] Skin lesions associated with Cowden syndrome/PHTS 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.[478,484,496] Trichilemmomas associated with Cowden syndrome/PHTS tend to appear on the face, particularly the eyes, mouth, nose, and forehead.[478] Most individuals with Cowden syndrome/PHTS exhibit characteristic mucocutaneous lesions by their twenties, and such lesions have been reported to occur in 99% of individuals with Cowden syndrome/PHTS, showing nearly complete penetrance, although this may be a reflection of selection bias in the cases reported.[127,469] The presence of three or more mucocutaneous neuromas is considered a major diagnostic criterion of Cowden syndrome/PHTS,[478] while the presence of two or more trichilemmomas has been reported to be pathognomonic for Cowden syndrome/PHTS.[497,498] However, since most of the evidence regarding trichilemmomas is from the older literature, it is possible that the association with Cowden syndrome/PHTS is somewhat overestimated.[72] There are reports of individuals with a solitary trichilemmoma who do not have Cowden syndrome/PHTS.[497,498] Nevertheless, due to the strong association between these lesions and Cowden syndrome/PHTS 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/PHTS have gastrointestinal polyps.[499] However, this was almost certainly an underestimate.[499,500] In an analysis of 67 *PTEN* mutation carriers undergoing colonoscopy, colorectal polyps were found in 92.5% of patients.[499] About half of the patients undergoing colonoscopy had hyperplastic polyps, and about 25% had polyps that were hamartomatous, ganglioneuromatous, or adenomatous.[499] 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.[499] A systematic review of published case series (N = 102) regarding gastrointestinal manifestations in Cowden syndrome/PHTS and component syndromes showed that 92.5% of these patients had polyps, with 64% having 50 or more.[501] 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.[478,502] 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.[484] Early-onset (<50 years of age) colorectal cancer has been reported in 13% of patients with *PTEN* mutation-associated Cowden syndrome/PHTS, suggesting that routine colonoscopy may be warranted in this population.[499] The lifetime risk for colorectal cancer has been estimated as 9% to 16%.[480,481]

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/PHTS (N = 211; identified from published literature and records from a single institution), the cumulative lifetime risk for any cancer was 89%.[480] *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.[480] In a prospective study that evaluated genotype-phenotype associations between *PTEN* mutations and cancer risks,[481] 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.[481] 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).[479] 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 Cowden syndrome/PHTS were found to have a 2-fold greater cancer risk compared with men with Cowden syndrome/PHTS.[479] It is important to note, however, that all three of these studies suffer from 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%.[503]

The BRRS variant of Cowden syndrome/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,[504] 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.[505] 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.[487]

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. Clinical diagnostic criteria have also been developed to help identify clinical features associated with Cowden syndrome/PHTS (see *Revised Clinical Diagnostic Criteria for PTEN Hamartoma Tumor Syndrome* in the algorithm, and discussed below under *Clinical Diagnostic Criteria*). Patients who meet clinical diagnostic criteria for Cowden syndrome/PHTS as described in this section are candidates for testing for *PTEN* pathogenic or likely pathogenic variants.

Testing Criteria

Testing criteria for Cowden syndrome/PHTS are grouped into three 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 three categories. The first criteria category includes individuals meeting diagnostic criteria for Cowden syndrome[506]: a personal history of BRRS, adult LDD, autism spectrum disorder with macrocephaly, or two 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 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 and are described in the Guidelines (see *Cowden Syndrome/PHTS Testing Criteria* in the algorithm).[470,473,482,486,506] 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 two or more major criteria where one criterion is macrocephaly meets the testing threshold. An individual with three or more major criteria (without macrocephaly) is also considered to meet the threshold for testing. In addition, individuals exhibiting one major criterion with three or more minor criteria (see *Cowden Syndrome/PHTS Testing Criteria* in the algorithm) also meet the testing threshold; if an individual exhibits two or more major criteria but does not have macrocephaly, then one of the major criteria may be included as one of the three minor criteria to meet the testing threshold.

The final category of criteria represents features with a "minor" association with Cowden syndrome/PHTS.[470,473,482,506] These criteria are described in the Guidelines (see *Cowden Syndrome/PHTS Testing Criteria* in the algorithm). An individual would need to exhibit four or more minor criteria or, as discussed above, three or more minor criteria and one major criterion to meet testing.

Lastly, an individual who has a first-degree relative diagnosed with Cowden syndrome/PHTS or BRRS for whom testing has not been performed would also meet the threshold for *PTEN* testing if the individual meets at least one major criterion or two or more minor criteria. *PTEN*

mutations are commonly found in tumor tissue.[507-509] If a *PTEN* mutation is detected through tumor profiling, and there are clinical implications if a *PTEN* mutation is identified in the germline, then germline testing for a *PTEN* variant may be considered, depending on a careful examination of the individual's personal and family history.

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%.[478,505] 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[473] for Cowden syndrome.[470] 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.[478] 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.[478] 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 (see *Revised Clinical Diagnostic Criteria for PTEN Hamartoma Tumor Syndrome* in the algorithm).

Screening Recommendations

Cancer is the major health risk associated with Cowden syndrome/PHTS. Therefore, the NCCN Panel has 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, 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. 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, though consideration of screening can begin as early as age 35. 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. Though endometrial cancer screening does not have proven benefit in women with Cowden syndrome, 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 TVUS 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, TVUS 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,[72] compared to about 1% in the general population.[510] An annual thyroid ultrasound should be performed, starting at age 7.[511] Children at risk of a *PTEN* mutation (based on a parent's carrier status) whose parents wish to delay genetic testing may also undergo annual thyroid ultrasound, since this is a noninvasive procedure. 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. Annual dermatologic examination is recommended. 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 and assisted reproduction including PGD 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 Options* under *Risk Assessment, Counseling, and Management* for *BRCA-Related Breast/Ovarian Cancer Syndrome*.

Hereditary Pancreatic Cancer

Pancreatic cancer is thought to have a familial or hereditary component in approximately 10% of cases.[185,186,512-514] Harboring a pathogenic or likely pathogenic variant has been found to be associated with a greater incidence of pancreatic cancer than family history alone (without the presence of an associated germline variant).[515] Germline mutations commonly found in pancreatic adenocarcinoma include *BRCA1, BRCA2, CDKN2A,* mismatch repair genes associated with Lynch syndrome (*MSH2, MLH1, MSH6, PMS2, EPCAM*), *ATM, PALB2, STK11,* and *TP53.*[179,181,183,186,322,379,513,515-522] *BRCA2* and *CDKN2A* are generally the most prevalent, with rates in moderate- to high-risk families ranging from

2% to 6% for *BRCA2* and 1.5% to 2.5% for *CDKN2A*.[176,180,185,186] In addition, hereditary pancreatitis, which is associated with a significantly increased risk for pancreatic cancer, is associated with the genes *PRSS1* and *SPINK1*.[513] Patients with pancreatic cancer and Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, with mutations being more common for *BRCA2*.[178,179,181,187]

Given the considerable rate of predisposing mutations in patients with pancreatic cancer, as well as the fact that typical clinical factors (eg, young age of onset, family history of cancer) are poorly predictive for identifying mutation carriers, universal genetic testing for these individuals is warranted. Given the elevated rates of pathogenic or likely pathogenic variants in pancreatic cancer and that pancreatic cancer risk increases when there is a family history,[523] testing of first-degree relatives of patients may be beneficial. However, testing the patient is preferred. Testing of second-degree relatives is generally not recommended but may be considered in select cases. Given that mortality rates for this cancer are high,[524,525] 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. Family history of pancreatic cancer with unknown histology is often presumed to be exocrine. Detecting a germline mutation can potentially aid in treatment decision-making, particularly regarding systemic therapy options (see *Systemic Therapy Decision-Making* above).

Pancreas Screening

Evidence to support screening for pancreatic cancer comes from studies including those who harbor an associated germline mutation and/or those who have a particularly strong family history of pancreatic cancer (two or more first-degree relatives on the same side of the family, or three or more first- or second-degree relatives on the same side of the family). An analysis of outcomes from three European centers including 411 asymptomatic individuals showed that pancreatic cancer was detected in 7% of *CDKN2A* mutation carriers and <1% of those with familial pancreatic cancer.[526] For the *CDKN2A* mutation carriers for whom a lesion was detected, 75% were resectable, with a 5-year OS rate of 24%. Another analysis from six high-volume centers in Italy including 187 high-risk individuals, abnormalities were detected in about 28%.[527] Out of the cysts detected, 62.2% were branch-duct intraductal papillary mucinous neoplasms. Pancreatic adenocarcinomas made up 2.6% of the findings (n = 5). A third analysis including screening of 354 asymptomatic high-risk individuals showed suspicious pancreas lesions in 19%.[528] Out of the lesions detected from screening, 90% were resectable, and the 3-year OS rate was 85% in those with resectable lesions. The considerable rate of resectable asymptomatic lesions found from routine screening of high-risk individuals demonstrates the potential for downstaging (ie, identification of lesions at an earlier stage). There is also the potential for impact on mortality rates, though long-term studies are needed in this area. Lesions detected through routine screening may not always require resection (eg, sporadic branch-duct intraductal papillary mucinous neoplasms). Therefore, larger long-term studies are needed to further determine the risks and benefits of routine pancreas screening in high-risk individuals, as well as the threshold for surgical intervention and biopsy.[528]

With the exception of *CDKN2A* and *STK11*, pancreas cancer screening in individuals who have a pathogenic or likely pathogenic variant associated with increased risk of exocrine pancreatic cancer is not recommended unless there is additional family history of pancreatic cancer (at least 1 first- or second-degree relative).[529] If family history criteria are met, then pancreas screening may be considered at age 50, or 10 years younger than the earliest pancreatic cancer diagnosis in the family, whichever is earlier.[529] The International Cancer of the Pancreas Screening Consortium recommendations for pancreas screening in individuals with increased risk for hereditary pancreatic cancer do not include carriers of a *TP53*

pathogenic or likely pathogenic variant in this group,[529] as there are very limited data on pancreatic cancer screening in these carriers. However, the NCCN Guidelines panel recommends that pancreatic cancer screening be considered in carriers of a *TP53* pathogenic or likely pathogenic variant, if there is additional family history of pancreatic cancer (at least 1 first- or second-degree relative), as there is some evidence of a modestly increased risk of pancreatic cancer in these carriers.[183,186]

For carriers of a *CDKN2A* or *STK11* pathogenic or likely pathogenic variant, no additional family history is needed to warrant screening. For carriers of a *CDKN2A* pathogenic or likely pathogenic variant, screening may be considered at age 40, or 10 years younger than the earliest pancreatic cancer diagnosis in the family, whichever is earlier.[529] For carriers of a *STK11* pathogenic or likely pathogenic variant, screening may be considered beginning at ages 30 to 35, or 10 years younger than the earliest pancreatic cancer diagnosis in the family, whichever is earlier.[354,529]

Hereditary pancreatitis is associated with increased lifetime risk of exocrine pancreatic cancer and is sometimes caused by pathogenic or likely pathogenic variants such as PRSS1 and SPINK1.[530-533] However, the clinical significance of these variants is unclear without a clinical history of pancreatitis. Therefore, germline testing for PRSS1, SPINK1, and other genes associated with pancreatitis is generally not recommended unless one's personal or family history is suggestive of hereditary pancreatitis.[532] Pancreas cancer screening is recommended in individuals harboring one of these variants only in the presence of a clinical phenotype consistent with hereditary pancreatitis. For individuals meeting these criteria, screening may begin at age 40, or 20 years after onset of pancreatitis, whichever is earlier.[529]

When screening is recommended, it may be done with contrast-enhanced MRI/MRCP and/or endoscopic ultrasound (EUS).[528,529,534] MRI and EUS have been shown to be superior in detection of subcentimeter pancreatic cysts, compared to CT.[534] Screening at a high-volume center of expertise and in the context of a research study is preferred. In those for whom screening show shows concerning features that suggest progression, shorter screening intervals may be indicated.

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.

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.

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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