NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 2.2016

NCCN.org

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 2.2016 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2016 include:

BRCA-1

- **BRCA1/2 Testing Criteria, the following bullets were revised,**
  - **Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative with *ovarian carcinoma at any age or* breast cancer ~~and/or ovarian carcinoma~~ ≤*50 y or two relatives with breast,* pancreatic or prostate cancer (Gleason score ≥7) at any age**
  - **Personal history of pancreatic cancer at any age with ≥1 close blood relative with *ovarian carcinoma at any age or* breast cancer ~~and/or ovarian carcinoma and/or~~ ≤*50 y or two relatives with breast,* pancreatic cancer or prostate cancer (Gleason score ≥7) at any age**

MS-1

- **The discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 1.2016 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 2.2015 include:

Global

- **"Invasive ovarian cancer" was replaced by either "ovarian cancer" or "ovarian carcinoma" as appropriate.**
- **Hereditary Breast and/or Ovarian Cancer Syndrome was changed to BRCA-Related Breast and/or Ovarian Cancer Syndrome.**

Breast and Ovarian Cancer Genetic Assessment

BR/OV-1

- **First column was revised as follows,**
  - **"An individual with a cancer diagnosis meeting any of the following" was removed as a heading.**
  - **The 1st bullet was added, "An individual with a breast cancer diagnosis meeting any of the following" and the following 6 previous bullets were moved as sub-bullets under this new bullet**
    - ◊ **A known mutation in a cancer susceptibility gene within the family**
    - ◊ **Early-age-onset breast cancer**
    - ◊ **Triple negative (ER-, PR-, HER2-) breast cancer *diagnosed* ≤60 y**
    - ◊ **Two breast cancer primaries in a single individual**
    - ◊ **Breast cancer at any age, and**
      - **≥1 close blood relative with breast cancer ≤50 y, or**
      - **≥1 close blood relative with invasive ovarian cancer at any age, or**
      - **≥2 close blood relatives with breast cancer and/or pancreatic cancer at any age, or**
      - **From a population at increased risk**
    - ◊ **Male breast cancer**
  - **A new bullet was added, "An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age."**
  - **3rd bullet was revised, "*An individual with a* personal and/or family history of three or more of the following (especially if early onset *and can include multiple primary cancers in same individual*): *breast,* pancreatic cancer, prostate cancer (Gleason score ≥7), *melanoma*, sarcoma, adrenocortical carcinoma, brain tumors, *leukemia*, diffuse gastric cancer, *colon cancer*, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract."**
- **Second column was revised as follows,**
  - ◊ **The heading, "An individual with no personal history of cancer but with a family history of any of the following" was replaced by bullets that says, "An individual with no personal history of cancer but a close relative with any of the following."**
  - ◊ **3rd sub-bullet was revised as, "≥2 individuals with breast cancer primaries on the same side of family *at least one diagnosed ≤50 y*."**
  - **6th sub-bullet was revised, "~~Personal and/or~~ Family history of three or more of the following (especially if early onset *and can include multiple primary cancers in same individual*): *breast,* pancreatic cancer, prostate cancer (Gleason score ≥7), *melanoma*, sarcoma, adrenocortical carcinoma, brain tumors, *leukemia*, diffuse gastric cancer, *colon cancer*, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract."**
- **Footnote "e" was modified, "~~Other cancer genetic syndromes may be associated with mucinous ovarian cancer. Non-epithelial ovarian cancer may be associated with PJS and possibly other cancer syndromes. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome; be attentive for clinical evidence of this syndrome.~~ *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 Peutz-Jeghers syndrome or Sertoli-Leydig umors and DICER1-Related disorders.*" (Also for footnote e on BRCA-1)**
- **Footnote "f" was revised, "For populations at increased risk, requirements for inclusion may be modified ~~(eg, individuals of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age)~~."**

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Updates in Version 2.2016 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2016 include:

BRCA-Related Breast and/or Ovarian Cancer Syndrome

BR/OV-2
- Detailed family history
  - 1st bullet was modified, "Expanded pedigree, particularly around ~~affected~~ individuals *with a diagnosis of cancer*, to include *a three-generational pedigree* ~~first-, second-, and third-degree relatives (parents, siblings, children, grandparents, aunts, uncles, nieces, nephews, grandchildren, half-siblings, great-grandparents, great-aunts, great-uncles, greatgrandchildren, and first cousins)~~."

BR/OV-A 1 of 2
- Under 2nd bullet, the 4th sub-bullet was added, "Preparing the patient for possible outcomes of testing including positive, negative, and uncertain findings and obtaining informed consent."

BRCA-1
- BRCA1/2 Testing Criteria
  - 2nd statement under heading was revised as, "Testing of ~~unaffected~~ individuals *without a cancer diagnosis* should only be considered when an appropriate affected family member is unavailable for testing."
  - 5th bullet was revised as, "Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative with breast ~~(≤50 y)~~ and/or ~~invasive~~ ovarian *carcinoma* and/or pancreatic or prostate cancer (Gleason score ≥7) at any age."
  - 6th bullet was revised as, "Personal history of pancreatic cancer at any age with ≥1 close blood relative with breast ~~(≤50 y)~~ and/or ~~invasive~~ ovarian *carcinoma* and/or pancreatic cancer *or prostate cancer (Gleason score ≥7)* at any age."

BRCA-A
- BRCA Mutation-Positive Management for Women
  - 3rd bullet, Breast screening
    - ◊ 1st sub-bullet was revised as, "Age 25–29 y, annual breast MRI screening (preferred) or mammogram if MRI is unavailable or individualized based on family history if breast cancer diagnosis before age ~~25~~ *30* is present."
  - 5th bullet was revised as, "Recommend risk-reducing salpingo-oophorectomy (RRSO) ~~(ideally in consultation with a gynecologist-oncologist~~), typically between 35 and 40 y, and upon completion of child bearing. *Because ovarian cancer onset in patients with BRCA2 mutations is an average of 8–10 years later than in patients with BRCA1 mutations, it is reasonable to delay RRSO until age 40–45 y in patients with BRCA2 mutations who have already maximized their breast cancer prevention (ie, undergone bilateral mastectomy)..."*
    - ◊ 2nd sub-bullet was revised, "Salpingectomy alone is not the standard of care *for risk reduction although clinical trials are ongoing* ~~and is discouraged outside a clinical trial~~... In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer by *up to* 50% *depending upon age of procedure."*
  - Footnote was removed: "SGO Clinical Practice Statement: Salpingectomy for Ovarian Cancer Prevention November 2013."

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Updates in Version 2.2016 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2016 include:

Li-Fraumeni Syndrome

LIFR-1

- Chompret criteria were updated based on, "Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33:2345-2352."
- The criteria, "Individual with breast cancer ≤35 y" was removed and the qualifier statement, "TP53 testing can be ordered alone, concurrently with BRCA1/2 testing and/or other gene testing or as a follow-up test after negative BRCA1/2 testing" was moved to a footnote.

LIFR-2

- Genetic testing, the category desingation of "category 2A for adults; category 2B for children" was removed from "Consider TP53 testing for specific familial mutation."

LIFR-A

- Breast cancer risk for women
  - 2nd bullet was revised, "Clinical breast exam, every 6–12 mo, starting at age 20–25 y ~~or 5–10 y before the earliest known breast cancer in the family (whichever comes first~~)" with a corresponding footnote 2, "Or at the age of the earliest diagnosed breast cancer in the family, if below age 20 y."

Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

COWD-A

- Cowden syndrome/PHTS management for women
  - 5th bullet was added, "Discuss option of hysterectomy upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires."
  - 6th bullet was revised, "Discuss option of risk-reducing mastectomy ~~and hysterectomy~~ and counsel regarding degree of protection, extent of cancer risk, and reproductive options."
- Cowden syndrome/PHTS management for men and women
  - 3rd bullet was revised as, "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.*"

Multi-Gene Testing

GENE-1

- 6th bullet was revised by adding a sentence, "In addition, certain mutations in a gene may pose higher or lower risk than other mutations in that same gene."
- 8th bullet was added, "Mutations in many breast cancer susceptibility genes involved in DNA repair may be associated with the rare autosomal recessive condition, Fanconi anemia."
- Footnote "a" was added, "Research is evolving, and gene carriers should be encouraged to participate in clinical trials or genetic registries."

Example of Additional Genetic Mutations Associated with Breast/Ovarian Cancer Risk

ADDIT-2

- Discuss Option of RRM
  - PALB2 was moved from "Insufficient evidence for intervention" to "Intervention warranted based on gene and/or risk level."
- Recommend/Consider RRSO
  - BRIP1, RAD51C, RAD51D were moved from "Insufficient evidence for intervention" to "Intervention warranted based on gene and/or risk level."
- BARD1 was removed from insufficient evidence for intervention row to footnote "c."
- Footnote "c" was added, "Insufficient evidence for any recommendations for breast MRI, RRSO, or RRM include but are not limited to: BARD1, FANCC, MRE11A, MUTYH, NF1, NBN, RAD50, SMARCA, or XRCC2."

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- **An individual with a breast cancer diagnosis meeting any of the following:**
  - **A known mutation in a cancer susceptibility gene within the family**
  - **Early-age-onset breast cancer[b]**
  - **Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y**
  - **Two breast cancer primaries[c] in a single individual**
  - **Breast cancer at any age, and**
    - **◊ ≥1 close blood relative[d] with breast cancer ≤50 y, or**
    - **◊ ≥1 close blood relative[d] with invasive ovarian[e] cancer at any age, or**
    - **◊ ≥2 close blood relatives[d] with breast cancer and/or pancreatic cancer at any age, or**
    - **◊ From a population at increased risk[f]**
  - **Male breast cancer**
- **An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age**
- **An individual with a personal and/or family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract[h]**
- **An individual with an ovarian[e] cancer**
- **An individual with no personal history of cancer but with**
  - **A close relative with any of the following:[d,f]**
    - **◊ A known mutation in a cancer susceptibility gene within the family**
    - **◊ ≥2 breast cancer primaries in a single individual**
    - **◊ ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y**
    - **◊ Ovarian[e] cancer**
    - **◊ Male breast cancer**
  - **First- or second-degree relative with breast cancer ≤45 y**
  - **Family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of GI tract[h]**

→ **Referral to cancer genetics professional recommended[j]** → **See Assessment (BR/OV-2)**

[a]The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.
[b]Clinically use age ≤50 y because studies define early onset as either ≤40 or ≤50 y.
[c]Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
[d]Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-B)
[e]Includes fallopian tube and primary peritoneal cancers. *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 Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.
[f]For populations at increased risk due to founder mutations, requirements for inclusion may be modified.
[g]For dermatologic manifestations, see COWD-1.
[h]For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, *STK11* testing should be considered. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal—Peutz-Jeghers syndrome. Melanoma has been reported in some *BRCA*-related families.
[i]For lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.
[j]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

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ASSESSMENT

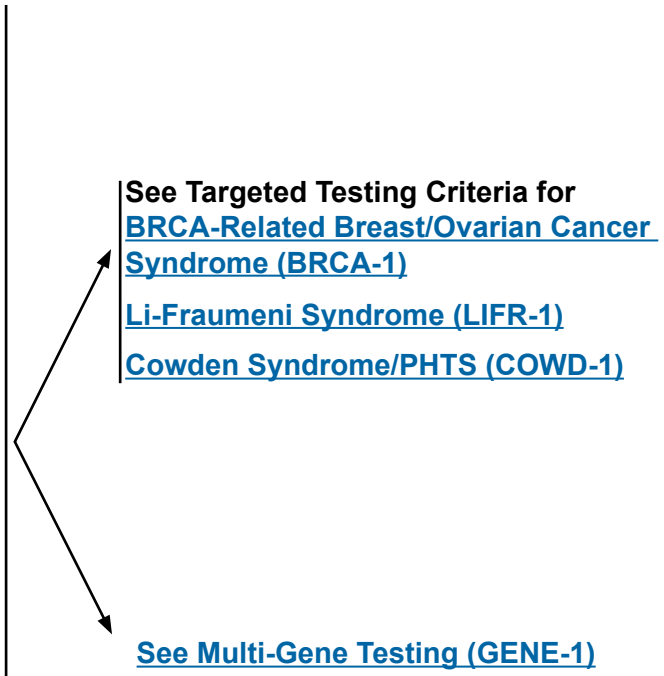
Patient needs and concerns:
- Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
- Goals for cancer family risk assessment

Detailed family history:
- Expanded pedigree, particularly around individuals with a diagnosis of cancer, to include a three-generational pedigree (See BR/OV-B)
- Types of cancer, bilaterality, age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation as needed, particularly pathology reports of primary cancers

Detailed medical and surgical history:
- Any personal cancer history (eg, age, histology, laterality)
- Carcinogen exposure (eg, history of radiation therapy)
- Reproductive history
- Hormone or oral contraceptive use
- Previous breast biopsies and pathology results
- History of salpingo-oophorectomy

Focused physical exam (conducted by qualified clinician):
- Breast/ovarian
- Cowden syndrome/PTEN Hamartoma Tumor Syndrome (PHTS) specific:
  - Dermatologic,[k] including oral mucosa
  - Head circumference
  - Thyroid (enlarged or nodular on palpation)

GENE TESTING[l]



[k]For Cowden syndrome dermatologic manifestations, see COWD-1 and for PJS dermatologic manifestations, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[l]In some cases, multi-gene testing may be a preferable way to begin testing over the single-gene testing process.

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling).[1-5] A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in the counseling of patients.
- Pre-test counseling includes:
  - Collection of a comprehensive family history
    - Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family (See BR/OV-B)
  - Evaluation of a patient's cancer risk
  - Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity
  - Preparing the patient for possible outcomes of testing including positive, negative, and uncertain findings and obtaining informed consent
- Post-test counseling includes discussions of:
  - Results along with their significance and impact and recommended medical management options
  - Informing and testing at-risk family members
  - Available resources such as disease-specific support groups and research studies.

Genetic Testing Considerations

- Testing should be considered in appropriate high-risk individuals where it will impact the medical management of the tested individual and/or their at-risk family members. It should be performed in a setting in which it can be adequately interpreted and impact the medical management of the tested individual and/or their at-risk family members.[1]
- The probability of mutation 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 mutation detection. The estimated likelihood of mutation detection may be very low in families with a large number of unaffected female relatives.
- Patients who have received an allogenic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. 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.
- Comprehensive genetic testing includes full sequencing and testing for large genomic rearrangements.
- Genetic testing for adult onset diseases (eg, *BRCA1/2*) in children <18 y is generally not recommended.[6]

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PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

Genetic Testing Approach

- **If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider testing first 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 living 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, pancreas, melanoma 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.**
- **If no mutation is found, consider other hereditary cancer syndromes. For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see ADDIT-1 and ADDIT-2.**
- **Testing family members for a variant of unknown significance should not be used for clinical purposes. Consider a referral to research studies that aim to define the functional impact of variants.**

Risk to relatives

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

Reproductive options

- **For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.**
- ***BRCA2* gene mutations may be associated with the rare autosomal recessive condition, Fanconi anemia. Thus, for this gene, consideration would be given to carrier testing the partner for mutations in the same gene if it would inform reproductive decision-making and/or risk assessment and management.**

1. Robson ME, Storm CD, Weitzel J, Wollins DS, Offit K. American Society of Clinical Oncology policy statement update: Genetic and genomic testing for cancer susceptibility. J Clin Oncol 2010;28:893-901.
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.

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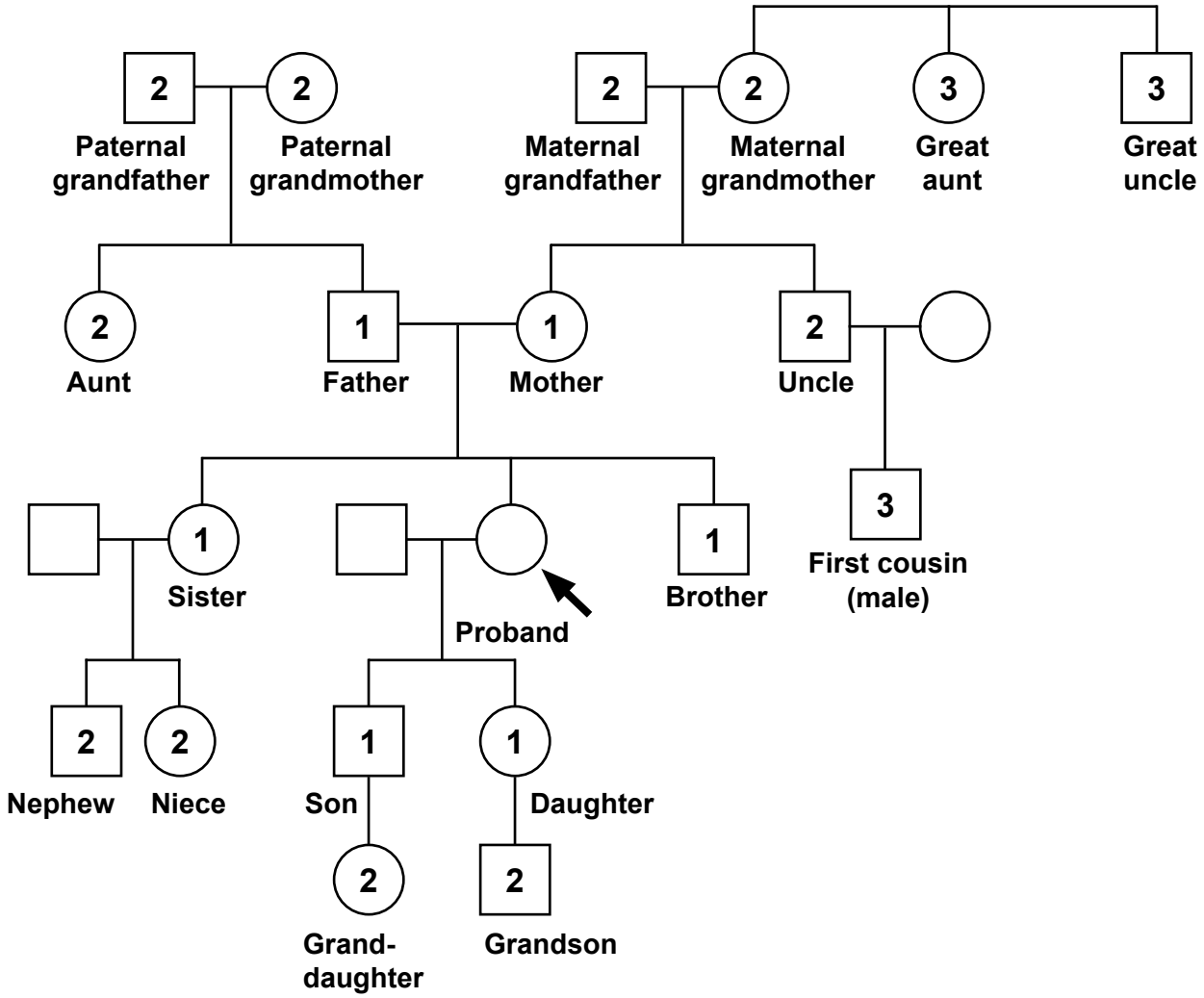
PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[a]



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

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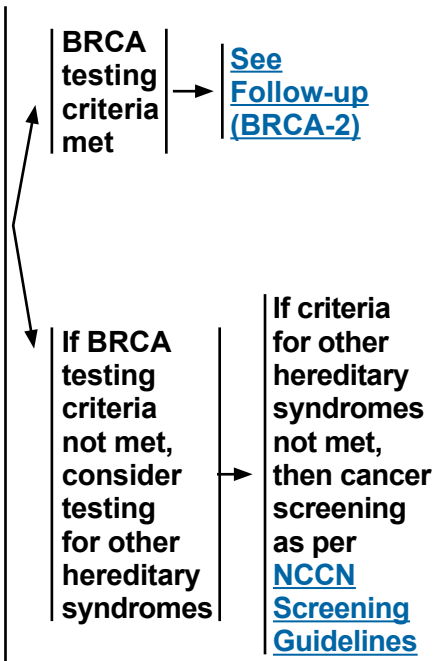
BRCA1/2 TESTING CRITERIA[a,b]

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - ◊ An additional breast cancer primary[c]
    - ◊ ≥1 close blood relative[d] with breast cancer at any age
    - ◊ ≥1 close relative with pancreatic cancer
    - ◊ ≥1 relative with prostate cancer (Gleason score ≥7)
    - ◊ An unknown or limited family history[a]
  - Diagnosed ≤60 y with a:
    - ◊ Triple negative breast cancer
  - Diagnosed at any age with:
    - ◊ ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ◊ ≥2 close blood relatives[d] with breast cancer at any age
    - ◊ ≥1 close blood relative[d] with ovarian[e] carcinoma
    - ◊ ≥2 close blood relatives[d] with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - ◊ A close male blood relative[d] with breast cancer
    - ◊ For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of ovarian[e] carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[d] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or ovarian[e] carcinoma and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[e] carcinoma



[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
[b]For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
[c]Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
[d]Close blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-B)
[e]Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial non-mucinous histology. Lynch syndrome can be associated with both nonmucinous 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 Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.
[f]Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. Founder mutations exist in other populations.

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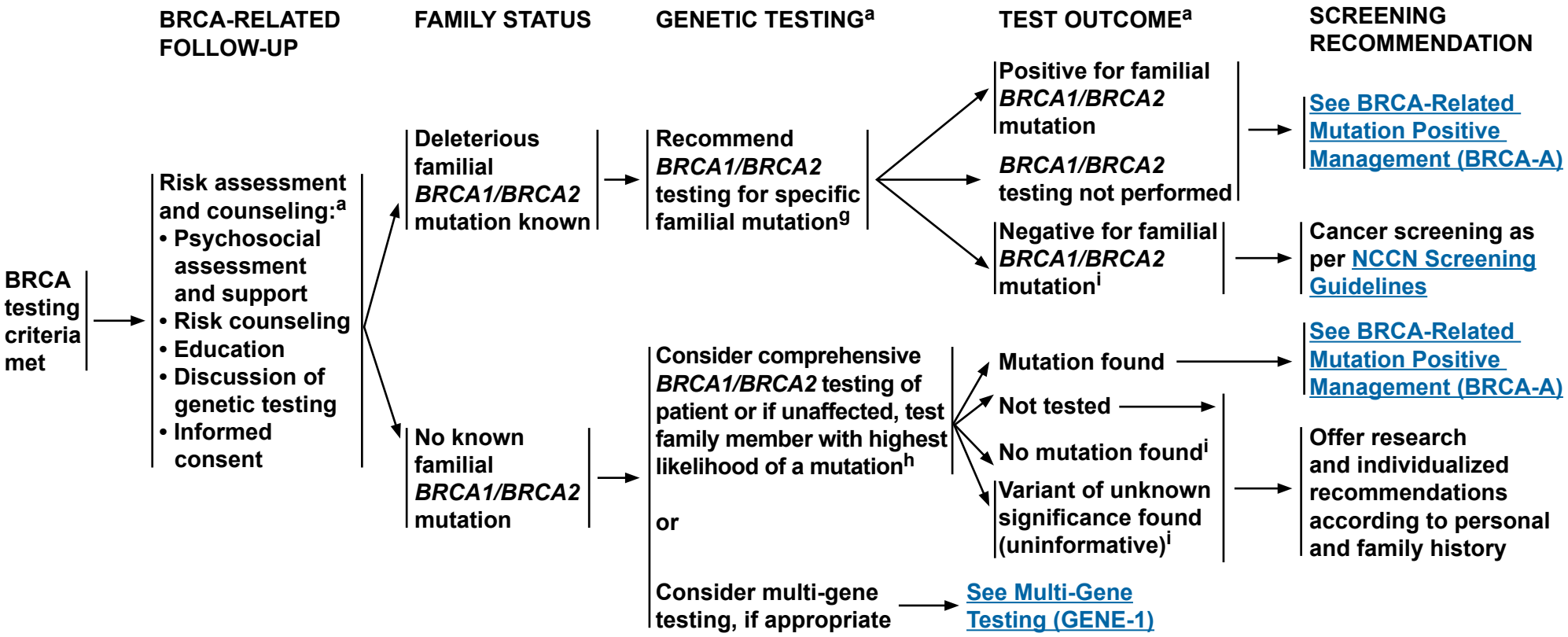

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

[g]If of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations. Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known mutation.

[h]For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations and ancestry also includes non-Ashkenazi Jewish relatives or other BRCA-related criteria are met, consider comprehensive genetic testing. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial mutation, comprehensive genetic testing is the approach, if done.

[i]If no mutation found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni (LIFR-1) and/or Cowden syndrome (COWD-1) or multi-gene testing (GENE-1). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see ADDIT-1.

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BRCA MUTATION-POSITIVE MANAGEMENT

WOMEN

- **Breast awareness[1] starting at age 18 y.**
- **Clinical breast exam, every 6–12 mo,[2] starting at age 25 y.**
- **Breast screening[3]**
  - **Age 25–29 y, annual breast MRI[4] screening (preferred) or mammogram if MRI is unavailable or individualized based on family history if a breast cancer diagnosis before age 30 is present.**
  - **Age 30–75 y, annual mammogram and breast MRI[4] screening.**
  - **Age >75 y, management should be considered on an individual basis.**
  - **For women with a *BRCA* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.**
- **Discuss option of risk-reducing mastectomy**
  - **Counseling may include a discussion regarding degree of protection, reconstruction options, and risks.**
- **Recommend risk-reducing salpingo-oophorectomy (RRSO),[5] typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* mutations is an average of 8–10 years later than in patients with *BRCA1* mutations, it is reasonable to delay RRSO until age 40–45 y in patients with *BRCA2* mutations who have already maximized their breast cancer prevention (ie, undergone bilateral mastectomy). 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, possible short-term hormone replacement therapy to a recommended maximum age of natural menopause, and related medical issues.**
  - **Salpingectomy alone is not the standard of care for risk reduction although clinical trials are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer by up to 50% depending upon age of procedure.**
- **Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.**
- **For those patients who have not elected RRSO, while there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening. Transvaginal ultrasound for ovarian cancer 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 starting at age 30–35 y. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.**
- **Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).**
- **Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.**

Continued on next page

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

[2]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.

[3]The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Annual screening strategies in *BRCA1* and *BRCA2* gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118:2021-2030.

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

[5]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 MUTATION-POSITIVE MANAGEMENT

MEN[7]

- **Breast self-exam training and education starting at age 35 y**
- **Clinical breast exam, every 12 mo, starting at age 35 y**
- **Starting at age 40 y:**
  - **Recommend prostate cancer screening for *BRCA2* carriers**
  - **Consider prostate cancer screening for *BRCA1* carriers**

MEN AND WOMEN

- **Education regarding signs and symptoms of cancer(s), especially those associated with *BRCA* gene mutations.**
- **No specific screening guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers observed in the family.**[8]

RISK TO RELATIVES

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

REPRODUCTIVE OPTIONS

- **For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.**
- ***BRCA2* gene mutations may be associated with the rare autosomal recessive condition, Fanconi anemia. Thus, for this gene, consideration would be given to carrier testing the partner for mutations in the same gene if it would inform reproductive decision-making and/or risk assessment and management.**[9]

[7]There are only limited data to support breast imaging in men.
[8]Consider full-body skin and eye exam for melanoma and investigational protocols for pancreatic cancer.
[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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LI-FRAUMENI SYNDROME TESTING CRITERIA[a]

- **Individual from a family with a known *TP53* mutation**
- **Classic Li-Fraumeni syndrome (LFS) criteria:[b]**
  - **Combination of an individual diagnosed age <45 y with a sarcoma[c]**
    AND
    A first-degree relative diagnosed age <45 y with cancer
    AND
    An additional first- or second-degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age
- **Chompret criteria:[d,e]**
  - **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 the family history**
    OR
  - **Breast cancer before age 31 yr**

FOLLOW-UP

LFS testing criteria met[f] → **See Follow-up (LIFR-2)**

LFS testing criteria not met → **Individualized recommendations according to personal and family history**

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
[b]Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. Cancer Res 1988;48:5358-5362.
[c]To date, there have been no reports of Ewing sarcoma, GIST, desmoid tumor, or angiosarcoma in *TP53* mutation carriers.
[d]Chompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. J Med Genet 2001;38:43-47.
[e]Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol 2015;33:2345-2352.
[f]TP53 testing can be ordered alone, concurrently with BRCA1/2 testing and/or other gene testing or as a follow-up test after negative BRCA1/2 testing.

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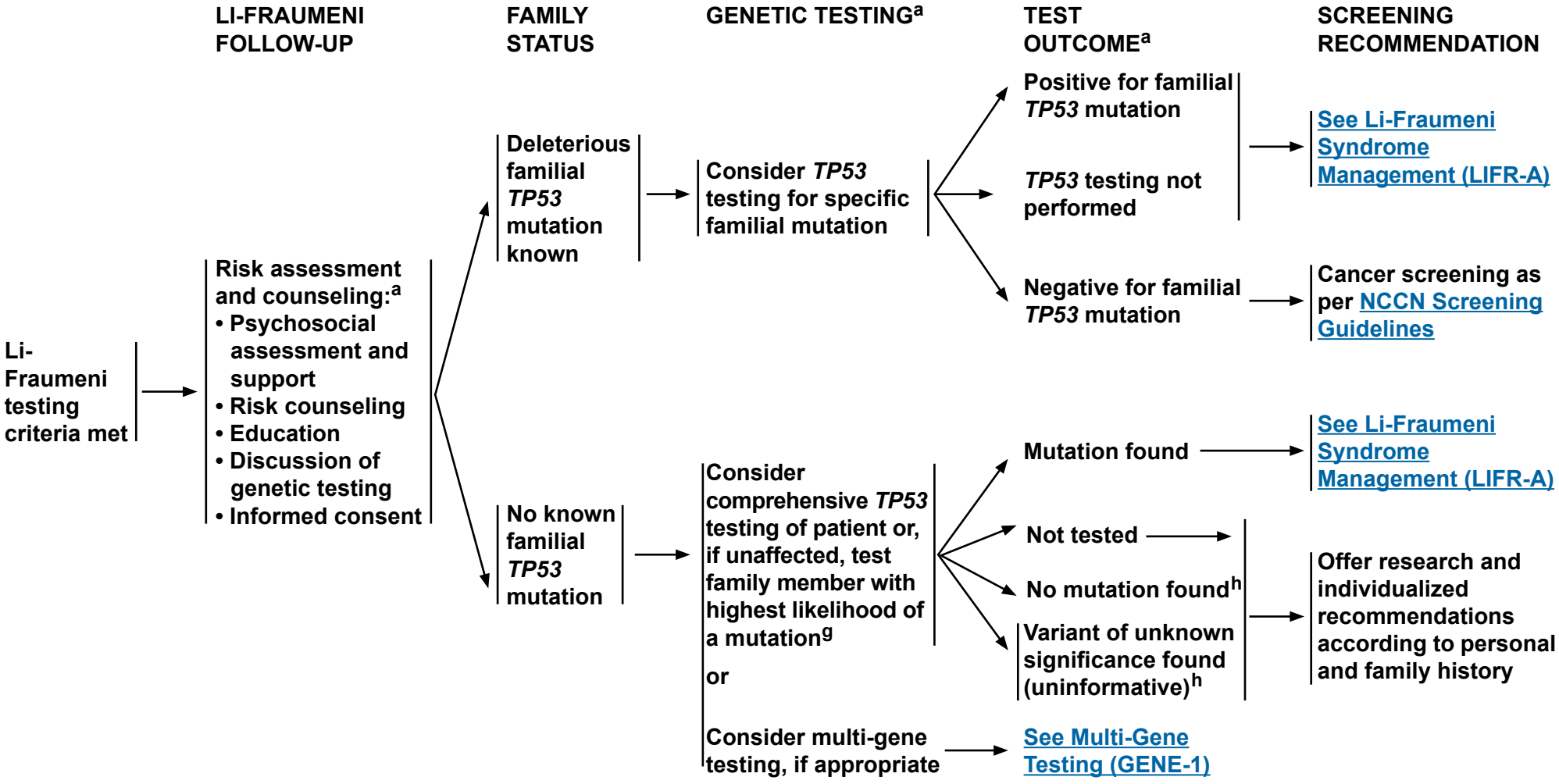

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
[g]Youngest age at diagnosis, bilateral disease, multiple primaries, or sarcoma at age <45 y.
[h]If no mutation is found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast cancer syndromes such as BRCA-related (BRCA-1) and/or Cowden syndrome (COWD-1) or multi-gene testing (GENE-1). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see ADDIT-1.

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LI-FRAUMENI SYNDROME MANAGEMENT

BREAST CANCER RISK FOR WOMEN

- **Breast awareness[1] starting at age 18 y.**
- **Clinical breast exam, every 6–12 mo, starting at age 20–25 y[2]**
- **Breast screening[3]**
  - **Age 20–29[2] y, annual breast MRI[4] screening (preferred) or mammogram if MRI is unavailable**
  - **Age 30–75 y, annual mammogram and breast MRI[4] screening**
  - **Age >75 y, management should be considered on an individual basis.**
  - **For women with a TP53 mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.**
- **Discuss option of risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options.**
- **Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy.**

OTHER CANCER RISKS

- **Address limitations of screening for many cancers associated with LFS. 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).**
- **Pediatricians should be apprised of the risk of childhood cancers in affected families.**
- **Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors: include neurologic examination.**
- **Therapeutic RT for cancer should be avoided when possible.**
- **Consider colonoscopy every 2–5 y starting at 25 y or 5 y before the earliest known colon cancer in the family (whichever comes first).**
- **Perform annual dermatologic examination.**
- **Perform annual whole body MRI (rapid non-contrast exams per ACRIN model).[5]**
- **The brain may be examined as part of whole body MRI or as a separate exam.[5]**
- **Provide additional surveillance based on family history of cancer.**
- **Provide education regarding signs and symptoms of cancer.**

Continued on next page

[1]Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.
[2]Or at the age of the earliest diagnosed breast cancer in the family, if below age 20 y.
[3]The appropriateness of imaging modalities and scheduling is still under study.
[4]High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women.
[5] Whole body MRI is being evaluated in multiple international trials. Other components of screening are being evaluated in protocols, including regular blood screening for hematologic malignancies, and biochemical screening.

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LI-FRAUMENI SYNDROME MANAGEMENT

REPRODUCTIVE OPTIONS

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

RISK TO RELATIVES

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

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COWDEN SYNDROME/PTEN HAMARTOMA TUMOR SYNDROME TESTING CRITERIA[a,b,c,d]

- **Individual from a family with a known *PTEN* mutation**
- **Individual meeting clinical diagnostic criteria[e] for CS/PHTS**
- **Individual with a personal history of:**
  - **Bannayan-Riley-Ruvalcaba syndrome (BRRS) or**
  - **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[f] 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**

FOLLOW-UP

CS/PHTS testing criteria met → **See Follow-up (COWD-2)**

CS/PHTS testing criteria not met → **Individualized recommendations according to personal and family history**

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

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

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.
[b]These are testing criteria; clinical diagnostic criteria can be found on COWD-3.
[c]If two criteria involve the same structure/organ/tissue, both may be included as criteria.
[d]Current evidence does not support testing for succinate dehydrogenase (*SDH*) gene mutations in patients with PHTS. (Am J Hum Genet 2011;88:674-675).
[e]Pilarski R, Burt R, Kohlmann W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616. See COWD-3.
[f]If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.
[g]Multiple polyp types are often seen in patients with PHTS, and less commonly may include adenomas, hyperplastic polyps, and other histologies.
[h]Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: Birth to 18 years. Pediatrics 1987;79:706-712.
[i]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.
[j]Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

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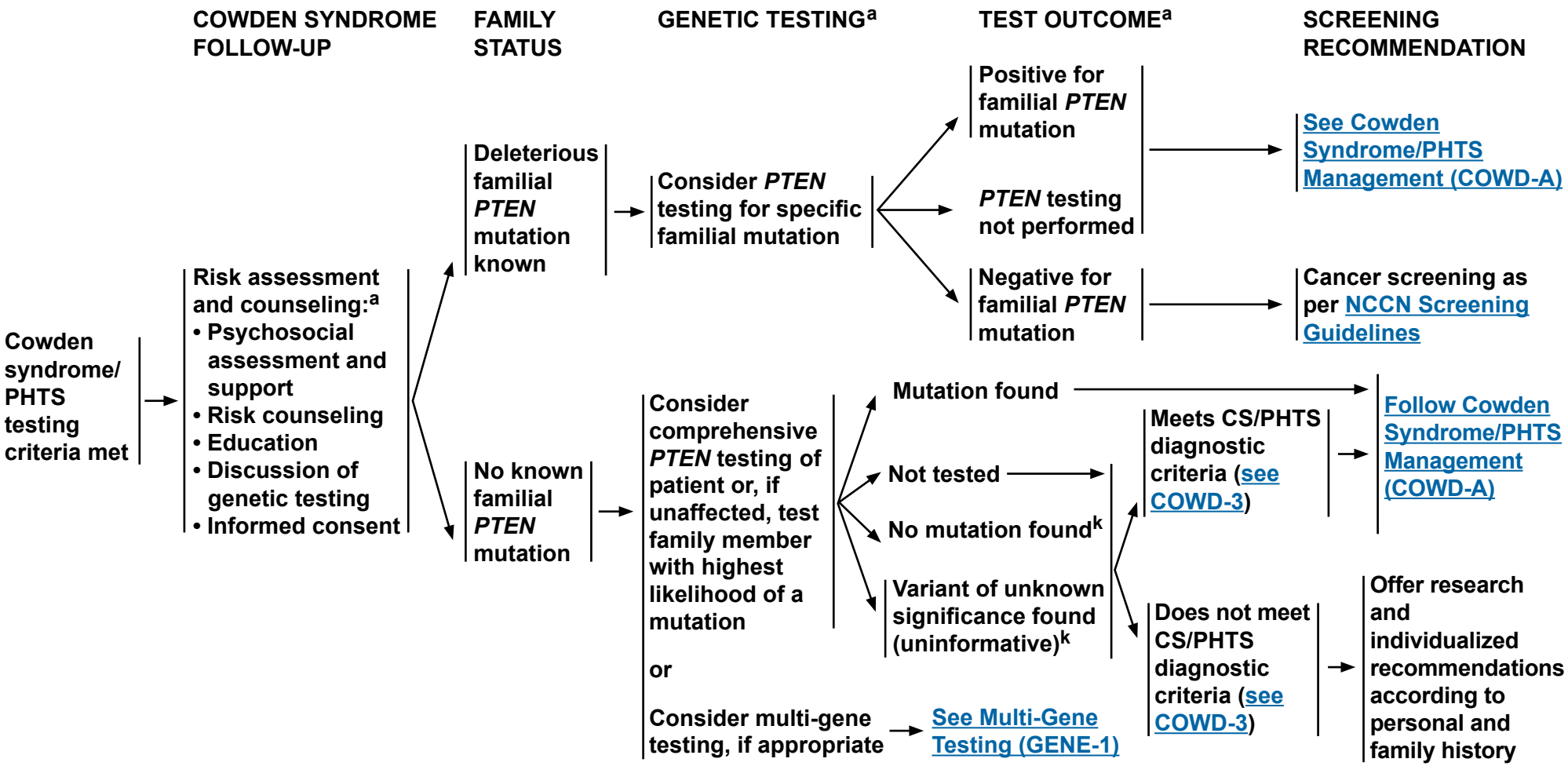

[a]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

[k]If no mutation is found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast cancer syndromes such as BRCA-related (BRCA-1) and/or Li-Fraumeni syndrome (LIFR-1) or multi-gene testing (GENE-1). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see ADDIT-1.

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REVISED PTEN HAMARTOMA TUMOR SYNDROME CLINICAL DIAGNOSTIC CRITERIA[I]

MAJOR CRITERIA:
- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- GI hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97 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 (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* mutation:
1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

[I]Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616.

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COWDEN SYNDROME/PHTS MANAGEMENT

WOMEN

- **Breast awareness[1] starting at age 18 y.**
- **Clinical breast exam, every 6–12 mo, starting at age 25 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).**
- **Breast screening**
  - **Annual mammography and breast MRI screening starting at age 30–35 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).[2,3]**
  - **Age >75 y, management should be considered on an individual basis.**
  - **For women with a *PTEN* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.**
- **For endometrial cancer screening,[4] encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Consider annual random endometrial biopsies and/or ultrasound beginning at age 30–35 y.**
- **Discuss option of hysterectomy[5] upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.**
- **Discuss option of risk-reducing mastectomy and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.**
- **Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.**

MEN AND WOMEN

- **Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.**
- **Annual thyroid ultrasound starting at time of PHTS diagnosis**
- **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 found.**
- **Consider renal ultrasound starting at age 40 y, then every 1–2 y**
- **Dermatologic management may be indicated for some patients**
- **Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.**
- **Education regarding the signs and symptoms of cancer.**

Continued on next page

[1]Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.
[2]The appropriateness of imaging modalities and scheduling is still under study.
[3]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 preformed on days 7–15 of a menstrual cycle for premenopausal women.
[4]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.
[5]Oophorectomy is not indicted for CS/PHTS alone but may be indicated for other reasons.

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COWDEN SYNDROME/PHTS MANAGEMENT

RISK TO RELATIVES

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

REPRODUCTIVE OPTIONS

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

[1]Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.
[2]The appropriateness of imaging modalities and scheduling is still under study.
[3]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 preformed on days 7–15 of a menstrual cycle for premenopausal women.
[4]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.
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MULTI-GENE TESTING

Overview of multi-gene testing

- **The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.**
- **Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective.**
- **There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.**
- **As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.**
- **Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes.[a] For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene tests are necessarily clinically actionable.**
- **As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain mutations in a gene may pose higher or lower risk than other mutations in that same gene. Therefore, it may be difficult to use a known mutation alone to assign risk for 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.**
- **Mutations in many breast cancer susceptibility genes involved in DNA repair may be associated with the rare autosomal recessive condition, Fanconi anemia.**
- **There is an increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes.**
- **It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.**

References (GENE-2)

See Breast and Ovarian Management Based on Genetic Test Results (ADDIT-2)

[a]Research is evolving, and gene carriers should be encouraged to participate in clinical trials or genetic registries.

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MULTI-GENE TESTING

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EXAMPLES OF ADDITIONAL GENETIC MUTATIONS ASSOCIATED WITH BREAST/OVARIAN CANCER RISK

- **Hereditary Diffuse Gastric Cancer Syndrome (See NCCN Guidelines for Gastric Cancer for more information)**
  - ***CDH1* gene**
  - **Diffuse gastric cancer: 67%–83% risk**
  - **Lobular cancer of the breast: 39%–52% risk**

- **Peutz-Jeghers Syndrome (PJS) (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for more information)**
  - ***STK11/LKB1* gene**
  - **Breast cancer: 44%–50% risk**
  - **Ovarian cancer: 18%–21% risk (ovarian sex cord tumors are the most common)**
  - **For other cancers associated with PJS, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**

- **Lynch Syndrome (LS) (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal for more information)**
  - **Mismatch Repair (*MMR*) genes — *MLH1, MSH2, MSH6, PMS2***
  - ***EPCAM* gene deletion**
  - **Ovarian cancer: 9% risk**
  - **Breast cancer: conflicting data regarding increased risks**
  - **For other cancers associated with LS, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.**

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

	Recommend Breast MRI[d] (>20% risk of breast cancer[e])	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	***ATM*** ***BRCA1*** ***BRCA2*** ***CDH1*** ***CHEK2*** ***PALB2*** ***PTEN*** ***STK11*** ***TP53***	***BRCA1*** ***BRCA2*** ***CDH1*** ***PTEN*** ***TP53*** ***PALB2***	***BRCA1*** ***BRCA2*** **Lynch syndrome[f]** ***BRIP1*** ***RAD51C*** ***RAD51D***
Insufficient evidence for intervention[b,c]	***BRIP1***	***ATM*** ***CHEK2*** ***STK11***	***PALB2***

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

[a]Other genes may be included in multi-gene testing.
[b]Intervention may still be warranted based on family history or other clinical factors.
[c]Insufficient evidence for *any* recommendations for breast MRI, RRSO, or RRM include but are not limited to: BARD1, FANCC, MRE11A, MUTYH, NF1, NBN, RAD50, SMARCA, or XRCC2.
[d]See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
[e]May be modified based on family history or specific gene mutation.
[f]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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

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

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

All recommendations are category 2A unless otherwise noted.

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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 a high probability of cancer development (ie, a high penetrance phenotype), vertical transmission through either mother or father, and an association with other types of tumors.[3,4] They often have an early age of onset and exhibit an autosomal dominant inheritance pattern (ie, occur when the individual has a mutation in only one copy of a gene). Familial cancers share some but not all features of hereditary cancers. For example, although familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.[5-8]

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

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

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Guidelines® is on the management of breast and ovarian cancer risk in these individuals. During the last few years, a number of genetic aberrations that may contribute to increased risks for development of breast and/or ovarian cancers have been identified. The current NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian focus primarily on assessment of mutations in *BRCA1/2, TP53,* and phosphatase and tensin homolog (*PTEN*), and recommended approaches to genetic testing/counseling and management strategies in individuals with these genetic mutations. Where possible, mutations in more recently identified genes have been addressed to the extent possible given the limited information available.

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian, an electronic search of the PubMed database was performed to obtain key literature published between November 14, 2014 and September 30, 2015, 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). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[13]

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

The PubMed search resulted in 40 citations, and their potential relevance was examined. 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).

Hereditary Breast or Breast/Ovarian Cancer Syndromes

Breast cancer is the most prevalent type of cancer in women in the United States and is the second leading cause of cancer death in women.[14] In the United States, approximately 234,190 new cases of breast cancer and 40,730 deaths are estimated for 2015 (estimated figures include both genders).[14] Up to 10% of breast cancers are due to specific mutations in single genes that are passed down in a family.[6,8] Specific patterns of hereditary breast/ovarian cancers are linked to mutations in the *BRCA1/2* genes.[15,16] 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 mutations in the *TP53* and *PTEN* genes, respectively.[17,18] Similar to the *BRCA1/2* genes, the *TP53* and *PTEN* genes encode for proteins involved in processes related to tumor suppression, such as DNA repair and cell cycle regulation. Hereditary diffuse gastric cancer (HDGC) is another rare hereditary syndrome that is also associated with development of lobular breast cancer. This syndrome arises from mutation(s) in the *CDH1* (cadherin 1, type 1, E-cadherin [epithelial]) gene, which encodes for a tumor suppressor gene

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product.[19] In an analysis of 4 predominantly gastric cancer pedigrees from Newfoundland with a specific *CDH1* mutation, the cumulative risk for female lobular breast cancer by the age of 75 was estimated to be as high as 52%.[20,21] Furthermore, germline *CDH1* mutations may be associated with lobular breast cancer in the absence of diffuse gastric cancer.[22] More information about HDGC can be found in the NCCN Guidelines for Gastric Cancer (available at www.NCCN.org).

These hereditary syndromes share several features beyond elevation of breast cancer risk. These syndromes arise from germline gene mutations that are not within sex-linked genes; hence, the mutations 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 mutation. In addition, individuals with these hereditary syndromes share increased risks for multiple cases of early-onset disease as well as bilateral disease. The gene mutations associated with these hereditary syndromes are considered to be highly penetrant, although a subsequent alteration or silencing in the second copy of the gene without the hereditary mutation is believed to be necessary for the initiation of cancer development (ie, 2-hit hypothesis).[23,24] In addition, the manifestations (ie, expression) of these hereditary syndromes are often variable in individuals within a single family (eg, age of onset, tumor site, number of primary tumors). The risk of developing cancer in individuals with one of these hereditary syndromes depends on numerous variables including the gender and age of the individual.

BRCA-Related Breast/Ovarian Cancer Syndrome

The overall prevalence of disease-related mutations in *BRCA1/2* genes has been estimated as 1 in 300 and 1 in 800, respectively.[25,26] Currently, hundreds of unique mutations have been identified in both *BRCA1* and *BRCA2* genes. However, a number of founder effects (see Table 1) have been observed in certain populations, wherein the same mutation has been found in multiple, ostensibly unrelated families and can be traced back to a common ancestor. Among the Ashkenazi Jewish population, for example, the frequency of 187delAG and 5385insC mutations in *BRCA1* and the 6174delT mutation in *BRCA2* approximates 1 in 40.[6,27] Certain founder mutations have also been identified in other populations.[25,28-33]

It has been estimated that over 90% of hereditary families with both breast and ovarian cancers are caused by mutation(s) in the *BRCA1/2* genes.[34] Hence, the degree of clinical suspicion for a *BRCA* mutation in a single individual with both breast and ovarian cancer or someone with a family history of both breast and ovarian cancer should be very high.

Both the *BRCA1* and *BRCA2* genes encode for proteins involved in tumor suppression. The *BRCA1* gene is located on chromosome 17 and is believed to be involved in both DNA repair and the regulation of cell-cycle checkpoints in response to DNA damage. However, the molecular mechanism through which *BRCA1* functions to preserve genomic stability remains unclear.[35] The *BRCA2* gene, located on chromosome 13, is involved in repair of replication-mediated double-strand DNA breaks.[36,37]

Mutations in the *BRCA1/2* genes can be highly penetrant (for definition, see Table 1), although the probability of cancer development in carriers of *BRCA1/2* mutations is variable, even within families with the same mutation.[38-40] Estimates of penetrance range from 41% to 90% lifetime

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risk for breast cancer, with an increased risk for contralateral breast cancer.[41-48] In addition, female carriers of these genes have an estimated 8% to 62% lifetime risk for ovarian cancer, depending on the population studied.[42 54,43-47,49,50] In a 2007 meta-analysis of published data that evaluated *BRCA1/2* penetrance, estimates for mean cumulative risks for breast and ovarian cancer by age 70 years for *BRCA1* mutation carriers were 57% and 40%, respectively.[43] The corresponding estimates for *BRCA2* mutation carriers were 49% and 18%, respectively. In a recent prospective analysis of risk estimates from individuals with *BRCA1/2* mutations in the United Kingdom (N = 1887), estimates for mean cumulative risks for breast cancer and ovarian cancer by age 70 years for *BRCA1* mutation carriers were 60% and 59%, respectively.[46] The corresponding estimates for *BRCA2* mutation carriers were 55% and 16.5%, respectively. Among the patients diagnosed with unilateral breast cancer (n = 651), the mean cumulative risks for contralateral breast cancer by age 70 years were estimated to be 83% for *BRCA1* carriers and 62% for *BRCA2* carriers.[46] An international study including 19,581 *BRCA1* mutation carriers and 11,900 *BRCA2* mutation carriers showed that 46% of the *BRCA1* mutation carriers and 52% of the *BRCA2* mutation carriers eventually developed breast cancer, and 12% of the *BRCA1* mutation carriers and 6% of the *BRCA2* mutation carriers eventually developed ovarian cancer.[51] At present, it is unclear whether penetrance is related only to the specific mutation identified in a family or whether additional factors, either genetic or environmental, affect disease expression. It is generally accepted, however, that carriers of mutations in *BRCA1/2* genes have an excessive risk for both breast and ovarian cancer that warrants consideration of more intensive screening and preventive strategies.

Some histopathologic features have been reported to occur more frequently in breast cancers characterized by a *BRCA1/2* mutation. 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”).[52-57] Studies have reported *BRCA1* mutations in 8.5% to 28% of patients with triple-negative breast cancer.[57-63] A recent meta-analysis examining 12 studies with 2,533 breast cancer patients showed that women with triple-negative breast cancer are more likely to be carriers of a *BRCA1* mutation, relative to women with breast cancer that is not classified as triple-negative (relative risk [RR] = 5.65, 95% CI = 4.15–7.69).[64] Several reports have also suggested the role of *BRCA2* mutations in triple-negative breast cancer. The incidence of *BRCA2* mutations range from 3% to 17% in studies of triple-negative breast cancer cases unselected for age or family history.[58,63,65]

An increased incidence of *BRCA1/2* mutations was reported in triple-negative breast cancer cases from at-risk populations. Among Ashkenazi Jewish women with breast cancer unselected for family history (N = 451), triple-negative disease was observed in 14% of patients and *BRCA* founder mutations were found in 11% of patients.[66] Among the subgroup with triple-negative breast cancer (n = 65), the incidence of *BRCA* mutations was 39% (*BRCA1* mutation in 30%; *BRCA2* mutation in 9%).[66] In addition, it appears that among patients with triple-negative disease, *BRCA* mutation carriers were diagnosed at a younger age compared with non-carriers.[60,67] 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.[59] 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%

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among those diagnosed before age 50 years (n = 208). For patients with triple-negative breast cancer with a family history of breast and/or ovarian cancer (n = 105), *BRCA1* mutations were found in 48% of patients.[59]

Male carriers of a *BRCA1/2* mutation also have a greater risk for cancer susceptibility.[68] In one study of 26 high-risk families with at least one case of male breast cancer, 77% demonstrated a *BRCA2* mutation.[34] Among male patients with breast cancer who were not selected on the basis of family history, 4% to 14% tested positive for a germline *BRCA2* mutation.[69-72] In a series of male breast cancer cases (N = 115; primarily from cancer registry data), *BRCA2* mutations were detected in 16% of cases; the incidence of *BRCA2* mutations was 40% among patients selected for family history of breast cancer and 13% among those unselected for family history.[71] For males with a *BRCA2* mutation, the cumulative lifetime risk for breast cancer has been estimated at 7% to 8%.[73,74] The cumulative lifetime risk for *BRCA1* mutation carriers is 1.2%.[74] In contrast, for men without a *BRCA1/2* mutation, the lifetime risk for breast cancer has been estimated at approximately 0.1% (1 in 1,000).[71,75]

Relatively few studies have examined *BRCA1/2* mutation rates in black women. An observational study including 396 black women who were diagnosed with invasive breast cancer before age 50 showed that 12.4% were carriers of a *BRCA1/2* mutation.[76] Carriers of a *BRCA1/2* mutation were also significantly more likely to have triple-negative disease ($P < .001$), a family history of breast and/or ovarian cancer ($P < .001$), and a diagnosis before age 45 ($P < .05$). Based on these findings, study authors suggested that black women diagnosed with invasive breast cancer at a young age (ie, younger than 50 years) should be considered for *BRCA* testing.

The evidence that a *BRCA1/2* mutation is associated with poor survival outcomes for breast cancer has been inconsistent.[77,78] A meta-analysis including 13 studies showed that *BRCA1* mutation carriers with breast cancer had worse 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.[79] Another recent meta-analysis including 66 studies 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.[80] An analysis of 119 Swedish women who were diagnosed with early-onset breast cancer showed that not receiving chemotherapy treatment was associated with poor survival in *BRCA1/2* mutation carriers (HR, 3.0; 95% CI, 1.2—7.7; $P = .014$).[81] Carrying a *BRCA1/2* mutation is not significantly associated with nodal metastasis.[82]

Increased risks for cancers of the ovary, fallopian tube, and peritoneum are observed in carriers of *BRCA1/2* mutations.[83,84] Germline mutations in *BRCA1/2* are responsible for at least 10% of epithelial ovarian cancers .[85,86] An analysis of 2,222 epithelial ovarian cancer patients showed that 11% carried a *BRCA1/2* mutation when disease was high-grade serous.[87] In the setting of an invasive ovarian cancer diagnosis, as many as 13% to 20% of women have a germline *BRCA1/2* mutation.[47,88-90] However, it has been reported that about half of families showing a genetic predisposition to ovarian cancer do not have identifiable *BRCA1/2* mutations.[91] Hence, other gene mutations predisposing a patient to ovarian cancer are likely to exist.[92] Of note, ovarian cancer is a component tumor of Lynch syndrome that is associated with germline mutations in mismatch repair genes.[93] Interestingly, results from a prospective study suggest that women from families at increased risk for hereditary breast cancer without site-

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specific *BRCA* mutations are not at increased risk for ovarian cancer. However, these results may have been confounded by the ethnic characteristics and size of the study population.[94]

Several studies have reported more favorable survival outcomes among *BRCA1/2* mutation carrier patients with ovarian cancer compared with non-carrier patients.[95-100] In a case-control study of patients with epithelial ovarian cancer (N = 66), patients with a *BRCA1/2* mutation had improved outcomes compared with patients with non-hereditary ovarian cancer, including significantly longer median survival from time of diagnosis (101 months vs. 35 months; $P < .002$).[99] In a large case-control study of Jewish patients with epithelial invasive ovarian cancer (N = 779), patients with a *BRCA1/2* mutation had significantly longer median survival compared with non-carrier patients (54 months vs. 38 months; $P = .002$).[98] Results from a pooled analysis from 26 observational studies that included invasive epithelial ovarian cancer cases from *BRCA1/2* mutation carriers (n = 1213) and non-carriers (n = 2666) showed favorable survival outcomes for patients with a *BRCA1/2* mutation.[96] The 5-year survival rate for non-carriers, *BRCA1* carriers, and *BRCA2* carriers was 36%, 44%, and 52%, respectively. The survival advantage compared with non-carriers was significant for both the *BRCA1* carriers (HR, 0.78; 95% CI, 0.68–0.89; $P < .001$) and *BRCA2* mutation carriers (HR, 0.61; 95% CI, 0.50–0.76; $P < .001$).[96] In a population-based case-control study of women with invasive epithelial (nonmucinous) ovarian cancer (N = 1001) from the Australian Ovarian Cancer Study Group, *BRCA1/2* mutation carriers had improved survival outcomes compared with non-carriers in terms of median progression-free survival (20 months vs. 16 months; not statistically significant) and median survival (62 months vs. 55.5 months; $P = .031$).[95] Moreover, *BRCA1/2* mutation carriers appeared to be more responsive to cytotoxic chemotherapy (regardless of class of agent) compared with non-carrier patients.

Survival outcomes appear to be most favorable for *BRCA2* mutation carriers; in a subgroup of patients with *BRCA2* mutations (n = 53), the median survival was 70 months.[95] In an observational study of patients with high-grade serous ovarian cancer (N = 316), patients with *BRCA2* mutations had significantly favorable survival outcomes (HR, 0.33; 95% CI, 0.16–0.69; $P = .003$; 5-year rate: 61% vs. 25%) and progression-free survival (HR, 0.40; 95% CI, 0.22–0.74; $P = .004$; 3-year rate: 44% vs. 16%) compared with non-carrier patients (having wild-type *BRCA*).[100] An observational study including 1,345 women with ovarian cancer who participated in clinical trials from the Gynecologic Oncology Group showed that *BRCA2* mutation carriers had significantly longer progression-free survival (HR, 0.60; 95% CI, 0.45–0.79; $P < .001$) and overall survival (HR, 0.39; 95% CI, 0.25–0.60; $P < .001$), relative to those without mutations.[86] 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.[100]

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.[85,89,101-104] Mutations are also associated with non-mucinous ovarian carcinoma as opposed to mucinous.[88,90] Mucinous epithelial ovarian carcinomas may be associated with other gene mutations, such as *KRAS* and *TP53* mutations.[105] *TP53* mutations are implicated in LFS (see below). Non-epithelial ovarian carcinomas (eg, germ cell and sex cord stromal tumors) are not significantly associated

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with a *BRCA1/2* mutation,[106] but they may be associated with other cancer genetic syndromes. For example, sex cord tumors may be associated with Peutz-Jeghers syndrome (see below), while Sertoli-Leydig tumors are associated with both Peutz-Jeghers syndrome and DICER1-related disorders.[107-112] Current data show that ovarian low malignant potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with a *BRCA1/2* mutation.[88] Therefore, the panel does not consider the presence of an ovarian low malignant potential tumor to be a criterion for genetic testing.

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.[113-115] 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.[113,116,117] 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.[113,117,118] Although TIC appeared to present more frequently among *BRCA1/2* mutation carriers compared with non-carriers undergoing RRSO,[117,118] TIC has also been documented among patients with serous carcinomas unselected for family history or *BRCA* mutation status.[119] Because TIC was identified in individuals who underwent surgery for risk reduction (for *BRCA1/2* mutation carriers) or other gynecologic indications, the incidence and significance of these early lesions within the general population is unclear. Hence, at the present time, there is no justifiable role for *BRCA* testing for cases based solely on the finding of TIC during pathology evaluation for gynecologic indications.

An increased frequency of other malignancies has been reported in families with mutations in the *BRCA1/2* genes.[44,68,120] Germline *BRCA1/2* mutations have been associated with an increased risk for prostate cancer in numerous reports.[44,68,120-126] In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in risk for prostate cancer,[121-123,126-128] while increased risks were not observed for *BRCA1* mutation carriers in some studies.[121-123,127,128] An analysis of 1,522 *BRCA1/2* male mutation carriers undergoing prostate-specific antigen (PSA) testing showed that 2.3% of *BRCA1* carriers and 3.3% of *BRCA2* carriers had a detected prostate cancer based on biopsy results.[129] Prostate cancers with germline *BRCA1/2* mutations appear to have a more aggressive phenotype (eg, more frequently associated with Gleason score ≥8) than tumors from non-carrier patients.[130,131] A recent study in a large cohort of patients from Spain with prostate cancer (N = 2019) showed that the group of 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.[130] Moreover, cause-specific survival outcome was significantly poorer in *BRCA1/2* mutation carriers compared with non-carriers (median survival 8.6 years vs. 15.7 years; $P = .015$). Subgroup analysis by mutation type showed poor outcomes in patients with *BRCA2* mutations (n = 61); the role of *BRCA1* mutations was not well defined, possibly due to the small patient size (n = 18) and limited follow-up in this subgroup.[130] Prostate cancer in patients with *BRCA2* mutations has also been associated with a higher histologic grade in other studies.[121,122] In addition, analyses of data obtained from cancer registries and treatment center databases showed that *BRCA2* mutation carriers with prostate cancer had more aggressive or rapidly progressive disease, and significantly decreased survival compared with patients who were *BRCA1* mutation carriers or non-carriers.[132-134] In a study of patients with prostate cancer from a population-based cancer

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registry in Iceland (N = 596), patients with *BRCA2* mutations had significantly decreased median survival compared with non-carriers (having wild-type *BRCA2*) (2 years vs. 12 years; $P < .001$).[134] Moreover, in a study of patients with prostate cancer using data obtained from cancer center databases (N = 301), patients with *BRCA2* mutations had significantly decreased median survival compared with patients with *BRCA1* mutations (4 y vs. 8 y; $P < .01$).[132]

BRCA2 mutation carriers have also been reported to have a higher risk for pancreatic cancer and melanoma.[68,120,126,128,135,136] 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).[127] Both *BRCA1* and *BRCA2* mutations have been associated with increased propensity for developing pancreatic cancer.[126,136-141] In an analysis of samples taken from patients with familial pancreatic cancer (kindreds in which ≥3 family members had pancreatic cancer, at least 2 of who were first-degree relatives), *BRCA2* mutations were detected in 17% of patient samples.[139] A recent analysis including 727 unrelated probands with a family history of pancreatic cancer showed that 1.2% tested positive for a *BRCA1* mutation, and 3.7% tested positive for a *BRCA2* mutation.[142]

An analysis of 159 patients with pancreatic adenocarcinoma showed that 8% harbored a *BRCA2* mutation.[140] However, it is important to note that participants of this study were not unselected pancreatic cancer patients; they were presenting for genetic counseling, and, thus, were weighted towards stronger family histories. Also, 56% of the sample was Ashkenazi Jewish. Pancreatic cancer patients with 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*.[135,140,141,143] In 211 Ashkenazi Jewish breast cancer patients with a family history of pancreatic cancer, 6.6% had a *BRCA1* mutation and 7.6% had a *BRCA2* mutation.[144]

Some data related to cancer risk in *BRCA1/2* mutation carriers at some sites other than the breast/ovary are contradictory.[145] For example, it has been suggested that the increased risk for endometrial cancer observed in some *BRCA1/2* mutation carriers is mainly due to the use of tamoxifen therapy by these women rather than the presence of a gene mutation.[146]

NCCN Recommendations

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

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

- Diagnosed at age 45 years or younger;
- Diagnosed with at least two breast cancer primaries (ie, bilateral tumors or 2 or more clearly separate ipsilateral tumors, occurring synchronously or asynchronously), the first at age 50 years or younger;
- Diagnosed at age 50 years or younger with 1 or more close relatives with breast cancer at any age (or with an unknown or limited family history), 1 or more close relatives with pancreatic cancer, or 1 or more close relatives with prostate cancer (Gleason score ≥7);
- Diagnosed with triple-negative breast cancer at age 60 years or younger;
- Diagnosed at any age with 1 or more close relatives with breast cancer diagnosed at age 50 years or younger;
- Diagnosed at any age with 2 or more close relatives with breast cancer at any age;
- Diagnosed at any age with 1 or more close relatives with ovarian carcinoma (including fallopian tube and primary peritoneal cancers) diagnosed at any age;
- Diagnosed at any age with 2 or more close relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age; or
- Having a close male relative with breast cancer at any age.

In patients with a personal history of breast cancer and Ashkenazi Jewish heritage, no additional family history may be needed to meet testing criteria. In addition, the NCCN Panel recommends testing for patients with a personal history of ovarian carcinoma or male breast cancer, either diagnosed at any age.

Testing is recommended for those with a personal history of prostate cancer (Gleason score ≥7) diagnosed at any age, with a family history of at least one relative with ovarian carcinoma at any age or breast cancer younger than age 50 or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥ 7) diagnosed at any age. Those with a personal history of pancreatic cancer should meet the same testing criteria. Further, a personal history of pancreatic cancer combined with Ashkenazi Jewish ancestry warrants testing.

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

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

Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* gene mutations.[18] It has been estimated to be involved in only

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about 1% of hereditary breast cancer cases,[147] although results from other studies suggest that germline *TP53* gene mutations may be more common than previously believed, with estimates of 1 in 5,000 to 1 in 20,000.[148,149] There are only about 300 families reported in an LFS registry maintained by an NCCN Member Institution and the National Cancer Institute.[150] The tumor suppressor gene, *TP53*, is located on chromosome 17,[151,152] 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.[151-153] Germline mutations in the *TP53* gene have been observed in over 50% (and in over 70% in some studies) of families meeting the classic definition of LFS (see Li-Fraumeni Syndrome Testing Criteria in the algorithm).[18,148,154] Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.[155]

LFS, a highly penetrant cancer syndrome associated with a high life-time risk for cancer, is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (although Ewing's sarcoma is less likely to be associated with LFS), premenopausal breast cancer, acute leukemia, colon cancer, adrenocortical carcinoma, and brain tumors.[18,148,153,156-161] 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 mutations in the *TP53* gene, 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.[148] Interestingly, two retrospective studies have reported a very high frequency of HER2-positive breast tumors (67%–83% of evaluated breast tumors) among patients with germline *TP53* mutations, which suggests that amplification of HER2 may arise in conjunction with *TP53* mutations.[162,163] This association between HER2-positive breast cancer and germline *TP53* mutations warrants further investigation, as such patients may potentially benefit from chemoprevention therapies that incorporate HER2-targeted agents.

Individuals with LFS often present with certain cancers (eg, soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood,[158] and have an increased risk of developing multiple primary cancers during their lifetimes.[164] 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.[165] 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.[148] It is important to mention that estimations of cancer risks associated with LFS are limited to at least some degree by selection bias since dramatically affected kindreds are more likely to be identified and become the subject of further study.

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

Classic LFS criteria, based on a study by Li and Fraumeni involving 24 LFS kindreds, include the following: a member of a kindred with a known *TP53* mutation; a combination of an individual diagnosed at age 45 years or younger with a sarcoma and a first-degree relative diagnosed with cancer at age 45 years or younger; and an additional first- or second-degree relative in the same lineage with cancer

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diagnosed at age younger than 45 years 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%).[148] Thus, it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.[161,166] Classic LFS criteria make up one set of criteria included in the guidelines to guide selection of individuals for *TP53* gene mutation 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.[156,167-169] One set of these less strict criteria proposed by Birch and colleagues shares many of the features of classic LFS criteria, although a larger range of cancers is included.[148,156] Individuals with de novo germline *TP53* mutations (no mutation in either biological parent) have also been identified.[148,149,157] These cases would not be identified as *TP53* testing candidates based on classic LFS criteria due to requirement of a family history. This issue is circumvented, in part, by the criteria for *TP53* testing proposed by Chompret and colleagues, which recommends testing for patients with multiple primary tumors of at least 2 “core’ tumor types (ie, sarcoma, breast cancer, adrenocortical carcinoma, brain tumors) diagnosed at age <36 years or patients with adrenocortical carcinoma diagnosed at any age, regardless of family history (see Li-Fraumeni Syndrome Testing Criteria in the algorithm).[168] The Chompret criteria have an estimated positive predictive value of 20% to 35%,[148,168] 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).[148] 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.[148,157,170-172] 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.[170,172]

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.[171] Several studies have investigated the likelihood of a germline *TP53* mutation in this population.[148,170,173-176] In a study of *TP53* mutations evaluated at a single reference laboratory, Gonzalez et al found that all women younger than 30 years of age with breast cancer who had a first- or second-degree relative with at least one of the core cancer types (n = 5) had germline *TP53* mutations.[148] In an analysis of patients with early-onset breast cancer (age of diagnosis <30 years) tested for *TP53* mutation at a single institution (N = 28), 6 patients (33%) were found to have *TP53* mutations.[177] Among the patients who were tested, a *TP53* mutation was found in approximately 8% who did not meet traditional LFS criteria for testing. In another study in patients with *BRCA1/2* mutation-negative early-onset breast cancer (age of diagnosis ≤35 years) tested for *TP53* mutation at a single institution (N = 83), approximately 5% were found to have *TP53* mutations.[175] 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

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tissue sarcoma, brain tumors or adrenocortical carcinoma) and in 1 of 17 patients (6%) with a family history of breast cancer only.[175] 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%.[148,174,176,177] 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 age 33 were carriers of a germline *TP53* mutation.[170] 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.[173]

Finally, a member of a family with a known *TP53* mutation is considered to be at sufficient risk to warrant gene mutation 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.

Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome

The spectrum of disorders resulting from germline mutations in *PTEN*[178] are referred to as the *PTEN* hamartoma tumor syndrome (PHTS). The spectrum of PHTS includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Adult Lhermitte-Duclos disease (LDD), Proteus-like syndrome,[17,179,180] and autism spectrum disorders with macrocephaly.[17,180,181]

The estimated penetrance of *PTEN* mutation is high, at approximately 80%.[182] The incidence of Cowden syndrome has been reported to be 1 in 200,000, although it is likely to be underestimated due to difficulties associated with making a clinical diagnosis of the disease.[183,184] Cowden syndrome is an autosomal dominant disorder, and most cases are associated with germline mutations in the *PTEN* gene, though one study found that germline *KILLIN* methylation may also be associated with this syndrome.[185]

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.[17,186] However, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* mutations should be assumed to have Cowden syndrome-associated cancer risks.

The lifetime risk for breast cancer for women diagnosed with Cowden syndrome has been estimated at 25% to 50%, with an average age of 38 to 50 years at diagnosis.[17,186-188] Some studies (as discussed above) have reported a higher cumulative lifetime risk for breast cancer (77%–85%) in individuals with Cowden syndrome or *PTEN* mutations.[189-191] There have been only 2 cases of breast cancer reported in men with Cowden syndrome.[188] Although many women with Cowden syndrome experience benign breast disease,[17] there is no evidence that the rate is higher than in the general population.[188]

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,[180,192] and the lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.[17,193] However, data tend to be aggregated, so it is difficult to calculate rates for multinodular goiter vs. solitary nodules.[188]

As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.[182] Although not well defined, women with Cowden syndrome may have a

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5% to 10% risk for endometrial cancer.[17,194 188] While many women with Cowden syndrome may also have uterine fibroids, this risk is not likely to be much greater than in women without Cowden syndrome or *PTEN* mutation.[188]

In addition, brain tumors and vascular malformations affecting any organ are occasionally seen in individuals with Cowden syndrome, although the risks for developing these conditions are not well defined.[17,188] It is important to note, however, that most of the data on the frequencies of the clinical features of Cowden syndrome are from compilations of case reports of relatively young individuals who may have subsequently developed additional signs of the disease (ie, new cancerous lesions), and these data are also likely to be confounded by selection bias.[17] 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.[17,195]

Benign skin lesions are experienced by most to all Cowden syndrome patients.[180,186] Skin lesions associated with Cowden syndrome include trichilemmomas (ie, benign tumors derived from the outer root sheath epithelium of a hair follicle), oral papillomas, mucocutaneous neuromas (hamartoma of the peripheral nerve sheath), palmoplantar keratoses, penile pigmentation in men, lipomas and vascular anomalies, and fibromas.[188,196] Trichilemmomas associated with Cowden syndrome tend to appear on the face, particularly the eyes, mouth, nose, and forehead.[188] Most individuals with Cowden syndrome exhibit characteristic mucocutaneous lesions by their twenties, and such lesions have been reported to occur in 99% of individuals with Cowden syndrome, showing nearly complete penetrance, although this may be a reflection of selection bias in the cases reported.[85,179] The presence of three or more mucocutaneous neuromas is considered a major diagnostic criterion of PHTS,[188] while the presence of 2 or more trichilemmomas has been reported to be pathognomonic for Cowden syndrome.[197,198] However, since most of the evidence regarding trichilemmomas is from the older literature, it is possible that the association with Cowden syndrome is somewhat overestimated.[17] There are reports of individuals with a solitary trichilemmoma who do not have Cowden syndrome.[197,198] Nevertheless, due to the strong association between these lesions and Cowden syndrome and the difficulty in clinically distinguishing between a trichilemmoma and another mucocutaneous lesion, it is important that a diagnosis of trichilemmoma is histologically confirmed.

It was previously estimated that about half of individuals with Cowden syndrome have gastrointestinal polyps.[199] However, this was almost certainly an underestimate.[199,200] In an analysis of 67 *PTEN* mutation carriers undergoing colonoscopy, colorectal polyps were found in 92.5% of patients.[199] About half of the patients undergoing colonoscopy had hyperplastic polyps, and about 25% each had polyps that were hamartomatous, ganglioneuromatous, or adenomatous.[199] Adenomatous or hyperplastic polyps were associated with development of colorectal cancer in this sample. Out of 39 *PTEN* mutation carriers undergoing esophagogastroduodenoscopy, upper gastrointestinal polyps were found in 67% of patients.[199] A systematic review of published case series (N = 102) regarding gastrointestinal manifestations in PHTS and component syndromes showed that 92.5% of these patients had polyps, with 64% having 50 or more.[201] Histologies were described as: hyperplastic (44%), adenomatous (40%), hamartomatous (38%), ganglioneuroma (33%), and inflammatory (24.5%). Other studies have also reported ganglioneuromatous polyps

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(ie, rare, benign peripheral nervous system tumors) in this population.[188,202] Early-onset (age <50 years) colorectal cancer has been reported in 13% of patients with *PTEN* mutation-associated Cowden syndrome, suggesting that routine colonoscopy may be warranted in this population.[199] The lifetime risk for colorectal cancer has been estimated as 9% to 16%.[190,191]

Several studies have projected lifetime estimates of cancer risk that are significantly higher than previously estimated. In a study of patients meeting diagnostic criteria for Cowden syndrome (N = 211; identified from published literature and records from a single institution), the cumulative lifetime risk for any cancer was 89%.[190] *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.[190] In a prospective study that evaluated genotype-phenotype associations between *PTEN* mutations and cancer risks,[191] deleterious germline mutations in *PTEN* were identified in 368 patients. Calculation of age-adjusted standardized incidence ratios (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.[191] 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).[189] The cumulative lifetime risks in these individuals were 77% for female breast cancer and 38% for thyroid cancer. The cumulative lifetime risk for any cancer was 85% overall, and women with PHTS were found to have a 2-fold greater cancer risk compared with men with PHTS.[189] 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 age 60, while male carriers have a cumulative risk of 56%.[203]

Adult LDD and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome.[179,182,190,204] A rare, slow growing, benign hamartomatous lesion of the brain, LDD, is a dysplastic gangliocytoma of the cerebellum.[17,190] In a multicenter prospective study examining 3042 probands who met clinical criteria for Cowden syndrome, 6% met criteria for LDD.[192] In a study of individuals meeting the diagnostic criteria for Cowden syndrome, the cumulative lifetime risk for LDD was reported to be 32%.[190] The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a *PTEN* gene mutation,[182,205] although exceptions have been reported.[206] 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.[181,207-210] Macrocephaly (defined as head circumference greater than the 97th percentile)[211] is a common finding in patients with Cowden syndrome. It has been estimated that approximately 80% to 100% of individuals with this syndrome will exhibit this clinical finding.[188]

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The BRRS variant of PHTS has been characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay, and, in males, pigmented macules on the glans penis,[212] 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.[213] 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.[204]

Other Genetic Mutations Associated with Breast/Ovarian Cancer

In the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the panel specifically focuses on assessment of known high-penetrance mutations (ie, *BRCA1/2, TP53, PTEN*) and recommendations for genetic testing, counseling, and management strategies in individuals with these mutations. Below is a description of additional gene mutations that the panel argues warrants additional screening beyond what is recommended in the general population (ie, those without the specific gene mutation). These include mutations for *CDH1, STK11, CHEK2, PALB2, ATM*, *BRIP1,* and *RAD51C* and *RAD51D.* Risk management for genetic mutations associated with Lynch syndrome is also described. Risk management recommendations within each gene mutation may be modified based on family history. A retrospective analysis of 337 patients who met NCCN criteria for *BRCA1/2* mutation testing and underwent multigene testing showed that 25 patients (7.4%) had non-*BRCA* mutations.[214] The most common of these mutations were *PALB2* (23%), *CHEK2* (15%), and *ATM* (15%).

Germline mutations in *CDH1* are associated with HDGC and lobular breast cancer, and studies have reported a cumulative lifetime risk for breast cancer of 39% to 52% among women who carry *CDH1* mutations.[20,215] Given the considerable risk for breast cancer in women with a *CDH1* mutation, the panel recommends screening with breast MRI, and the option of risk-reducing mastectomy should be discussed.

Germline mutations in *STK11* are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers as well as breast or non-epithelial ovarian cancers. Breast cancer risk in women with Peutz-Jeghers syndrome is 8% at age 40, 13% at age 50, 31% at age 60, and 45% at age 70.[216] The panel recommends breast MRI screening for women with this syndrome. Further information on Peutz-Jeghers syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

Another breast cancer susceptibility gene that has been identified is *CHEK2*. In a study of breast cancer patients in the United States with a strong family history of breast or ovarian cancer but who tested negative for a *BRCA1/2* mutation, 5% had *CHEK2* mutations.[217] Deleterious *CHEK2* mutations have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America.[218-221] 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.[222,223] The panel recommends breast MRI screening for women with this gene mutation.

PALB2 (partner and localizer of *BRCA2*) is a Fanconi anemia gene. Mutations in this gene are associated with increased risk for breast cancer, with studies including women with breast cancer showing that 1% to 3% harbor a pathogenic *PALB2* mutation.[63,224-226] In a study of 115

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men with breast cancer, a pathogenic *PALB2* mutation was detected in 1% to 2% of men who tested negative for a *BRCA2* mutation.[71] Breast cancer risk increases with age in women with a *PALB2* mutation, with a 14% lifetime risk by age 50 and a 35% lifetime risk by age 70.[227] The risk also increases with increasing number of relatives affected with breast cancer. Lifetime breast cancer risk for those with two first-degree relatives with breast cancer is 58% by age 70.[227] The panel recommends breast MRI screening for women with this gene mutation, and risk-reducing mastectomy should be considered. Though some studies suggest that there may be an association between *PALB2* and increased ovarian cancer risk,[86,228] there is currently insufficient evidence to recommend RRSO in these mutation carriers.

Mutations in the *ATM* (ataxia-telangiectasia mutated) gene may also increase risk for breast cancer. 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.[229] The presence of ATM heterozygotes was associated with a 9-fold increased risk for early-onset breast cancer and frequent bilateral occurrence. This study also showed an association between *ATM* heterozygotes and longer survival. However, the association between other *ATM* genetic variants and breast cancer susceptibility is less clear.[230-233] An analysis of 2,570 women with breast cancer estimated that carriers of a mutated *ATM* gene have a 60% lifetime risk for breast cancer by age 80 (HR, 6.88; 95% CI, 2.33–20.3; $P < .001$), with an even greater risk for those with the c.7271T > G variant (HR, 8.0; 95% CI, 2.3–27.4; $P < .001$).[234] The panel recommends breast MRI screening for women with a mutated *ATM* gene.

Lynch syndrome is a hereditary syndrome that usually results from a germline mutation in 1 of 4 DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), though deletions in the *EPCAM* gene have also been found to be associated.[235,236] Lynch syndrome is most commonly associated with increased risk for colorectal cancer, but women with Lynch syndrome are at an increased risk for endometrial and ovarian cancer (up to 60% and 24%, respectively).[237-241] Ovarian cancers in Lynch syndrome are not associated with a specific histology; that is, they may be mucinous or non-mucinous.[242] Total abdominal hysterectomy and bilateral salpingo-oophorectomy are risk-reducing options that should be considered for women who have completed childbearing and carry an *MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6* mutation.[243-245] Annual endometrial sampling is an option for carriers of mutations associated with Lynch syndrome,[243,246-248] but there is no clear evidence to support routine screening for gynecologic cancers, like routine transvaginal ultrasound and serum CA-125 testing.[243,246-248] Female *MLH1* mutation carriers have been suggested to be at increased risk for breast cancer, with one study estimating a cumulative risk to age 70 being 18.6% (95% CI, 11.3–25.9).[249] However, there is currently not enough evidence for the panel to recommend breast screening for women with Lynch syndrome beyond that which is recommended for the average-risk population. More information regarding Lynch syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

In an observational study including 1,915 unselected ovarian cancer cases, 1.4% of patients had a mutation in the *BRCA1* interaction protein C-terminal helicase 1 gene (*BRIP1*),[86] which is a Fanconi anemia gene. An analysis of 3,236 women with epithelial ovarian cancer, 3,431 controls, and 2,000 unaffected high-risk women from an ovarian cancer screening trial (UKFOCSS) showed that *BRIP1* is associated with an increased risk for ovarian cancer ($P < .001$), with the RR for invasive epithelial ovarian cancer being 11.22 (95% CI, 3.22–34.10, $P < .001$)

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and 14.09 for high-grade serous disease (95% CI, 4.04–45.02, $P < .001$).[250] An analysis of an Icelandic population (656 ovarian cancer cases, 3,913 controls) also showed an association between *BRIP1* and increased risk of ovarian cancer (OR, 8.13; 95% CI, 4.74–13.95; $P < .001$).[251] The panel recommends that RRSO be considered in women with a *BRIP1* mutation.

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 of ovarian cancer. In an observational study including 1,915 unselected ovarian cancer cases, 1.1% of patients had either a *RAD51C* or *RAD51D* mutation.[86] In a comparison of 1,132 probands with a family history of ovarian cancer and 1,156 controls, *RAD51C* was associated with an increased risk of ovarian cancer (RR, 5.88; 95% CI, 2.91–11.88; $P < .001$).[252] Analyses from the same trial (911 probands and 1,060 controls) also showed an association between *RAD51D* and increased risk of ovarian cancer (RR, 6.30; 95% CI, 2.86–13.85; $P < .011$).[253] An analysis of 409 unselected cases of ovarian cancer in Finland also showed an association between *RAD51C* and increased risk of ovarian cancer (OR, 6.31; 95% CI, 1.15–34.6; $P = .033$), with higher prevalence in patients with familial ovarian cancer but without a family history of breast cancer (OR, 33.8; 95% CI, 5.15–221.0; $P = .005$).[254] In another study from Finland, a non-significant association was found between *RAD51D* and increased risk for ovarian cancer ($n = 541$, $P = .08$), but a significant association was found among those with a family history of breast and ovarian cancer ($n = 105$; OR, 37.83; 95% CI, 3.90, 366.91; $P = .002$).[255] In a case-control analysis of 3,429 women with epithelial ovarian cancer and 2,772 controls, both *RAD51C* (OR, 5.2; 95% CI, 1.1–24; $P = .035$) and *RAD51D* (OR, 12.0; 95% CI, 1.5–90; $P = .019$) were associated with an increased risk for ovarian cancer.[256] The panel recommends that RRSO be considered in women with these gene mutations. There is currently insufficient evidence to recommend routine breast screening in carriers of these gene mutations.

The gene mutations noted above may be tested for concurrently using panel testing (see *Multi-Gene Testing* below). Lower penetrance genes for which there is currently insufficient evidence to recommend breast MRI, risk-reducing mastectomy, or RRSO include, but are not limited to: *BARD1*, *FANCC*, *MRE11A*, *MUTYH*, *NF1*, *NBN*, *RAD50*, *SMARCA*, and *XRCC2*. Risk management recommendations should take into account family history and other clinical factors. A more comprehensive review of these lower-penetrance genes is included in a recent publication.[218]

Initial Risk Assessment

For a patient concerned about or suspected of having a hereditary propensity for breast and/or ovarian cancer, an initial risk evaluation should be performed in order to determine if a formal risk assessment should be undertaken (see Criteria for Further Genetic Risk Evaluation in the algorithm). The first step in this preliminary assessment is a broad and flexible evaluation of the personal and family history of the individual with respect to breast and/or ovarian cancer.[257,258] The magnitude of the risk increases with the number of affected relatives in the family and the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.[259,260] The younger the age at diagnosis, the more likely it is that a genetic component is present. When assessing a family history for a hereditary pattern, the equal likelihood of paternal or maternal transmission of a gene that predisposes to breast cancer must also be kept in mind.

If an individual or a close family member of that individual meets any one of the criteria presented in the NCCN Guidelines (see Criteria for

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Further Genetic Risk Evaluation in the algorithm), that individual may be at increased risk for breast and/or ovarian cancer, and a referral for genetic assessment is recommended. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

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

Formal Risk Assessment and Genetic Counseling

Risk Assessment

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

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

Statistical models based on personal and family history characteristics have been developed to estimate a person's interval and lifetime risks of developing breast cancer. For example, the Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first- or second-degree female relatives with breast cancer.[261] The Gail model was also developed to assess risk for breast cancer.[262] The modified model is a computer-based, multivariate, logistic regression model that uses age, race, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous breast biopsies, and histology of the breast biopsies to produce actuarial estimates of future breast cancer risk.[263-265] This model considers only family history of breast cancer in first-degree relatives[266] and is heavily weighted by benign breast disease. Therefore, the Gail model may underestimate breast cancer risk for women with a significant family history and should not be used for women suspected of having a hereditary syndrome associated with increased risk for breast cancer.[266]

Decision models developed to estimate the likelihood that a *BRCA1/2* mutation is present include BRCAPRO[267,268] and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).[267] 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 incorporates MRI.[269,270]

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First-degree relatives of individuals with a known deleterious gene mutation in *BRCA1/2*, *TP53*, or *PTEN* genes are considered to have a 50% risk of carrying that mutation.

Evaluation of Patient's Needs and Concerns

The first step in evaluating an individual's risk for hereditary breast cancer is to assess her/his concerns and reasons for seeking counseling and to guarantee that her/his personal needs and priorities will be addressed in the counseling process. Several studies have documented a highly exaggerated perception of risk among women with a family history of breast cancer who seek cancer risk counseling.[271] This is a situation that can interfere with the adoption of appropriate health behaviors. In addition, the patient's knowledge about the benefits, risks, and limitations of genetic testing should be assessed as well as the patient's goals. A positive, supportive interaction with the counseling team is an important determinant of ultimate satisfaction with the counseling process and of adherence to recommended health behaviors.

Detailed Family History

A detailed family history is the cornerstone of effective genetic counseling. An examination of family history involves development of an expanded pedigree collected beginning with the health of the individual diagnosed with cancer and proceeding outward to include first-, second-, and third-degree relatives on both the maternal and paternal sides. Standardized pedigree nomenclature should be used.[272,273] Unaffected family members, both living and deceased, are also included, as their histories also provide information about the magnitude of genetic risk.

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

Other medical conditions that may be associated with or predispose an individual to breast and/or ovarian cancer should also be noted. Family history data are then graphically represented on a pedigree that follows standard nomenclature to illustrate family relationships and disease information. Factors that limit the informativeness of the pedigree are small family size, a small number of individuals of the susceptible gender for sex-limited cancers, reduced penetrance, early deaths in family members (which precludes the possibility that they will develop adult diseases), prophylactic surgeries that remove an organ from subsequent risk for cancer (eg, hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members.[5,274]

A prospective registry study of 306 women diagnosed with breast cancer at <50 years of age, who had no first- or second-degree relatives with breast or ovarian cancer, showed that those individuals with a limited family history (defined as fewer than 2 first- or second-degree female relatives or fewer than 2 female relatives surviving beyond age 45 years in either lineage) may have an underestimated probability of a *BRCA1/2* mutation based on models dependent on family history.[275]

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Medical and Surgical History

The collection of a detailed medical and surgical history from the proband allows the counselor to estimate the contribution of other risk factors that may interact with or modify family history to determine the risk for cancer. Any personal cancer history should include age of diagnosis, histology, and laterality. A history of previous breast biopsies and pathology results, especially those in which the pathology revealed atypical hyperplasia or lobular carcinoma in situ (LCIS), is associated with an increased risk for breast cancer.[276,277] Pathologic verification of these diagnoses is encouraged. History of salpingo-oophorectomy and potential exposure to carcinogens (eg, radiation therapy) should also be included in the patient's assessment. When taking the medical history, the clinician should also be alert to the physical manifestations of Cowden syndrome, especially skin conditions (see section below on *Focused Physical Examination*).

Reproductive variables are important determinants of risk for both breast and ovarian cancer, suggesting a significant contribution of hormones to the etiology of these cancers. This possible link is supported by the increased breast cancer risk seen among women who have had prolonged exposure to exogenous estrogens and progestins and the reduction in risk for ovarian cancer observed among women who report using oral contraceptives.[278-281]

Focused Physical Examination

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

Genetic Counseling

Genetic counseling is a critical component of the cancer risk assessment process. Many patients undergoing genetic testing do not receive proper counseling. In the national ABOUT study, patients undergoing genetic testing (*N* = 3,628) completed a survey regarding their experience. About 37% of respondents reported receiving counseling prior to testing.[282]

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

Pre-test counseling is an essential element of the genetic counseling process in the event that genetic testing for a gene mutation associated with a hereditary cancer syndrome is under consideration.[7] The

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foundation of pre-test genetic counseling is based on the principle of informed consent.[9] Pre-test counseling should include a discussion of why the test is being offered and how test results may impact medical management, cancer risks associated with the gene mutation in question, the significance of possible test results (see *Genetic Testing*, below), the likelihood of a positive result, technical aspects and accuracy of the test, economic considerations, risks of genetic discrimination, psychosocial aspects, confidentiality issues, the potential significance of the test results for family members, and other topics.[7] The patient should be educated regarding inheritance patterns, penetrance, variable expressivity, and the potential for genetic heterogeneity. A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act (GINA) enacted in 2008, which prohibits most health insurers and employers from discrimination on the basis of genetic test results.[283]

Post-test counseling must also be performed and includes disclosure of results, a discussion of the significance of the results, an assessment of the impact of the results on the emotional state of the individual, a discussion of the impact of the results on the medical management of the individual, and how and where the patient will be followed.[9] In addition, identification of a gene mutation associated with a hereditary predisposition to breast and/or ovarian cancer in an individual necessitates a discussion of possible inherited cancer risk to relatives and the importance of informing family members about test results.[7] It may also be appropriate to offer genetic testing to both parents of an individual who tests positive for one of these gene mutations to confirm which side of the family carries the mutation and is at increased risk. Counseling should also include making the individual aware of any available resources, such as disease-specific support groups, advocacy groups, and research studies.[284] Individuals who have tested positive for a mutation may have greater distress than anticipated, so provisions for supportive interventions should be provided.

Genetic Testing

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

In the statement on Genetic and Genomic Testing for Cancer Susceptibility from ASCO updated in 2003, genetic testing is recommended when: 1) there is a personal or family history suggesting genetic cancer susceptibility; 2) the test can be adequately interpreted; and 3) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk for cancer.[285] These recommendations were reiterated in the latest 2010 ASCO update on Genetic and Genomic Testing for Cancer Susceptibility with respect to testing individuals for gene mutations known to cause hereditary breast and/or ovarian cancer(s).[286]

As part of pre-test counseling, the counselor reviews the distinctions between true-positive, true-negative, indeterminate (or uninformative), and inconclusive (or variants of unknown significance) test results (see

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Table 2), as well as the technical limitations of the testing process. A clear distinction is made between the probability of being a mutation carrier and the probability of developing cancer. The probabilistic nature of genetic test results and the potential implications for other family members must also be discussed.

Individuals who have received allogeneic hematopoietic stem cell transplantation (HSCT) should not have molecular genetic testing performed on blood samples, as these blood cells would represent donor-derived DNA. In such cases, DNA of the individual being tested should be extracted from a fibroblast culture, if available. If this is not possible, buccal cells may be considered as an alternative source for DNA; however, a study has reported that over time, buccal epithelial cells are replaced by donor-derived cells in allogeneic HSCT recipients.[287,288] Therefore, genetic testing using buccal swab samples may be limited given this known risk of donor DNA contamination.

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

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

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

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

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

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Another counseling dilemma is posed by the finding of a variant of unknown significance (VUS) (see Table 2), a genetic alteration that may actually represent a benign polymorphism unrelated to an increased breast cancer risk or may indicate an increased breast cancer risk. The individual must be counseled in such a situation, because additional information about that specific mutation will be needed before its significance can be understood. These patients should be considered for referral to research studies that aim to define the functional impact of the gene variant. Clinicians and scientists should work together to develop a VUS classification system as more information is discovered in research studies.[289]

Finally, it is important to mention that certain large genomic rearrangements are not detectable by a primary sequencing assay, thereby necessitating supplementary testing in some cases.[290-293] For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the *BRCA1/2* genes that are otherwise not detected by direct sequencing of the *BRCA1/2* genes. Therefore, the NCCN Guidelines Panel emphasizes the need for comprehensive testing, which encompasses full *BRCA1/2* sequencing and detection of large gene rearrangements.

Following testing, the proband should be advised regarding possible inherited cancer risk to relatives and his/her options for risk assessment and management. The counselor should recommend genetic counseling and testing for at-risk relatives.

Multi-Gene Testing

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. The NCCN Guidelines Panel added information regarding multi-gene testing for the 2014 update. The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.

Multiple studies have shown that this approach may detect mutations not found in single-gene testing. In a study of 300 probands who tested negative for a *BRCA1/2* mutation (wild-type) in a commercially available single-gene test, multi-gene testing revealed that 12% had detected *BRCA1/2* genomic rearrangements, 5% had detected *CHEK2* mutations, and 1% had *TP53* mutations. Multiple DNA- and RNA-based methods were used.[217] A study of 198 women referred for *BRCA1/2* testing who underwent multi-gene testing showed 16 deleterious mutations out of 141 women who tested negative for *BRCA1/2* (11.4%, 95% CI = 7.0–17.7).[294] The discovery of these mutations led to recommendations for further screening. Therefore, findings from multi-gene testing have the potential to alter clinical management.[295]

Multi-gene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available.[296] The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a mutation known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of a mutation. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. For example, though ovarian cancer is mainly associated with *BRCA1/2* mutations, it may also be associated with mutations in the following genes: *BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN,*

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PALB2, RAD50, RAD51C, and *TP53*.[297] Highly penetrant genes associated with hereditary breast cancer include the following that could potentially be included in a multi-gene test: *BRCA1/ 2, PALB2, TP53, PTEN, STK11,* and *CDH1*.[10,294,298-300] In these cases where more than one gene mutation could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective.[296] Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is strongly suggestive of an inherited susceptibility.[296,301]

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, turn-around time, and insurance coverage, among others. Tests requiring a longer turn-around time may not be suitable for patients who need rapid results. The specific laboratory and multi-gene test should be chosen carefully.[296] Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis.[296] Third, mutations identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.[301] A management plan should only be developed for identified gene mutations 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 in multi-gene testing, and how to communicate and manage risk for carriers of these genes.[299,301,302] This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.[302] Some multi-gene tests may include moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management.[296,299,303-305] Further, it is possible that the risks associated with these genes may not entirely be due to that gene only, but may be influenced by gene/gene or gene/environment interactions. Also, certain mutations in a gene may be associated with a different degree of risk than other mutations in that gene. For example, the presence of certain *ATM* mutations is associated with an increased risk for early-onset breast cancer and frequent bilateral occurrence, but the association between other *ATM* genetic variants and breast cancer susceptibility is less clear.[230-233]

As a result of these dilemmas, risk management following detection of a mutation for a moderate-risk gene, and how risk should best be communicated to relatives, is currently unknown.[305] Further, the information gained from testing for moderate-penetrance genes may not change risk management recommendations significantly compared to that based on family history only. Multi-gene tests also increase the likelihood of detecting a VUS.[214,294,296,299-301,305] In a multi-gene analysis of 2,158 DNA samples from individuals with breast cancer, a VUS was found in about 40% of individuals.[300] Another multi-gene sequencing analysis that included 42 genes in 192 women showed a VUS identified in 88% of participants.[294] The considerable possibility of detecting a VUS adds to the complexity of counseling following multi-gene testing. However, as multi-gene testing is increasingly used, the frequency of a VUS being detected is expected to decrease.

Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when mutations are found for moderate-penetrance genes and when a VUS is found. For this reason, the NCCN Panel recommends that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, who issued an

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updated statement regarding genetic testing in 2015.[306] Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries.

Risk Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome

Detailed in the NCCN Guidelines is a set of specific risk assessment criteria that form part of the decision-making process in evaluating whether an individual suspected of being a carrier of a *BRCA1/2* mutation should be considered for genetic testing (see *BRCA1/2 Testing Criteria* in the algorithm). Following risk assessment and counseling, genetic testing should be considered for individuals for whom hereditary breast/ovarian cancer syndrome testing criteria are met. Testing is generally not recommended in children less than 18 years of age, since conditions associated with *BRCA1/2* mutations generally have an adult onset.[307]

Individuals from a family with a known deleterious *BRCA1/2* mutation should be tested for this mutation. For individuals from a family without a known *BRCA1/2* mutation (and who meet testing criteria), genetic testing should be comprehensive, including full sequencing of *BRCA1/2*, and testing for large genomic rearrangements. Individuals from a family with a known deleterious *BRCA1/2* mutation who test positive for the familial mutation, or for whom *BRCA1/2* mutation testing is not performed, should follow the screening recommendations outlined in *BRCA Mutation-Positive Management* in the algorithm (and discussed below).

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

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

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

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Counseling issues specific for both female and male carriers of a *BRCA1/2* mutation include the increased incidence of pancreatic cancer and melanoma. In addition, the risks to family members of individuals with a known *BRCA1/2* gene mutation (see *Risk Assessment* and *Genetic Testing*) should also be discussed as well as the importance of genetic counseling for these individuals. Counseling issues pertaining specifically to male breast cancer have also been described, and include an increased risk for prostate cancer and pancreatic cancer in male carriers of a *BRCA1/2* mutation.[308-310]

Recommendations for the medical management of hereditary breast/ovarian cancer syndrome are based on an appreciation of the early onset of disease, the increased risk for ovarian cancer, and the risk for male breast cancer in *BRCA1/2* carriers. An individual with a known deleterious *BRCA1/2* mutation in a close family member who does not undergo gene testing should be followed according to the same screening/management guidelines as a carrier of a *BRCA1/2* mutation. An individual from a family with a known deleterious *BRCA1/2* mutation who tests negative for the familial mutation 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.[311] For a woman who is a carrier of a *BRCA1/2* mutation, training in breast awareness with regular monthly practice should begin at age 18 years, and semiannual clinical breast examinations should begin at age 25 years. Between the ages of 25 and 29 years, the woman should have annual breast MRI screening (to be performed on days 7–15 of menstrual cycle for premenopausal women) or annual mammograms if MRI is not available. The age to begin screening can be individualized if the family history includes a breast diagnosis prior to age 30.[269,311-314] 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 ages 30 and 75, annual mammogram and breast MRI should both be done. After age 75, management should be considered on an individual basis. In women treated for breast cancer, mammography and breast MRI screening should be done on remaining breast tissue.

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.[315] 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,[316-319] 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.[316,320] 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%).[311-313,321-323] The sensitivity with ultrasound screening (33%–65%) appeared similar to that of

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mammography in this high-risk population.[311,321-323] In a prospective screening trial (conducted from 1997–2009) that evaluated the performance of annual MRI and mammography in women (age 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%; $P < .0001$).[324] Sensitivity with MRI was higher during the early years (1997–2002; 74% vs. 35%) as well as the later years of the study (2003–2009; 94% vs. 9%). Factors such as age, mutation type, or invasiveness of the tumor did not significantly influence the relative sensitivity of the 2 screening modalities. Importantly, the large majority (97%) of cancers detected by MRI screening were early-stage tumors.[324] Among previously unaffected women diagnosed with invasive breast cancer during the study (n = 28), 1 patient died due to the cancer and 3 additional patients died due to other causes; the annual breast cancer-specific mortality rate was 0.5%. At a median follow-up of 8 years from diagnosis, none of the surviving patients (n = 24) has developed distant recurrence.[324] All of the 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. In a retrospective study, a different screening interval was evaluated, using alternating mammography and MRI screening every 6 months in women with confirmed *BRCA1/2* mutation (N = 73).[325] 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.[325]

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,[326,327] a report from a large cohort study suggested an increased risk in women exposed to radiation at a young age.[328] A retrospective cohort study (from the GENE-RAD-RISK study) showed that exposure to diagnostic radiation (including mammography) prior to age 30 years was associated with increased risk for breast cancer in women with a *BRCA1/2* mutation (N = 1993).[328] 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 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 age 25 years combined with alternating digital mammography/MRI starting at age 30 years was shown to be the most effective strategy when radiation risks, life expectancy, and false-positive rates were considered.[329] 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 for breast cancer is supported by guidelines from the ACS.[269]

Post-test counseling in women with a confirmed *BRCA1/2* mutation (or highly suspected of having the mutation based on presence of known deleterious mutation in the family) includes discussion of risk-reducing mastectomy and/or salpingo-oophorectomy. Counseling for these risk-

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reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, 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.

For women who have not elected ovarian cancer risk-reducing surgery, transvaginal ultrasound may be considered starting at age 30 to 35 years. Determining serum CA-125 levels may also be considered as a screening test. However, routine transvaginal ultrasound and determination of serum CA-125 levels are not endorsed, but may be done at the clinicians' discretion. These screening procedures have not been shown to be sufficiently sensitive or specific, and current research does not provide evidence that they are a reasonable substitute for a bilateral risk-reduction salpingo-oophorectomy in this population.[330,331]

Men testing positive for a *BRCA1/2* mutation should have an annual clinical breast examination, and undergo training in breast self-examination with regular monthly practice starting at age 35 years. Regularly scheduled mammography is not recommended by the panel, as there are only limited data to support breast imaging in men, since male breast cancer is rare. Screening for prostate cancer starting at age 40 years should be recommended for *BRCA2* carriers and considered for *BRCA1* carriers.

For both men and women testing positive for a *BRCA1/2* mutation, a full body skin and eye exam for melanoma screening and investigational protocols for pancreatic cancer screening should be considered. Although no specific screening guidelines exist for these tumor types, individualized screening approaches may be provided according to personal or family history of cancer.

Risk Reduction Surgery

Bilateral Total Mastectomy

Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that bilateral risk-reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known *BRCA1/2* mutation carriers.[332,333] Results from smaller prospective studies with shorter follow-up periods have provided support for concluding that RRM provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation.[334,335]

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.

It is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well-studied.[336] 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.[337]

Bilateral Salpingo-oophorectomy

Women with a *BRCA1/2* mutation are at increased risk for both breast and ovarian cancers (including fallopian tube cancer and primary peritoneal cancer).[83,84] Although the risk for ovarian cancer is generally considered to be lower than the risk for breast cancer in a *BRCA1/2* mutation carrier,[41,42,338] the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian

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cancer have lent support for the performance of bilateral RRSO after completion of childbearing in these women. Rebbeck and colleagues found that the mean age of diagnosis of ovarian cancer was 50.8 years for *BRCA1/2* carriers.[339]

An observational prospective study of 5,783 women with a *BRCA1/2* mutation showed that ovarian cancer is more prevalent in individuals with *BRCA1* (4.2%) than *BRCA2* (0.6%) mutations.[340] In *BRCA1* mutation carriers, prevalence of ovarian, fallopian tube, and peritoneal cancers found during risk-reducing surgery was 1.5% for those younger than age 40 and 3.8% in those between the ages of 40 and 49.[340] 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* mutation than for women with a *BRCA2* mutation.

The effectiveness of RRSO in reducing the risk for ovarian cancer in carriers of a *BRCA1/2* mutation 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.[341] 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; $P = .005$).[342] An observational study of 5,783 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).[340] 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.[340] However, a 1% to 4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.[114,339,341,343-345] 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.[346] Presence of a *BRCA1/2* mutation was associated with detection of clinically occult neoplasms during RRSO ($P = .006$).

RRSO is also reported to reduce the risk for breast cancer in carriers of a *BRCA1/2* mutation by approximately 50%.[339,341,345,347] In the case-control international study by Eisen et al, a 56% (OR, 0.44; 95% CI, 0.29–0.66; $P < .001$) and a 43% (OR, 0.57; 95% CI, 0.28–1.15; $P = 0.11$) breast cancer risk reduction (adjusted for oral contraceptive use and parity) was reported following RRSO in carriers of a *BRCA1* and a *BRCA2* mutation, respectively.[347] HRs of 0.47 (95% CI, 0.29–0.77)[339] and 0.30 (95% CI, 0.11–0.84; $P = .022$)[344] were reported in two other studies comparing breast cancer risk in women with a *BRCA1/2* mutation who had undergone RRSO with carriers of these mutations who opted for surveillance only. These studies are further supported by a meta-analysis that found similar reductions in breast cancer risk of approximately 50% for *BRCA1/2* mutation carriers following RRSO.[341] Results of a prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA2* mutation carriers compared with *BRCA1* mutation carriers.[342] 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

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BRCA1 mutation carriers (HR, 0.38; 95% CI, 0.19–0.77, *P* = .007), but not in carriers of a *BRCA2* mutation (*P* = .23).[348] Mortality risk was also significantly impacted in *BRCA1/2* mutation carriers who had ER-negative breast cancer (HR, 0.07; 95% CI, 0.01–0.51, *P* = .009).

A recent prospective cohort study from the Netherlands (*N* = 822) did not find a statistically significant difference in breast cancer incidence between *BRCA1/2* mutation carriers who opted for an RRSO and women who did not, regardless of whether the mutation was for *BRCA1* or *BRCA2*.[349] 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).[350]

Reductions in breast cancer risk for carriers of a *BRCA1/2* mutation undergoing RRSO may be associated with decreased hormonal exposure following surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a *BRCA1* mutation who had an RRSO at age 40 years 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).[347] 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.[347] However, results from Rebbeck et al also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.[345] Due to the limited data, an optimal age for RRSO is difficult to specify.

It has been reported that short-term hormone replacement therapy (HRT) in women undergoing RRSO does not negate the reduction in breast cancer risk associated with the surgery.[351] In addition, results of a case-control study of *BRCA1* mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.[352] However, caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.[353,354]

Salpingectomy (surgical removal of the fallopian tube) completion rates are increasing, especially in women younger than age 50.[355] Despite some evidence regarding the safety and feasibility of this procedure,[355,356] more data are needed regarding its efficacy in reducing the risk for ovarian cancer.[357] 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.

The NCCN Guidelines Panel recommends RRSO for women with a known *BRCA1/2* mutation, typically between ages 35 and 40 years for women with a *BRCA1* mutation. For women with a *BRCA2* mutation who have undergone efforts to maximize their breast cancer prevention (ie, bilateral mastectomy), it is reasonable to delay RRSO until between ages 40 and 45 years since ovarian cancer onset tends to be later in women with a *BRCA2* mutation.[340] 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.[115,116] The protocol published by the College of American Pathologists (2009) can be consulted for details on specimen evaluation.[358] See the NCCN

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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, age 35). 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.[359-364] However, only limited data are available on the specific use of these agents in patients with *BRCA1/2* mutations. As previously discussed, patients with *BRCA1/2* mutations 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.[46] 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.[365] Case-control studies from the Hereditary Breast Cancer Clinical Study Group reported that the use of tamoxifen protected against contralateral breast cancer with an 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.[366,367] 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 with regards 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).[368] 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.[368] 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). Recently, common single-nucleotide polymorphisms were identified in genes (*ZNF423* and *CTSO*) that are involved in estrogen-dependent regulation of *BRCA1* expression.[369] These gene variants were associated with alterations in breast cancer risk during treatment with selective estrogen receptor modulators, and may eventually pave the way for predicting the likelihood of benefit with these chemopreventive approaches in individual patients.

With respect to the evidence regarding the effect of oral contraceptives on cancer risks in women with a known *BRCA1/2* gene mutation, case-control studies have demonstrated that oral contraceptives reduced the

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risk for ovarian cancer by 45% to 50% in *BRCA1* mutation carriers and by 60% in *BRCA2* mutation carriers[370,371]; moreover, risks appeared to decrease with longer duration of oral contraceptive use.[371] 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).[372] A more recent 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).[373]

Studies on the effect of oral contraceptive use on breast cancer risk among *BRCA1/2* mutation carriers have reported conflicting data. In one case-control study, use of oral contraceptives was associated with a modest but statistically significant increase in breast cancer risk among *BRCA1* mutation carriers (OR, 1.20; 95% CI, 1.02–1.40), but not among *BRCA2* mutation carriers.[374] Among *BRCA1* mutation carriers, breast cancer risks with oral contraceptives were significantly associated with ≥5 years of oral contraceptive use (OR, 1.33; 95% CI,1.11–1.60), breast cancer diagnosed before age 40 (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).[374] In another case-control study, oral contraceptive use for at least 1 year was not significantly associated with breast cancer risks in either *BRCA1/2* mutation carriers.[375] However, among *BRCA2* mutation carriers, use of oral contraceptives for at least 5 years was associated with a significantly increased risk for breast cancer (OR, 2.06; 95% CI, 1.08–3.94); results were similar when only the cases with oral contraceptive use on or after 1975 were considered.[375] Other case-control studies have reported no significant associations with oral contraceptive use (especially with the use of low-dose formulations after 1975) and risks for breast cancer in *BRCA1/2* mutation carriers.[376,377] In fact, in one study, the use of low-dose oral contraceptives for at least 1 year was associated with significantly decreased risks for breast cancer among *BRCA1* mutation carriers (OR, 0.22; 95% CI, 0.10–0.49; $P < .001$), though not for *BRCA2* mutation carriers.[377] Differences in the study design employed by these case-control studies make it difficult to compare outcomes between studies, and likely account for the conflicting results. The study design might have differed with regard to factors such as the criteria for defining the “control” population for the study (eg, non-*BRCA1/2* mutation carriers vs. mutation carriers without a cancer diagnosis), consideration of family history of breast or ovarian cancer, baseline demographics of the population studied (eg, nationality, ethnicity, geographic region, age groups), age of onset of breast cancer, and formulations or duration of oral contraceptives used. Two meta-analyses showed that oral contraceptive use is not significantly associated with breast cancer risk in *BRCA1/2* mutation carriers.[372,373]

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 *BRCA1/2* mutations. Counseling for reproductive options such as prenatal diagnosis, preimplantation genetic diagnosis (PGD), and assisted reproduction may therefore be warranted for couples expressing concern over the *BRCA1/2* mutation carrier status of their future offspring. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options.

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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.[310,378] During the past 2 decades, PGD has emerged as an alternative method of genetic testing in early embryos. PGD involves the testing of 1 or 2 cells from embryos in very early stages of development (ie, 6 to 8 cells) after in vitro fertilization (IVF). This procedure allows for the selection of unaffected embryos to be transferred to the uterus,[310,378] 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.[310,378] For example, PGD may be considered in cases where both partners carry a *BRCA2* mutation, for which there may be a high risk for the offspring to develop Fanconi anemia, a rare autosomal recessive condition.[309] Although the use of prenatal diagnosis or PGD is relatively well established for severe hereditary disorders with very high penetrance and/or early onset, its use in conditions associated with lower penetrance and/or later onset (eg, hereditary breast or ovarian cancer syndrome) remains somewhat controversial from both an ethical and regulatory standpoint.

Personal considerations for the decision to utilize prenatal diagnosis or PGD may include individual ethical beliefs, value systems, cultural and religious beliefs, and social and economic factors. Based on results from surveys administered to women at high risk for hereditary breast or ovarian cancer, 50% to 75% of respondents felt that PGD was an acceptable option for high-risk individuals,[379,380] yet only about 14% to 33% would consider undergoing PGD themselves.[379,381] A survey in high-risk men (N = 228; carriers of a *BRCA* mutation; or having a partner or first-degree relative with a *BRCA* mutation) showed that 80% of these men were unaware of PGD; after being informed of the definition of PGD, 34% indicated that they would consider the option of using PGD.[382] Importantly, these surveys suggested that the majority of high-risk women and men have little or no knowledge of PGD,[380,382,383] highlighting the need for better awareness and education regarding potential reproductive options.

Successful births have been reported with the use of PGD and IVF in *BRCA1/2* mutation carriers,[384,385] 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 *BRCA1/2* mutation carriers are not yet available.

Risk Assessment, Counseling, and Management: Li-Fraumeni Syndrome

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

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and soft tissue sarcomas, CNS tumor, adrenocortical carcinoma, unusually early onset of other adenocarcinomas, or other childhood cancers.[148,164,171] Verification of these sometimes very rare cancers is particularly important.

Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met. The NCCN Guidelines Panel also suggests consideration of *TP53* mutation testing in those with early-onset breast cancer (≤30 years of age), given the association between early-onset breast cancer and *TP53* mutations.[148,173,175,176] This testing may be done alone, concurrently with *BRCA1/2* testing, or as a follow-up test if the *BRCA1/2* testing result is negative. The NCCN Guidelines Panel recommends comprehensive testing, which should include full sequencing and analysis of gene deletion/duplication. In the absence of additional family history, early breast cancer alone is associated with a low likelihood of mutation identification.

An individual with a known deleterious *TP53* mutation in a close family member who does not undergo testing should be followed according to the same recommendations as a carrier of a *TP53* mutation (see *Li-Fraumeni Syndrome Management* in the algorithm). In situations where an individual (or family member) from a family with no known familial *TP53* mutation undergoes genetic testing, and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met (see *BRCA-Related Breast and/or Ovarian Cancer Syndrome Testing Criteria* and *Cowden Syndrome Testing Criteria* in the algorithm). Alternatively, testing another family member with the next highest likelihood of having a mutation may be considered. As previously discussed in the *BRCA1/2* testing section above, testing of unaffected individuals should only be considered when an appropriate affected family member is not available for testing.

Importantly, the significant limitations of interpreting testing results for an unaffected individual should be discussed prior to testing.

Management of LFS should address the limitations of screening for the many cancers associated with this syndrome. For those at risk for breast cancer, training and education in breast self-examination should start at age 18 years, with the patient performing regular self-examination on a monthly basis. For members of families with LFS, it is recommended that breast cancer surveillance by clinical breast examination, every 6 to 12 months, begin between the ages of 20 and 25 years (or at the age of the earliest known breast cancer in the family, if below age 20 years) 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 (preferred) or mammogram if MRI is not available for women ages 20 to 29; annual mammogram and breast MRI screening in women ages 30 to 75; and management on an individual basis for women older than 75 years. For women with a family history of breast cancer diagnosed earlier than age 20 years, breast MRI screening may begin at the earliest age of diagnosis. In women treated for breast cancer, mammography and breast MRI screening should be done on remaining breast tissue.

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, and reconstructive options. It is also important to address the psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures.

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Many of the other cancers associated with germline mutations in *TP53* do not lend themselves to early detection. Thus, additional recommendations are general and include annual comprehensive physical examinations, especially when there is a high index of suspicion for second malignancies in cancer survivors and rare cancers (see *Li-Fraumeni Syndrome Management* in the algorithm). Clinicians should address screening limitations for other cancers associated with LFS. Colonoscopy should be considered every 2 to 5 years, starting at age 25, 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 and neurologic examination should be done. Pediatricians should be made aware of the risk for childhood cancers in affected families.

Whole-body MRI for screening of cancers associated with LFS is being evaluated in multiple international trials. Other LFS screening components are being evaluated in protocols, including regular blood screening for hematologic malignancies, and biochemical screening. In a prospective observational study, a clinical surveillance protocol for asymptomatic *TP53* mutation carriers from eight families affected by LFS was incorporated.[386] In this study, 18 of the 33 asymptomatic mutation carriers agreed to undergo surveillance while the remainder of the carriers did not. The surveillance protocol included biochemical methods and imaging techniques, such as annual brain MRI for brain tumor surveillance (both children and adults); annual rapid total-body MRI (both children and adults) and ultrasound of the abdomen and pelvis every 6 months (for adults only) for soft tissue/bone sarcoma surveillance; colonoscopy every 2 years beginning at age 40 years (or 10 years before earliest known colon cancer in the family); ultrasound of the abdomen and pelvis every 3 to 4 months, complete urinalysis every 3 to 4 months, and blood test every 4 months for adrenocortical carcinoma surveillance (children only); and complete blood counts and blood tests every 4 months for leukemia/lymphoma surveillance (both children and adults). For surveillance of breast cancers, the protocol was similar to the NCCN Guidelines for LFS Management.[386] Using this surveillance protocol, asymptomatic tumors were detected in 7 of the patients; after a median follow-up time of 24 months, all 7 of these carriers were alive. Ten individuals in the non-surveillance group developed high-grade, advanced-stage tumors; only 2 of these individuals were alive at the end of follow-up. The 3-year overall survival rate was significantly higher for the surveillance group compared with the non-surveillance group (100% vs. 21%; $P = .016$).[386] Although this was a small study in a limited number of patients, the clinical surveillance protocol employed was feasible and detected asymptomatic tumors in about 40% of individuals with *TP53* mutations. The protocol may represent an emerging option for surveillance/management of at-risk individuals from families with LFS; further evaluation of this protocol is warranted. Annual whole-body MRI with rapid non-contrast exams may be considered. 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.[387,388] Counseling for reproductive options such as prenatal diagnosis, PGD, and assisted reproduction may be warranted for couples expressing concern over the mutation carrier status of their future offspring. 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*

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Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome.

Risk Assessment, Counseling, and Management: Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome

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 (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 *PTEN* gene mutation testing (see Cowden Syndrome/PHTS Testing Criteria in the algorithm). These criteria are used to assess the need for further risk assessment and genetic testing, but are not intended to serve as clinical diagnostic criteria.

Testing Criteria

Testing criteria for Cowden syndrome/PHTS are grouped into 3 general categories. A patient is considered for *PTEN* gene mutation testing based on whether he/she meets certain criteria or combinations of criteria from these 3 categories. The first criteria category includes individuals meeting diagnostic criteria for Cowden syndrome[389]; or a personal history of BRRS, adult LDD, autism spectrum disorder with macrocephaly, or 2 or more biopsy-proven trichilemmomas. Any individual presenting with one or more of these diagnoses warrants *PTEN* testing. Previously, some of the criteria from this group have sometimes been referred to as “pathognomonic,” although it is unlikely that any of these conditions can stand alone as a definitive diagnostic criterion of Cowden syndrome/PHTS. Another criterion that can be considered to be sufficient to warrant *PTEN* gene mutation testing is a family history that includes the presence of a known deleterious *PTEN* mutation.

The next category of criteria represents “major” features associated with Cowden syndrome/PHTS.[180,184,192,389] The major criteria include the presence of breast cancer, macrocephaly (ie, megalocephaly),[211] endometrial cancer, follicular thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, macular pigmentation of glans penis, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (ie, one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multiple or extensive oral mucosal papillomatosis, multiple cutaneous facial papules). With respect to decisions related to the presence of mucocutaneous lesions, the panel did not consider the available literature to be adequate to accurately specify the number or extent of these lesions required for the condition to be defined as a major criterion for Cowden syndrome/PHTS, and clinical judgment is needed when evaluating such lesions. An individual exhibiting 2 or more major criteria where one criterion is macrocephaly meets the testing threshold. An individual with 3 or more major criteria (without macrocephaly) is also considered to meet the threshold for testing. In addition, individuals exhibiting 1 major criterion with 3 or more minor criteria (discussed below) also meet the testing threshold; if an individual exhibits 2 or more major criteria (eg, breast cancer, follicular thyroid cancer) but does not have macrocephaly, then one of the major criteria may be included as one of the 3 minor criteria to meet the testing threshold.

The final category of criteria represents features with a “minor” association with Cowden syndrome/PHTS.[180,184,192,389] These include autism spectrum disorder (without macrocephaly), colon cancer, esophageal glycogenic acanthosis (3 or more), lipomas, intellectual disability, papillary or follicular variant of papillary thyroid cancer, thyroid

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structural lesions other than follicular thyroid cancer (eg, adenoma, nodules, goiter), renal cell carcinoma, a single gastrointestinal hamartoma or ganglioneuroma, testicular lipomatosis, or vascular anomalies (including multiple intracranial developmental venous anomalies). The panel felt that evidence from the literature was insufficient to include fibrocystic breast disease, fibromas, or uterine fibroids as part of the testing criteria. An individual would need to exhibit 4 or more minor criteria or, as discussed above, 3 or more minor and one major criterion to meet testing.

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

Genetic Testing

Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met. The NCCN Guidelines Panel recommends comprehensive testing, which should include full sequencing, gene deletion/duplication analysis, and promoter analysis. A comprehensive clinical test should not include testing for succinate dehydrogenase (*SDH*), as there is no conclusive evidence that this gene is associated with PHTS.[390]

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%.[188,213] 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[184] for Cowden syndrome.[180] The authors concluded that the current Consortium diagnostic criteria are not as sensitive in identifying individuals with *PTEN* mutations as previously estimated. Since *PTEN* mutations 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.[188] 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.[188] The criteria were designed by focusing on clinical features associated with *PTEN* mutations. The panel recommends using these criteria for clinical diagnosis of PHTS.

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

Minor criteria include the following: autism spectrum disorder, colon cancer, 3 or more esophageal glycogenic acanthosis, 3 or more lipomas, mental retardation (IQ ≤75), renal cell carcinoma, testicular

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lipomatosis, thyroid cancer (papillary or follicular variant of papillary), thyroid structural lesions, and vascular anomalies (eg, multiple intracranial developmental venous anomalies).

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

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

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

Screening Recommendations

Cancer is the major health risk associated with Cowden syndrome/PHTS. Therefore, the NCCN Panel had outlined guidelines for prevention and early detection screening of commonly associated cancers with Cowden syndrome/PHTS. Current medical management recommendations for individuals with Cowden syndrome/PHTS include annual physical examinations, starting at age 18 years (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 age 18 and have a semiannual clinical breast examination beginning at age 25 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 starting at ages 30 to 35 years, or 5 to 10 years earlier than the earliest known breast cancer in the family (whichever comes first). After age 75, management should be considered on an individual basis. In women treated for breast cancer, mammography and breast MRI screening should be done on remaining breast tissue.

Although there are no data regarding risk reduction surgery in women with Cowden syndrome, the option of RRM and hysterectomy should be discussed on a case-by-case basis. Oophorectomy is not indicated for Cowden syndrome alone, but may be indicated for other reasons. Counseling for risk-reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries,

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reconstructive options, and reproductive desires. It is also important to address the psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures.

The panel recommends patient education regarding the symptoms of endometrial cancer including the necessity of a prompt response to such symptoms. For endometrial cancer screening, women diagnosed with Cowden syndrome should consider annual random endometrial biopsies and/or ultrasound beginning at age 30 to 35.

Both men and women with Cowden syndrome/PHTS have approximately at least a 3% to 10% lifetime risk of developing thyroid cancer,[17] compared to about 1% in the general population.[391] An annual thyroid ultrasound should be performed, beginning at the time of PHTS diagnosis. In addition, colonoscopy is recommended starting at age 35 years, or earlier if symptomatic. If a close relative was diagnosed with colon cancer before age 40, 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 age 40. Dermatologic management may be considered for some patients. If there are symptoms in children, then assessment of psychomotor abilities should be considered, as well as a brain MRI. Education regarding the signs and symptoms of cancer is important; patients should also be advised about the risk to relatives, and genetic counseling is recommended for at-risk relatives.

No published data exist on the use of prenatal diagnostics/genetic testing for *PTEN* mutations in families with Cowden syndrome. However, for couples expressing the desire that their offspring not carry a familial *PTEN* mutation, options for prenatal diagnosis, PGD, and assisted reproduction can be discussed. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options. For general discussions on the topic of reproductive options and counseling considerations, see the Discussion section above on *Reproductive Options* under *Risk Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome*.

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

Autosomal dominant
Autosomal dominant inheritance refers to genetic conditions that occur when a mutation 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 mutations are present in both copies of a given gene (ie, the person is homozygous for a mutation, or carries two different mutations 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 mutation in a germ cell (egg or sperm) of one of the parents, or a mutation 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 gene mutation 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 mutation that confers increased susceptibility to cancer from cancers occurring in people who are known to carry a mutation. Cancer developing in people who do not carry a high-risk mutation 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 mutation. Alternatively, sporadic is also sometimes used to describe cancer occurring in individuals without a family history of cancer.

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

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

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