Genetic/Familial High-Risk Assessment: Breast and Ovarian

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, but 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 (i.e., egg or sperm) or in the fertilized egg itself during early embryogen-
esis. However, family studies have long documented an increased risk for several forms of cancer among first-degree (i.e., parents, siblings, and children) and second-degree relatives (i.e., grandparents, aunts or uncles, grandchildren, and nieces or nephews) of affected individuals. These individuals may have an increased susceptibility to cancer as the result of 1 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 (i.e., a high penetrance genotype), vertical transmission through either mother or father, and an association with other types of tumors. They often have an early age of onset and exhibit an autosomal dominant inheritance pattern (i.e., occur when the individual has a mutation in only 1 copy of a gene).

Familial cancers share only some 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 a combination of these factors.

Assessment of an individual's risk for familial or hereditary cancer is based on a thorough evaluation of family history. With respect to hereditary cancers, advances in molecular genetics have identified several genes associated with inherited susceptibility.
**CRITERIA FOR FURTHER RISK EVALUATION**

One or more of the following:
- Early age at onset of breast cancer
- Two breast primaries or breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual or
- Two or more breast primaries or breast and ovarian/fallopian tube/primary peritoneal cancers in close relatives from the same side of family (maternal or paternal)
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations, or leukemia/lymphoma on the same side of family
- Family member with a known mutation in a breast cancer susceptibility gene
- Populations at risk
- Male breast cancer
- Ovarian/fallopian tube/primary peritoneal cancer

*Referral to cancer genetics professional recommended*

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

**Detailed family history:**
- Expanded pedigree to include first-, second-, and third-degree relatives (parents, children, siblings, aunts, uncles, grandparents, great-grandparents, nieces, nephews, grandchildren, first cousins; see facing page)
- Types of cancer
- Bilaterality
- Age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation, particularly pathology reports of primary cancers

**Detailed medical and surgical history:**
- Any personal cancer history
- Carcinogen exposure (e.g., history of radiation therapy)
- Reproductive history
- Hormone use
- Previous breast biopsies

Focused physical exam (refer to specific syndrome):
- Breast/ovarian
- Dermatologic, including oral mucosa
- Head circumference
- Thyroid

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*The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

*Clinically use age ≤ 50 y because studies define early onset as either ≤ 40 or ≤ 50 y. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

*Two breast primaries, including bilateral disease or the presence of ≥ 2 clearly separate ipsilateral primary tumors.

*For lobular breast cancer and diffuse gastric cancer, CDH1 gene testing can be considered.

*For dermatologic manifestations, see page 572.

*For populations at risk, requirements for inclusion may be lessened (e.g., women of Ashkenazi Jewish descent with breast or ovarian cancer at any age).

*A genetic counselor and/or medical geneticist should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

*Genetic counseling is advised when genetic testing is offered, and often after results are disclosed.

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Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

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**CRITERIA FOR FURTHER RISK EVALUATION**

Referral to cancer genetics professional recommended.

- One or more of the following:
  - Early age at onset of breast cancer
  - Two breast primaries or breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual or
  - Two or more breast primaries or breast and ovarian/fallopian tube/primary peritoneal cancers in close relatives from the same side of family (maternal or paternal)
  - A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations, or leukemia/lymphoma on the same side of family
  - Family member with a known mutation in a breast cancer susceptibility gene

*Populations at risk*

- Male breast cancer
- Ovarian/fallopian tube/primary peritoneal cancer

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**PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND**

- **Father**
- **Mother**
- **Proband**

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HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA

- Individual from a family with a known BRCA1/BRCA2 mutation
- Personal history of breast cancer + one or more of the following:
  - Diagnosed age ≤ 45 y
  - Diagnosed age ≤ 50 y with ≥ 1 close blood relative with breast cancer aged ≤ 50 y and/or ≥ 1 close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
  - Two breast primaries when first breast cancer diagnosis occurred before age 50 y
  - Diagnosed at any age, with ≥ 2 close blood relatives with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
  - Close male blood relative with breast cancer
  - Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
  - For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required
- Personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Family history only:
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with ≥ 2 close blood relatives with breast and/or ovarian cancer (≥ 1 close blood relative with breast cancer aged ≤ 50 y)

To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

a One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome, which warrants further professional evaluation. When investigating family histories for HBOC, the maternal and paternal sides should be considered independently. Early-onset breast cancer and/or epithelial ovarian/fallopian tube/primary peritoneal cancers at any age also increase suspicion of HBOC. Other malignancies reported in some families with HBOC include prostate, pancreatic, and melanoma.
b Other considerations: individuals with limited family history, such as < 2 first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation (Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and BRCA gene mutation status in single cases of breast cancer. JAMA 2007;297:2587-2595). Individuals with early-onset (age ≤ 40 y), triple-negative breast cancer may consider BRCA1/2 mutation testing (Young SR, Piliarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 2009;9:86).
c For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.
d Close blood relatives include first-, second-, and third-degree relatives. (See page 565)
e Two breast primaries, including bilateral disease or the presence of ≥ 2 clearly separate ipsilateral primary tumors.
f Ovarian cancer is a component tumor of hereditary non-polyposis colorectal cancer (HNPPC)/Lynch syndrome, and therefore clinicians should be attentive for clinical evidence of this syndrome. See NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening.1

testing for Ashkenazi Jewish founder-specific mutations should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other HBOC criteria is met. Examples of other founder populations include Icelandic, Swedish, Hungarian, and Dutch.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
### HEREDITARY BREAST AND/OR OVARIAN CANCER

**HBOC FOLLOW-UP**

<table>
<thead>
<tr>
<th>FAMILY STATUS</th>
<th>GENETIC TESTING</th>
<th>TEST OUTCOME</th>
<th>SCREENING RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deleterious familial BRCA1/BRCA2 mutation known</td>
<td>Recommend BRCA1/BRCA2 testing for specific familial mutation</td>
<td>Positive for familial BRCA1/BRCA2 mutation</td>
<td>See HBOC Syndrome Management, page 568</td>
</tr>
<tr>
<td>No known familial BRCA1/BRCA2 mutation</td>
<td>Consider testing affected family member with highest likelihood of BRCA1/BRCA2 mutation</td>
<td>Negative for familial BRCA1/BRCA2 mutation</td>
<td>Breast screening as per the NCCN Breast Cancer Screening and Diagnosis Guidelines</td>
</tr>
</tbody>
</table>

- **Risk assessment and counseling:**
  - Psychosocial assessment and support
  - Risk counseling
  - Education
  - Discussion of genetic testing
  - Informed consent

1. To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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1. A genetic counselor and/or medical geneticist should be involved early in counseling patients who potentially meet criteria for an inherited syndrome. Genetic counseling is advised when genetic testing is offered and often after results are disclosed.

2. Certain mutations (i.e., large rearrangements) are not detectable using the primary sequencing assay, and supplementary testing may be necessary.

3. If of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all 3 founder mutations.

4. If > 1 affected, first consider youngest age at diagnosis, bilateral disease, multiple primaries, ovarian cancer, and individual most closely related to the proband/patient/consultant. If no living family member with breast or ovarian cancer, consider testing first- or second-degree family members affected with cancers believed to be related to BRCA1/BRCA2 (e.g., prostate, pancreas, melanoma).

5. Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

6. BRCA1/BRCA2 testing: for both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the 3 common mutations. If results are negative for the these mutations, consider full sequence testing if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. If all affected family members are deceased, consider testing of paraffin-derived DNA from deceased relatives, if DNA is obtainable. For both affected and unaffected individuals who are non-Ashkenazi Jewish and have no known familial mutation, full-sequence testing is the approach, if testing is performed.

7. If individuals affected with breast cancer are aged < 30 y, especially if they have a family history of sarcoma, brain tumor, or adrenocortical carcinoma, p53 gene testing should be considered.

8. Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.
**HEREDITARY BREAST AND/OR OVARIAN CANCER**

**WOMEN**

- Breast self-exam (BSE) training and education and regular monthly BSE starting at age 18 y.
- Clinical breast exam, semiannually, starting at age 25 y.
- Annual mammogram and breast MRI\(^2\) screening starting at age 25 y, or individualized based on earliest age of onset in family.\(^3\)
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy, ideally between 35 and 40 y and on completion of childbearing, or individualized based on earliest age of onset of ovarian cancer in the family. Counseling includes 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 (HRT), and related medical issues.
- For patients who do not elect risk-reducing salpingo-oophorectomy, concurrent transvaginal ultrasound should be considered + CA-125, every 6 mo starting at age 35 y, or 5-10 y earlier than the earliest age of first diagnosis of ovarian cancer in the family, and preferably day 1-10 of menstrual cycle for premenopausal women.
- Consider chemoprevention options for breast and ovarian cancer, including discussion of risks and benefits (See NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Risk Reduction\(^1\)).
- Consider investigational imaging and screening studies when available (e.g., novel imaging technologies, more frequent screening intervals).

**MEN**

- BSE training and education and regular monthly BSE.
- Clinical breast exam, semiannually.
- Consider baseline mammogram; annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study.
- Adhere to screening guidelines for prostate cancer (See NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection\(^1\)).

**MEN and WOMEN**

- Education regarding signs and symptoms of cancers, especially those associated with BRCA gene mutations.\(^7\)
- Refer to appropriate NCCN guidelines for other cancer screening (see contents of NCCN Guidelines for Detection, Prevention, & Risk Reduction, available on the NCCN Web site at www.nccn.org).

**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 couples expressing the desire that their offspring not carry a familial BRCA mutation, advise about options for prenatal diagnosis and assisted reproduction, including preimplantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies.\(^9\)
- For BRCA2 mutations carriers who are of reproductive-age, risk for a rare (recessive) Fanconi anemia/brain tumor phenotype in offspring of populations with an increased population frequency of founder mutations should be discussed.\(^10\)

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**LFS-LIKE CRITERIA**

**Classic Li-Fraumeni Syndrome (LFS) Criteria:**
- Combination of an individual diagnosed at age < 45 y with a sarcoma, breast cancer diagnosed at any age.
- An additional first- or second-degree relative in the same lineage with cancer diagnosed at age < 45 y, or a sarcoma at any age.
- An additional first- or second-degree relative in the same lineage with a cancer diagnosed at age < 45 y, and a second first- or second-degree relative in the same lineage with any type of cancer diagnosed at age < 45 y.

**LFS-Like Criteria:**
- Individual from a family with a known TP53 mutation.

**REFERENCES**

1. Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending semiannual clinical breast exam is the concern for interval breast cancers.
2. 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 day 1-15 of menstrual cycle for premenopausal women.
3. The appropriateness of imaging scheduling is still under study.
5. Data show that annual transvaginal ultrasound and CA-125 are not effective strategies for screening for ovarian cancer in high-risk women. Limited data exist regarding the effectiveness of a 6-month screening interval. Thus, until these data are available, it is reasonable to consider this approach in high risk women, especially in the context of a clinical research setting.
6. Data suggest that oral contraceptives (OC) reduce ovarian cancer risk in BRCA mutation carriers. The risk/benefit ratio is uncertain because of contradictory evidence about OC increasing breast cancer risk; however, OC use for contraception is acceptable. (Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863-1870.)
7. Some families also have an increased incidence of prostate cancer, pancreatic cancer, and melanoma.
8. Consider full-body skin examination for melanoma and investigational protocols for pancreatic cancer.

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**HBOC SYNDROME MANAGEMENT**

**WOMEN**

- Breast self-exam (BSE) training and education and regular monthly BSE starting at age 18 y.
- Clinical breast exam, semiannually, starting at age 25 y.
- Annual mammogram and breast MRI\(^2\) screening starting at age 25 y, or individualized based on earliest age of onset in family.\(^3\)
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy, ideally between 35 and 40 y and on completion of childbearing, or individualized based on earliest age of onset of ovarian cancer in the family. Counseling includes 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 (HRT), and related medical issues.
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- For BRCA2 mutations carriers who are of reproductive-age, risk for a rare (recessive) Fanconi anemia/brain tumor phenotype in offspring of populations with an increased population frequency of founder mutations should be discussed.\(^10\)
**LI-FRAUMENI SYNDROME**

**LI-FRAUMENI SYNDROME TESTING CRITERIA**

- Individual from a family with a known TP53 mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:
  - Combination of an individual diagnosed at age < 45 y with a sarcoma and an additional first- or second-degree relative diagnosed at age < 45 y, or a sarcoma at any age
  - LFS-like criteria:
    - Combination of an individual diagnosed with a childhood tumor or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed at age < 45 y
    - Early-onset breast cancer:
      - Individuals with breast cancer aged < 30 y with a negative BRCA1/BRCA2 test especially if they have a family history of sarcoma, brain tumor, or adrenocortical carcinoma

<table>
<thead>
<tr>
<th>Cancers associated with LFS include but are not limited to:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal breast cancer</td>
</tr>
<tr>
<td>Bone and soft tissue sarcomas</td>
</tr>
<tr>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Brain tumor</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
</tr>
<tr>
<td>Colon cancer</td>
</tr>
<tr>
<td>Early onset of other adenocarcinomas or other childhood cancers</td>
</tr>
</tbody>
</table>

**FOLLOW-UP**

- Classic LFS or LFS-like testing criteria met → See Follow-up (page 570)
- Classic LFS or LFS-like testing criteria not met → Individualized recommendations according to personal and family history

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**LI-FRAUMENI SYNDROME**

<table>
<thead>
<tr>
<th>LI-FRAUMENI FOLLOW-UP</th>
<th>FAMILY STATUS</th>
<th>GENETIC TESTING</th>
<th>TEST OUTCOME</th>
<th>SCREENING RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deleterious familial TP53 mutation known</td>
<td>Consider TP53 testing for specific familial mutation (category 2A for adults; category 2B for children)</td>
<td>Positive for familial TP53 mutation</td>
<td>See Li-Fraumeni Syndrome Management (facing page)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TP53 testing not performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative for familial TP53 mutation</td>
<td>Breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines1</td>
<td></td>
</tr>
<tr>
<td>No known familial TP53 mutation</td>
<td>Consider testing affected family member with highest likelihood of TP53 mutation2,3</td>
<td>Family member tested and mutation found</td>
<td>See Li-Fraumeni Syndrome Management (facing page)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family member not tested or tested and no mutation found</td>
<td>Offer research and individualized recommendations according to personal and family history</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variant of unknown significance found (uninformative)4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk assessment and counseling:
- Psychosocial assessment and support
- Risk counseling
- Education
- Discussion of genetic testing
- Informed consent

1To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

2Youngest age at diagnosis, bilateral disease, multiple primaries, sarcoma at age < 45 y.
3Testing of unaffected family members when no affected member is available may be considered. Significant limitations of interpreting test results should be discussed.
4Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
**LI-FRAUMENI SYNDROME**

**LI-FRAUMENI SYNDROME MANAGEMENT**

<table>
<thead>
<tr>
<th><strong>Breast Cancer Risk</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BSE training and education and regular monthly BSE starting at age 18 y.</td>
<td></td>
</tr>
<tr>
<td>Clinical breast exam, semiannually, starting at age 20-25 y, or 5-10 y before the earliest known breast cancer in the family, (whichever comes first).</td>
<td></td>
</tr>
<tr>
<td>Annual mammogram and/or breast MRI screening starting at age 20-25 y, or individualized based on earliest age of onset in family.¹,²</td>
<td></td>
</tr>
<tr>
<td>Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, degree of cancer risk, and reconstruction options.</td>
<td></td>
</tr>
</tbody>
</table>

**Other Cancer Risks**

- Address limitations of screening for many cancers associated with LFS. Because of the remarkable risk for additional primary neoplasms, screening may be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).
- Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors, which should include careful skin and neurologic examinations.
- Consider colonoscopy every 2-5 y starting no later than age 25 y.
- Pediatricians should be apprised of the risk for childhood cancers in affected families.
- Discuss option to participate in novel screening approaches using technologies such as PET scan, abdominal ultrasound, and brain MRI within clinical trials when possible.³
- Target surveillance based on individual family histories.
- Education regarding signs and symptoms of cancer.

**Risk to Relatives**

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

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¹ The appropriateness of imaging scheduling is still under study.
² 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.
³ Some centers are evaluating novel imaging techniques as investigational tools.
COWDEN SYNDROME TESTING CRITERIA\textsuperscript{a,b}

- Individual from a family with a known PTEN mutation
- Individual with a personal history of:
  - Bannayan-Riley-Ruvalcaba syndrome (BRR) or
  - Adult Lhermitte-Duclos disease (LDD; cerebellar tumors) or
  - Autism spectrum disorder and macrocephaly or
  - 2 or more biopsy proven trichilemmomas or
  - 2 or more major criteria (1 must be macrocephaly) or
  - 3 major criteria, without macrocephaly or
  - One major and \geq 3 minor criteria\textsuperscript{c} or
  - \geq 4 minor criteria
- At-risk individual\textsuperscript{d} with a relative with a clinical diagnosis of Cowden syndrome or BRR for whom testing has not been performed
  - The at-risk individual must have the following:
    - Any one major criterion or
    - 2 minor criteria

FOLLOW-UP

Cowden syndrome testing criteria met

- Individualized recommendations according to personal and family history

Cowden syndrome testing criteria not met

<table>
<thead>
<tr>
<th>Major criteria:</th>
<th>Minor criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Other thyroid lesions (e.g., adenoma, nodules, goiter)</td>
</tr>
<tr>
<td>Mucocutaneous lesions\textsuperscript{a}</td>
<td>Mental retardation (i.e., IQ \leq 75)</td>
</tr>
<tr>
<td>One biopsy proven trichilemmoma</td>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>Multiple palmoplantar keratoses</td>
<td>Single GI hamartoma or ganglioneuroma</td>
</tr>
<tr>
<td>Multifocal or extensive oral mucosal papillomatosis</td>
<td>Fibrocystic disease of the breast</td>
</tr>
<tr>
<td>Multiple cutaneous facial papules (often verrucous)</td>
<td>Lipomas</td>
</tr>
<tr>
<td>Macular pigmentation of glans penis</td>
<td>Fibromas</td>
</tr>
<tr>
<td>Macrocephaly (megalocephaly; i.e., \geq 97th percentile, 58 cm in adult women, 60 cm in adult men)\textsuperscript{f}</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>Uterine fibroids</td>
</tr>
<tr>
<td>Non-medullary thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Multiple GI hamartomas or ganglioneuromas</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}These are testing criteria; not clinical diagnostic criteria.
\textsuperscript{b}If 2 criteria involve the same structure/organ/tissue, both may be included as criteria (e.g., breast cancer as a major criterion and fibrocystic breast disease as a minor criterion).
\textsuperscript{c}If an individual has \geq 2 major criteria, such as breast cancer and non-medullary thyroid cancer but does not have macrocephaly, 1 of the major criteria may be included as 1 of the 3 minor criteria to meet testing criteria.
\textsuperscript{d}At-risk individual can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing.
\textsuperscript{e}The literature available on mucocutaneous lesions is not adequate to specify accurately the number or extent of mucocutaneous lesions required to be a major criterion for Cowden syndrome. Clinical judgement should be used.
\textsuperscript{f}Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: birth to 18 years. Pediatrics 1987;79:706-712.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
**COWDEN SYNDROME**

**COWDEN SYNDROME FOLLOW-UP**

**FAMILY STATUS** | **GENETIC TESTING** | **TEST OUTCOME** | **SCREENING RECOMMENDATION**
--- | --- | --- | ---
Deleterious familial PTEN mutation known | Consider PTEN testing for specific familial mutation | Positive for familial PTEN mutation | See Cowden Syndrome Management (page 574)

**Risk assessment and counseling:**
- Psychosocial assessment and support
- Risk counseling
- Education
- Discussion of genetic testing
- Informed consent

No known familial PTEN mutation | Consider testing affected family member with highest likelihood of PTEN mutation | Family member tested and mutation found | See Cowden Syndrome Management (page 574)

**Variant of unknown significance found (uninformative)**

Family member not tested or tested and no mutation found

Variant of unknown significance found (uninformative)

Breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines

**Autism spectrum disorder and macrocephaly or**

**Adult Lhermitte-Duclos disease (LDD; cerebellar tumors) or**

**Bannayan-Riley-Ruvalcaba syndrome (BRR) or**

**Multiple GI hamartomas or ganglioneuromas**

**Endometrial cancer**

**Non-medullary thyroid cancer**

**Multiple palmoplantar keratoses**

**Multifocal or extensive oral mucosal papillomatosis**

**Lipomas**

**Renal cell carcinoma**

**Fibromas**

**Fibrocystic disease of the breast**

**Mental retardation (i.e., IQ 75)**

**Other thyroid lesions (e.g., adenoma, nodules, goiter)**

**Macular pigmentation of glans penis**

**Multiple cutaneous facial papules (often verrucous)**

**Uterine fibroids**

**Genetic/Familial High-Risk Assessment: Breast and Ovarian Version 1:2010**

**Screening and Diagnosis**

**COWDEN SYNDROME**

**Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.**

**Certain mutations (i.e., large rearrangements) are not detectable by the primary sequencing assay and supplementary testing may be necessary.**

**Testing of unaffected family members when no affected member is available may be considered. Significant limitations of interpreting test results should be discussed.**

**Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.**

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Testing of unaffected family members when no affected member is available may be considered. Significant limitations of interpreting test results should be discussed.

Certain mutations (i.e., large rearrangements) are not detectable by the primary sequencing assay and supplementary testing may be necessary.

Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.
**COWDEN SYNDROME**

COWDEN SYNDROME MANAGEMENT

**Women**
- BSE training and education and regular monthly BSE starting at age 18 y.
- Clinical breast exam, semiannually, starting at age 25 y, or 5-10 y before the earliest known breast cancer in the family.
- 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).
- For endometrial cancer screening, encourage patient education and prompt response to symptoms and participation in a clinical trial to determine the effectiveness and necessity of screening modalities.
- Discuss option of risk-reducing mastectomy and hysterectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.

**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 breast and thyroid exam.
- Baseline thyroid ultrasound at age 18 y, and consider annually thereafter.
- Consider annual dermatologic exam.
- Education regarding the signs and symptoms of cancer.

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

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1. The appropriateness of imaging scheduling is still under study.
2. 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.
3. Limited data exist regarding the lifetime risk for endometrial cancer in patients with Cowden syndrome. Surveillance screening and surgical intervention should be on an individual basis.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.
ity to breast and/or ovarian cancers (e.g., BRCA1, BRCA2, PTEN, TP53, CDH1) and provided a means of characterizing the specific gene 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 in individuals with hereditary or familial cancers, including prevention, screening, and treatment.

These guidelines were developed with an acute awareness of the preliminary nature of much of the 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, these guidelines were not developed as a substitute for professional genetic counseling. Rather, they are intended to help health care providers identify individuals who may benefit from cancer risk assessment and genetic counseling, to provide genetic counselors with an updated tool for assessing individual breast cancer and ovarian cancer risk and guide decisions related to genetic testing, and to facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancer. Although other cancers are associated with these hereditary syndromes, these guidelines mainly focus on management of breast and ovarian cancer risk in these individuals. Table 1 provides a glossary of genetic terms.

**Hereditary Breast or Breast/Ovarian Cancer Syndromes**

Breast cancer is the most prevalent type of cancer and the second leading cause of cancer death in women in the United States. Up to 10% of breast cancers are caused by specific mutations in single genes that are passed down in a family. Specific patterns of hereditary breast/ovarian cancers are linked to mutations in the BRCA1 or 2 genes. In addition, 2 very rare hereditary cancer syndromes exhibiting an increased risk for breast cancer are Li-Fraumeni and Cowden syndromes, which are related to germline mutations in the TP53 and PTEN genes, respectively. Similar to the BRCA 1/2 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 is another rare hereditary syndrome also associated with development of lobular breast cancer. This syndrome arises from mutations in the CDH1 (cadherin 1, type 1, E-cadherin [epithelial]) gene, which encodes for a tumor suppressor gene product. 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 75 years of age was estimated to be as high as 52%. Furthermore, germline CDH1 mutations may be associated with lobular breast cancer in the absence of diffuse gastric cancer.

These hereditary syndromes share several features beyond elevation of breast cancer risk. They are caused by germline mutations that are not in sex-linked chromosomes; hence, they can be inherited from the mother or father. They 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 individuals 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 and bilateral disease. The gene mutations associated with these hereditary syndromes are considered to be highly penetrant, although a subsequent alteration in the second copy of the gene without the hereditary mutation is believed to be necessary for the initiation of cancer development (2-hit hypothesis). In addition, the manifestations (i.e., expression) of these hereditary syndromes are often variable in individuals within a single family (e.g., age of onset, tumor site, number of primary tumors). The risk for developing cancer in individuals with one of these hereditary syndromes depends on numerous variables, including the gender and age of the individual.

**Hereditary Breast/Ovarian Cancer Syndrome**

The overall prevalence of disease-related mutations in BRCA1 and 2 genes has been estimated as 1 in 300 and 1 in 800, respectively. Currently, hundreds of unique mutations have been identified in both genes. However, several founder effects (see Table 1) have been observed in certain populations, wherein the
same mutation has been found in multiple, 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 40.6,21 Certain founder mutations have also been identified in populations from the Netherlands, Sweden, Hungary, Iceland, and French Canada19,22–27 (see page 566). Estimates show that more than 90% of early-onset cancers in families with both breast and ovarian cancers are caused by mutations in the BRCA 1 or 2 genes.28 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 should be very high.

The BRCA1 and 2 genes encode for proteins involved in tumor suppression. The BRCA1 gene is located on chromosome 17, and is believed to be involved in both the repair of DNA lesions 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.29 The BRCA2 gene, located on chromosome 13, is involved in repair of replication-mediated double-strand breaks.30,31

Mutations in the BRCA1 or 2 genes can be highly penetrant (see Table 1), although the probability of cancer development in carriers of these mutations is variable, even within families with the same mutation.32–34 Estimates of penetrance range from a 45% to 84% lifetime risk for developing breast cancer, and carriers have an increased risk for contralateral breast cancer.15–37 In addition, female carriers of these genes have an estimated 11% to 62% lifetime risk for ovarian cancer, depending on the population studied.35–39 Whether penetrance is related to the specific mutation identified in a family or whether additional factors, either genetic or environmental, affect disease expression is currently unclear. It is
Generally accepted, however, that carriers of mutations in BRCA1 or 2 genes have an excessive risk for both breast and ovarian cancers that warrants consideration of more intensive preventive and screening 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 estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative (i.e., “triple negative”). In a recent study, 11% of 54 young women (≤ 40 years) with high-grade, triple-negative breast cancer were found to be carriers of a BRCA1 gene mutation.

An increased frequency of other malignancies has been reported in families with 1 or more mutations in the BRCA 1 or 2 gene. Germline BRCA1 and 2 mutations have been associated with an increased risk for prostate cancer, and BRCA2 mutation carriers have been reported to also have a higher risk for pancreatic cancer and melanoma. Some data related to the risk for cancers in this population at some sites other than the breast/ovary are contradictory. For example, experts have suggested that the increased risk for endometrial cancer observed in some BRCA1 or 2 mutation carriers is mainly caused by the use of tamoxifen therapy rather than the presence of a gene mutation.

Germline mutations in BRCA1 and 2 are responsible for 5% to 10% of epithelial ovarian cancers (i.e., ovarian cancer developing on the surface of the ovary). Increased risks for cancers of the fallopian tube and primary peritoneal cancer are also observed in this population.

The histology of ovarian cancers in BRCA1 or 2 mutation carriers is more likely to be characterized as serous adenocarcinoma and high grade compared with ovarian cancers in nonmutation carriers, although endometrioid and clear cell ovarian cancers have also been reported in the former population.

In the setting of a diagnosis of invasive ovarian cancer, as many as 15% of unselected individuals will have a germline BRCA1 or 2 mutation. However, reports have shown that approximately half of families showing a genetic predisposition to ovarian cancer do not have identifiable mutations in BRCA1 or 2 genes. Hence, other gene mutations predisposing to ovarian cancer are likely to exist. Notably, ovarian cancer is a component tumor of Lynch syndrome, which is associated with germline mutations in mismatch repair genes. Interestingly, results from a prospective study suggest that women from families at increased risk for hereditary breast cancer without site-specific BRCA mutations are not at increased risk for ovarian cancer, although these results may have been confounded by the ethnic characteristics and size of the study population.

Male carriers of a BRCA gene mutation also have a greater risk for cancer susceptibility. In one study of 26 high-risk families with at least 1 case of male breast cancer, 77% showed a BRCA2 mutation. However, among men with breast cancer who were not selected based on family history, only 4% to 14% tested positive for a germline BRCA2 mutation. For men with a BRCA2 mutation, the risk for breast cancer by age 80 years is estimated at 6.9%. In contrast, lifetime risk for breast cancer in men without this mutation is estimated at approximately one tenth of 1% (1 in 1000).

**Li-Fraumeni Syndrome**

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline TP53 gene mutations. It has been estimated to be involved in only approximately 1% of hereditary breast cancer, although results from a recent study suggest that germline TP53 gene mutations may be more common than previously believed. The tumor suppressor gene, TP53, is located on chromosome 17, and the protein product of the TP53 gene (i.e., 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 cell cycling and apoptosis. Germline mutations in the TP53 gene have been observed in more than 50% (and > 70% in some studies) of families meeting the classic definition of LFS (see page 569). Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline TP53 mutations.

LFS, a highly penetrant cancer syndrome associated with a high lifetime 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, and cancer of the colon, adrenal cortex, and brain tumors.
breast cancer, adrenocortical tumors, and certain brain tumors have been referred to as the “core” cancers of LFS because they account for most cancers observed in individuals with germline mutations in the TP53 gene. One study showed that at least 1 of these cancers was found in 1 or more members of all families with a germline TP53 gene mutation.68

Individuals with LFS often present with certain cancers (e.g., soft tissue sarcomas, brain tumors, and adrenocortical carcinomas) in early childhood,76 and have an increased risk for developing multiple primary cancers during their lifetimes.86 Results of a segregation analysis of data collected on the family histories of 159 patients with childhood soft tissue sarcoma showed that carriers of germline TP53 mutations had estimated cancer risks of approximately 60% and 95% by age 45 and 70 years, respectively.81 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.68 Importantly, estimations of cancer risks associated with LFS are limited at least some degree by selection bias because dramatically affected kindreds are more likely to be identified and become the subject of further study.

Several different sets of criteria have been used to help identify individuals with LFS. For the purposes of the guidelines, 2 sets of these criteria are used to facilitate the identification of individuals who are candidates for TP53 gene mutation testing. Chompret et al.82 described 3 characteristics of an ideal set of testing criteria that would help experts find a mutation in situations in which it is likely to exist (i.e., the criteria should have a high positive predictive value), miss as few mutations as possible (i.e., the criteria should have a high sensitivity), and avoid selecting subjects who are not carriers of the mutations (i.e., the criteria should have a high specificity).

Classic LFS criteria, based on a study by Li and Fraumeni involving 24 LFS kindreds, include the following: member of a kindred with a known TP53 mutation; combination of a diagnosis at 45 years or younger with a sarcoma and a first-degree relative diagnosed with cancer at 45 years or younger; and an additional first- or second-degree relative in the same lineage with cancer diagnosed at younger than 45 years or a sarcoma diagnosed at any age (see page 569). Classic LFS criteria have been estimated to have a high positive predictive value and high specificity, although the sensitivity is relatively low (e.g., estimated at 40% in one study).68 Thus, it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline TP53 mutations.79,83 Classic LFS criteria are included in the guidelines to guide selection of individuals for TP53 gene mutation testing (see page 569).

Other groups have broadened the classic LFS criteria to facilitate identification of individuals with TP53,74,82,84,85 One set of these less-strict criteria proposed by Birch et al.74 shares many features of the classic LFS criteria, although a larger range of cancers are included. These criteria include 1) combination of an individual diagnosed with a childhood tumor or sarcoma, 2) brain tumor or adrenocortical carcinoma diagnosed at age younger than 45 years, and 3) a first- or second-degree relative with a typical LFS tumor at any age, and another first- or second-degree relative with cancer diagnosed before 60 years of age. The sensitivity of these Li-Fraumeni–like (LFL) criteria is estimated to be high, although the estimated specificity is relatively low.68 These LFL criteria are also included in the guidelines to help identify candidates for TP53 gene mutation testing (see page 569). Uncommonly, individuals with de novo germline TP53 mutations (no mutation in either biologic parent) have been identified.68,75 These cases would not be identified as TP53 testing candidates using either classic LFS or the LFL criteria mentioned earlier because both require the presence of a family history.

Women with early-onset breast cancer (< 30 years) with a negative BRCA1/2 gene mutation test are another group for whom TP53 gene mutation testing should be considered under certain circumstances. Several recent studies have investigated the likelihood of a germline TP53 mutation in this population.68,86,87 Gonzalez et al.68 found that 7% of women younger than 30 years with breast cancer had a germline TP53 mutation if they did not have a first- or second-degree relative with cancer. Other studies have found an even lower incidence of germline TP53 gene mutations in this population. For example, Bougeard et al.86 reported that only 0.7% of unselected women with breast cancer before 33 years of age were carriers of a germline TP53 mutation.86 Furthermore, Ginsburg et al.87 found no germline TP53 mutations in 95 women with early-onset breast cancer who did not have a family history char-
characterized by classic LFS or LFL criteria. Clearly, consideration of family history is important in women with early-onset breast cancer.

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.

Cowden Syndrome
Cowden syndrome, a rare hereditary cancer syndrome, was first described in 1963 and named after the Cowden family, the first family documented with signs of the disease. The incidence of Cowden syndrome has been reported to be 1 in 200,000, although it is likely to be underestimated because of difficulties associated with making a clinical diagnosis of the disease. It is considered part of the PTEN hamartoma tumor syndrome (PHTS), which also includes Bannayan-Riley-Ruvalcaba (BRRS), Proteus, and Proteus-like syndromes (although controversy exists as to whether true Proteus cases have been shown to have a PTEN mutation). Hamartomas, a common manifestation of these syndromes, are benign tumors resulting from overgrowth of normal tissue. The PTEN (“phosphatase and TENSin homologue deleted on chromosome TEN”) gene located on chromosome 10 encodes for a tumor-suppressor protein involved in cell cycle control and cell survival.

Cowden syndrome is the only PHTS disorder associated with a documented predisposition to malignancies, and there is the one addressed in these guidelines. However, experts have suggested that patients with other PHTS diagnoses associated with PTEN mutations should be assumed to have Cowden-associated cancer risks. 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.

Women diagnosed with Cowden syndrome have a high risk for developing benign fibrocystic breast disease, and a 25% to 50% estimated lifetime risk for developing breast cancer, with an average age of 38 to 46 years at diagnosis. Only 2 cases of breast cancer have been reported in men with Cowden syndrome. Thyroid disease, including benign multinodular goiter, adenomatous nodules, and follicular adenomas, has been reported to occur in approximately 70% of individuals with Cowden syndrome, and the lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%. As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.

Although not well defined, women with Cowden syndrome may have a 5% to 10% risk for developing endometrial cancer, and an increased risk for uterine fibroids. In addition, skin cancers, renal cell carcinomas, 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. Importantly, however, 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 (i.e., new cancerous lesions), and these data are also likely to be confounded by selection bias. Furthermore, a considerable number of these studies were published before the 1996 establishment 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.

Classic features of the disease include mucocutaneous papillomatous papules, palmoplantar keratoses, and trichilemmomas (i.e., benign tumors derived from the outer root sheath epithelium of a hair follicle). Most individuals with Cowden syndrome exhibit characteristic mucocutaneous lesions by their 20s, and reports show that 99% of affected individuals develop these lesions. This syndrome shows nearly complete penetrance. The presence of 2 or more trichilemmomas has been reported to be pathognomonic for Cowden syndrome. However, because most of this evidence is from older literature, the association between these 2 entities may be somewhat overestimated. Individuals with a solitary trichilemmoma have been reported who do not have Cowden syndrome. Nevertheless, because of the strong association between these lesions and Cowden syndrome, and the difficulty in clinically distinguishing between a trichilemmoma and another mucocutaneous lesion, a diagnosis of trichilemmoma must be histologically confirmed.

It has been historically reported that approximately 40% of individuals with Cowden syndrome
have gastrointestinal polyps (often colonic), although more recent data suggest that this risk may be 80% or higher. Most of the polyps are hamartomatous, although ganglioneuromas (i.e., rare, benign peripheral nervous system tumors) have also been reported.\textsuperscript{11,104}

Adult Lhermitte-Duclos disease (LDD) and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome.\textsuperscript{91,98,105} A rare, slow-growing, benign hamartomatous lesion of the brain, LDD is a dysplastic gangliocytoma of the cerebellum.\textsuperscript{11} The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a PTEN gene mutation,\textsuperscript{98} although exceptions have been reported.\textsuperscript{106} In addition, a relatively large body of evidence supports that 10% to 20% of individuals with autism spectrum disorder and macrocephaly carry germline PTEN mutations.\textsuperscript{107–111} Macrocephaly (defined as head circumference > 97th percentile)\textsuperscript{112} is a common finding in patients with Cowden syndrome. An estimated 80% of individuals with this syndrome will exhibit this clinical finding.\textsuperscript{11}

Although formal diagnostic criteria have not been established, the BRRS variant of PHTS has been characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay, and pigmented macules on the glans penis in men.\textsuperscript{113} PTEN gene mutations testing has been reported in approximately 60% of individuals characterized as having BRRS.\textsuperscript{114} Furthermore, another study showed that 10% of patients with BRRS for whom a PTEN gene mutation test was negative were carriers of large PTEN gene deletions.\textsuperscript{105}

The PTEN mutation frequency in individuals meeting International Cowden Consortium criteria for Cowden syndrome has been estimated at approximately 80%.\textsuperscript{11} The International Cowden Consortium criteria have been updated several times since 1996\textsuperscript{11,91,115,116} and have served as the basis for the criteria included in the guidelines. Based on literature reports and expert consensus, the panel recently revised the list of criteria associated with this genetic syndrome and the combinations of criteria that establish which individuals are candidates for PTEN gene mutation testing (see page 572 and “Cowden Syndrome,” page 579).

Similar to earlier versions, criteria are grouped into 3 general categories. Patients are considered for PTEN gene mutation testing based on whether they meet certain criteria or combinations of criteria from these 3 categories. The first category includes a personal history of BRRS, adult LDD, autism spectrum disorder with macrocephaly, or 2 or more biopsy-proven trichilemmomas (see page 572). Any individual presenting with 1 or more of these diagnoses should undergo PTEN testing. Previously, some of the criteria from this group were sometimes referred to as pathognomonic, although it is unlikely that any of these conditions can stand alone as a definitive diagnostic criterion of Cowden syndrome. Another criterion that can be considered 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 criterion represents major features associated with Cowden syndrome, including the presence of breast cancer, macrocephaly (i.e., megalencephaly),\textsuperscript{112} endometrial cancer, nonmedullary thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (e.g., one biopsy-proven trichilemmoma, multiple palmar-plantar keratoses; see page 572 for complete list). An individual exhibiting 2 or more major criteria that include macrocephaly meets the testing threshold. In addition, 3 or more major criteria are considered sufficient to warrant testing. Regarding decisions related to the presence of mucocutaneous lesions, the panel did not believe the available literature was 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, and clinical judgment is needed when evaluating these lesions.

The final category of criteria represents features with a minor association to Cowden syndrome, including thyroid lesions other than nonmedullary thyroid cancer, mental retardation, autism spectrum disorder, a single gastrointestinal hamartoma or ganglioneuroma, fibrocystic disease of the breast, lipomas, fibromas, renal cell carcinoma, and uterine fibroids. An individual would need to exhibit 4 minor criteria, or 3 minor and 1 major, to meet testing criteria. Furthermore, if an individual meets 2 or more major criteria but does not have macrocephaly, one of the major criteria can be substituted for a mi-
nor criterion (see page 572 and “Risk Assessment, Counseling, and Management: Cowden Syndrome,” page 588).

**Initial Risk Assessment**

For a patient concerned about or suspected of having a hereditary propensity to breast and/or ovarian cancer, an initial risk evaluation should be performed to determine if a formal risk assessment should be undertaken. The first step in this primary assessment is a broad and flexible evaluation of the personal and family history of the individual with respect to breast and/or ovarian cancer.\(^{117,118}\) The magnitude of the risk increases with the number of affected relatives in the family and the closeness of the relationship; it is affected by the age at which the affected relative was diagnosed.\(^{119,120}\) The younger the age at diagnosis, the more likely a genetic component is present. When assessing 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 considered.

If an individual or a close family member meets any of the criteria presented on page 564, 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 (see page 565).

For individuals potentially meeting established criteria for 1 or more of the hereditary cancer syndromes, genetic testing should be considered along with appropriate pretest counseling. A genetic counselor and/or medical geneticist should be involved in this process. 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 (e.g., a change in the frequency of, or modalities used for, breast cancer screening).\(^5\) The NCCN panel recommends that these individuals follow recommendations in the NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

**Formal Risk Assessment and Genetic Counseling**

**Risk Assessment**

Cancer genetic risk assessment and genetic counseling is a multistep 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 an evaluation of the absolute risk for breast and/or ovarian cancer and an estimation of the likelihood that a heritable genetic mutation is present in the 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 for 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 1 or 2 first- or second-degree female relatives with breast cancer.\(^{121}\) In addition, decision models developed to estimate the likelihood that a BRCA1/2 mutation is present include BRCAPRO\(^{122,123}\) and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).\(^{122}\) A lifetime risk for breast cancer of 20% to 25% or greater, as assessed using 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 a recent update to the American Cancer Society (ACS) guidelines on breast screening that incorporates MRI.\(^{124}\)

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 for carrying that mutation.

**Evaluation of Patient Needs and Concerns:** The first step in evaluating an individual’s risk for hereditary breast cancer is to assess the concerns and reasons for seeking counseling and to guarantee that 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,\(^{125}\) which 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 along with the 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 proband (index case) and proceeding outward to include first-, second-, and third-degree relatives on both the maternal and paternal sides (see page 565). Standardized pedigree nomenclature should be used. Unaffected family members, both living and deceased, are also included, because their histories also provide information about the magnitude of genetic risk.

Information collected includes cancer diagnoses according to primary site, age at diagnosis, bilateral- ity (when appropriate), and current age or age at death. Whenever possible, cancer diagnoses in the family are verified through obtaining medical records, pathology reports, or death certificates. This is particularly important in the case of a reported “abdominal” cancer in a female relative, because cancers of the cervix, uterus, ovary, and/or colon are often confused. It is also important to know the ancestry/ethnicity of the individual.

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 (e.g., hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members.

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

**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 breast cancer. A history of previous breast biopsies, especially those in which the pathology showed atypical hyperplasia or lobular carcinoma in situ, is associated with an increased risk for breast cancer. Pathologic verification of these diagnoses is encouraged. History of carcinogen exposure (e.g., radiation therapy) should also be included in the patient assessment. When taking the medical history, clinicians should also be alert to the physical manifestations of Cowden syndrome, especially skin conditions.

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

**Focused Physical Examination:** A physical examination may 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.

**Genetic Counseling**

Genetic counseling is a critical component of the cancer risk assessment process. 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, biologic, and environmental factors related to the individual’s cancer diagnosis and/
or risk for disease; help them derive personal meaning from cancer genetic information; and empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. Individuals must 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 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

Pretest counseling is an essential element of the genetic counseling process if genetic testing for a gene mutation associated with a hereditary cancer syndrome is being considered.7 The foundation of pretest genetic counseling is based on the principle of informed consent. Pretest 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 for genetic discrimination, psychosocial aspects, and confidentiality issues.7 A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act, enacted in 2008, which prohibits health insurers and employers from discriminating based on genetic test results.136

Post-test counseling must also be performed and includes disclosure of results, a discussion of their significance, an assessment of their impact on the emotional state of the individual, a discussion of their impact on the medical management of the individual, and how and where the patient will be followed up. 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 among relatives and the importance of informing family members about test results.7 Offering gene testing to both parents of an individual who tests positive for 1 of these gene mutations (i.e., BRCA1/2, PTEN, TP53) may also be appropriate when the lineage is in question.

**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 they show receiving genetic test results. The potential benefits, limitations, and risks associated with genetic testing are also important considerations in the decision-making process. Many women feel they are already doing everything they can to minimize their risk for developing breast cancer, and others fear the emotional toll of finding out they are a mutation carrier, especially if they have children who would be at risk for inheriting the mutation. For those who choose not to proceed with testing, the counseling team tailors recommendations for primary and secondary prevention to the personal and family history.

In the statement on Genetic Testing for Cancer Susceptibility from ASCO updated in 2003, genetic testing is recommended when 1) a personal or family history suggests 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.137 These recommendations were reiterated in the 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 cancers.138

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

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 up with routine breast screening. Individuals who meet testing criteria but do not undergo gene testing should be followed up as if a gene mutation (i.e., BRCA, PTEN, or TP53) is present if they have a close family member who is a
For most 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, full sequencing of the genes is usually 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.

Testing of unaffected family members may be considered when the family has no known deleterious mutation and no affected member is available. A negative test result in this case, however, is considered indeterminate (see Table 2) and does not provide the same level of information as when a deleterious mutation is known.

In the case of hereditary breast/ovarian cancer (i.e., BRCA mutation), 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 that are believed to be related to the deleterious mutation in question (e.g., prostate or pancreatic cancer).

Another counseling dilemma is posed by the finding of a variant or mutation of unknown significance (see Table 2)—a mutation 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 this 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.

Finally, certain large genomic rearrangements are not detectable using a primary sequencing assay, thereby necessitating supplementary testing in some cases. For example, tests are available that detect rare, large cancer-associated rearrangements of DNA in the BRCA1 and 2 genes that are not detected by sequencing the genes.

### Risk Assessment, Counseling, and Management: Hereditary Breast/Ovarian Cancer Syndrome

Detailed on page 566 are 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. For example, a personal history of female breast cancer diagnosed at age 45 years or younger, a personal history of male breast cancer, or a personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer is considered to be sufficient to meet the testing threshold. After risk assessment and counseling, genetic testing should be considered in individuals for whom hereditary breast/ovarian cancer syndrome testing criteria are met. The panel recommends this testing for patients who are members of a family with a known deleterious BRCA1 or 2 mutation. Initial testing for the 3 known founder mutations is recommended if the individual meeting testing criteria is of Ashkenazi Jewish descent. Full sequence testing is recommended for those from other ethnic groups who meet testing criteria.

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,” pages...

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<td>True-positive</td>
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</tr>
<tr>
<td>True-negative</td>
<td>The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member.</td>
</tr>
<tr>
<td>Indeterminate (uninformative)</td>
<td>The person is not a carrier of a known cancer-predisposing gene, and the carrier status of other family members is either negative or unknown.</td>
</tr>
<tr>
<td>Inconclusive (variants of unknown significance)</td>
<td>The person is a carrier of an alteration in a gene that currently has no known significance.</td>
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581 and 583, respectively) and the importance of genetic counseling for these individuals should also be discussed (see page 568). Counseling issues pertaining specifically to male breast cancer have also been described, and include an increased risk for prostate cancer in male carriers of a BRCA1/2 mutation. In addition, counseling related to the risks and benefits of reproductive options for couples expressing the desire that their offspring not carry a familial BRCA1/2 gene mutation may also be an option.

Recommendations for the medical management of hereditary breast/ovarian cancer syndrome are based on an appreciation of the early onset of disease, increased risk for ovarian cancer, and risk for male breast cancer in BRCA1/2 carriers (page 568). An individual with a known deleterious BRCA1/2 mutation in a close family member who does not undergo gene testing should be followed up according to the same guidelines as a carrier of a BRCA1/2 mutation. Individuals not meeting testing criteria, including those with an increased risk for familial breast cancer, should be followed up according to the recommendations in the NCCN Breast Cancer Screening and Diagnosis Guidelines (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

**Screening Recommendations:** The emphasis on initiating screening considerably earlier than standard recommendations is a reflection of the early age at onset seen in hereditary breast/ovarian cancer. For a woman who is a carrier of a BRCA1/2 mutation, training in breast self-examination with regular monthly practice should begin at 18 years, and semiannual clinical breast examinations should begin by 25 years of age. The woman should begin having annual mammograms and breast MRI screening at 25 years or according to an individualized timetable based on the earliest age of cancer onset in family members.

The overall sensitivity of screening mammography was reported to be only 33% in a study of women with suspected or known BRCA1/2 mutations who were more likely to be younger and to have dense breasts. Other reasons for the low sensitivity of mammography in women with BRCA1/2 mutations include an increased likelihood of developing tumors with more benign mammographic characteristics (e.g., less likely to appear as a spiculated mass). 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 recent guidelines from the ACS.

For individuals who have not elected ovarian cancer risk-reducing surgery, concurrent transvaginal ultrasound and CA-125 determination should be considered every 6 months starting at 35 years of age or 5 to 10 years earlier than the youngest age of first diagnosis of ovarian cancer in the family (page 568). Although retrospective data indicate that annual ovarian screening using transvaginal ultrasound and measurement of serum CA-125 levels is neither an effective strategy for the early detection of ovarian tumors nor a reasonable substitute for a bilateral risk-reduction salpingo-oophorectomy (RRSO), data are limited regarding the effectiveness of these screening interventions when used every 6 months. Investigational imaging and screening studies may be considered for this population. A full-body skin examination for melanoma screening and investigational protocols for pancreatic cancer screening should be considered.

Men testing positive for a BRCA1/2 mutation should have a semi-annual clinical breast examination and undergo training in breast self-examination with regular monthly practice. Baseline mammography should be considered, followed by annual screening with mammography for men with gynecomastia or parenchymal/glandular breast density on baseline study. Involvement in population screening guidelines for prostate cancer is recommended. A full-body skin examination for melanoma screening and investigational protocols for pancreatic cancer screening should be considered.

**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 for developing breast cancer by at least 90% in moderate- and high-risk women and in known BRCA1/2 mutation carriers. Results from smaller prospective studies with shorter follow-up also show that RRM provides a high degree of protection against breast cancer in women with a BRCA1/2 mutation.

The panel supports discussing the option of RRM with women on a case-by-case basis. Counseling regarding the degree of protection offered by this surgery...
and the degree of cancer risk should be provided.

The potential psychosocial effects of RRM must be addressed, although these effects have not been well studied. Multidisciplinary consultations are recommended before surgery and should include discussions of the risks and benefits of surgery, and surgical breast reconstruction options. Immediate breast reconstruction is an option for many women after RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction. 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). Although the risk for ovarian cancer is generally lower than for breast cancer in BRCA1/2 mutation carriers, the absence of reliable methods for early detection and the poor prognosis associated with advanced ovarian cancer support the performance of bilateral RRSO after completion of childbearing in these women. In the study by Rebbeck et al., the mean age at ovarian cancer diagnosis was 50.8 years for BRCA1/2 mutation carriers.

Several studies have shown the effectiveness of RRSO in reducing ovarian cancer risk in BRCA1/2 mutation carriers. 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 after RRSO. However, a 1% to 4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.

RRSO is also reported to reduce the risk for breast cancer in carriers of a BRCA1/2 mutation by approximately 50%. In the case-control international study, Eisen et al. reported 56% (odds ratio [OR], 0.44; 95% CI, 0.29–0.66) and 46% (OR, 0.57; 95% CI, 0.28–1.15) breast cancer risk reductions after RRSO in BRCA1 and 2 mutation carriers, respectively. Hazard ratios of 0.47 (95% CI, 0.29–0.77) and 0.30 (95% CI, 0.11–0.84) were reported in 2 other studies comparing breast cancer risk between women with a BRCA1/2 mutation who underwent RRSO and those who opted for surveillance only. These studies are further supported by a recent meta-analysis that found similar breast cancer risk reductions of approximately 50% for BRCA1 and 2 mutation carriers after RRSO, although results of a recent prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for BRCA1 mutation carriers.

Reductions in breast cancer risk for BRCA1/2 mutation carriers undergoing RRSO may be associated with decreased hormonal exposure after surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a BRCA1 mutation who underwent an RRSO at 40 years or younger (OR, 0.36; 95% CI, 0.20–0.64) than in BRCA1 carriers 41 to 50 years who had this procedure (OR, 0.50; 95% CI, 0.27–0.92). A nonsignificant reduction in breast cancer risk was found for women 51 years of age or older, although only a small number were included in this group. However, results from Rebbeck et al. also suggest that RRSO after 50 years of age is not associated with a substantial decrease in breast cancer risk. Because of limited data, an optimal age for RRSO is difficult to specify.

The panel recommends RRSO for women with a known BRCA1/2 mutation, ideally between ages 35 and 40 years and on completion of childbearing, or at an individualized age based on earliest age of ovarian cancer diagnosed in the family. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes. (For details on pathologic evaluation of surgical specimens, see www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/Ovary_09protocol.pdf.)

Other topics that should be addressed with respect to RRSO include the increased risk for osteoporosis and cardiovascular disease associated with premature menopause, and the potential effects of possible cognitive changes, accelerated bone loss, and vasomotor symptoms on quality of life.

Reports have shown that short-term hormone replacement therapy (HRT) in women undergoing RRSO does not negate the reduction in breast cancer risk associated with the surgery. In addition, results of a recent case-control study of BRCA1 mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal women. However, caution should be used when considering use of HRT in mutation carriers after RRSO, given the limitations inherent in nonrandomized studies.

Chemoprevention: Evaluation of the subset of
healthy individuals with a BRCA1/2 mutation in the Breast Cancer Prevention Trial study showed 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). However, tamoxifen use was not associated with a reduction in breast cancer risk in those with a BRCA1 mutation.177 These findings may be related to the greater likelihood for development of ER-positive tumors in carriers of a BRCA2 mutation than in those with a BRCA1 mutation. However, this analysis was limited by the very small number of individuals with a BRCA1/2 mutation. Regarding the evidence on the effect of oral contraceptives on cancer risks in women with known BRCA1/2 gene mutations, case-control studies have shown a substantially lower risk in women with 3 or more years of exposure.178,179 However, results of other studies suggest that oral contraceptive use may increase the risk for breast cancer in this population, especially if used for 5 or more years.180,181

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

The approach to families with other hereditary breast cancer syndromes, such as LFS, parallels that for hereditary breast/ovarian cancer in many ways. However, some differences are syndrome-specific with regard to assessment and management. In the case of LFS, multiple associated cancers, both pediatric and adult, should be reflected in the expanded pedigree (page 569).

Cancers associated with LFS include premenopausal breast cancer, bone and soft tissue sarcomas, acute leukemia, brain tumor, adenocortical carcinoma, unusually early onset of other adenocarcinomas, and other childhood cancers.68,80 Verification of these sometimes rare cancers is particularly important.

After risk assessment and counseling, genetic testing should be considered for individuals who meet testing criteria (see pages 569 and 570). This recommendation is category 2A for adults and 2B for children. The panel also suggests consideration of TP53 mutation testing in individuals with early-onset breast cancer (< 30 years) who had a negative BRCA1/2 test result, especially if they have a family history of LFS-related cancers. In the absence of additional family history, early breast cancer alone is associated with a low likelihood of mutation identification. Individuals who have tested positive for a TP53 mutation may have greater distress than anticipated, and therefore supportive interventions should be provided. An individual with a known deleterious TP53 mutation in a close family member who does not undergo gene testing should be followed up according to the same guidelines as a carrier of a TP53 mutation (see page 571). Individuals not meeting criteria for either classic LFS or LFL syndrome should be followed up according to their personal and family history.

Management of LFS should address the limitations of screening for the many cancers associated with this syndrome (see page 571). For those at risk for breast cancer, training and education in breast self-examination should start at age 18 years, with patients performing regular self-examination on a monthly basis. For members of families with LFS, breast cancer surveillance through clinical breast examination is recommended to begin between ages 20 and 25 years, or 5 to 10 years before the earliest known breast cancer in the family (whichever is earlier), because of the very early age of breast cancer onset seen in these families. Annual mammograms and/or breast MRI screening should begin at 20 to 25 years or be individualized, based on earliest age of onset in the family. Although no data are available on risk-reduction surgery in women with LFS, options for RRM should be discussed on a case-by-case basis (see “Bilateral Total Mastectomy,” page 585).

Many 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 starting at age 20 to 25 years among family members who have survived one cancer when a high index of suspicion is present for second malignancies (page 571). Clinicians should address screening limitations for other cancers associated with LFS. The option to participate in clinical trials evaluating novel screening approaches using technologies such as PET scan, abdominal ultrasound, and brain MRI should also be discussed if available. Colonoscopy should be considered every 2 to 5 years, starting at no later than 25 years. Education on signs and symptoms of cancer is important. Patients should be advised about risk to relatives, and genetic counseling for relatives is recommended. Annual physical examination is recommended for cancer survivors with a high index of suspicion for rare cancers and second
malignancies. Pediatricians should be made aware of the risk for childhood cancers in affected families.

**Risk Assessment, Counseling, and Management: Cowden Syndrome**

The assessment of individuals suspected of having Cowden syndrome incorporates 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 (page 572). The panel recently revised both the list of criteria associated with this genetic syndrome and the combinations of criteria that establish which individuals are candidates for PTEN gene mutation testing (page 572 and “Cowden Syndrome,” page 579). These criteria are meant to guide the direction of testing strategies and not to serve as clinical diagnostic criteria. After risk assessment and counseling, genetic testing should be considered in individuals who meet testing criteria (page 573). Unlike the “pathognomonic” criteria, the panel considers none of the individual major or minor criteria to be sufficient to warrant genetic testing in the absence of other clinical evidence of Cowden syndrome. However, the panel recommends genetic testing in individuals exhibiting 2 or more major criteria that include macrocephaly; 3 or more major criteria that do not include macrocephaly; 1 major criterion along with 3 or more minor criteria; or 4 minor criteria. Furthermore, any of the major criteria can be classified as a minor criterion for the purpose of meeting the threshold required for genetic testing if 2 or more major criteria are present in a single individual but the individual does not have macrocephaly. The testing threshold is lower for individuals considered to be “at risk” (e.g., a first-degree relative of an individual and/or proband with a diagnosis of Cowden syndrome or BRRS for whom genetic testing has not been performed). In this case, any 1 major criterion or 2 minor criteria are considered to be sufficient for genetic testing to be recommended. Recommendations for individuals not meeting these testing criteria should be individualized according to personal and family history.

Individuals with a known deleterious PTEN mutation in a close family member who do not undergo gene testing should be followed up according to the same guideline as carriers of a PTEN mutation (see page 574). Current medical management recommendations for individuals with Cowden syndrome focus on primary and secondary prevention options for breast cancer and annual physical examinations starting at age 18 years, or 5 years before the youngest age of diagnosis of a component cancer in the family, to detect skin changes and monitor the thyroid gland for abnormalities. A baseline thyroid ultrasound should be performed at 18 years of age and considered annually thereafter for both men and women. Annual dermatologic examination should also be considered. Education on 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.

Women should begin regular monthly breast self examinations at 18 years of age and have a semiannual clinical breast examination beginning at age 25 years or 5 to 10 years earlier than the earliest known breast cancer in the family. 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. Although no data exist on risk-reduction surgery in women with Cowden syndrome, the option of risk-reduction mastectomy and hysterectomy should be discussed on a case-by-case basis (see “Bilateral Total Mastectomy,” page 585). The panel recommends patient education on the symptoms of endometrial cancer, including the necessity of a prompt response to these symptoms. Women diagnosed with Cowden syndrome should consider participation in a clinical trial to determine the effectiveness and necessity of endometrial cancer screening.

**References**


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

<table>
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<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
<th>Patent, Equity, or Royalty</th>
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The NCCN guidelines staff have no conflicts to disclose.