



NCCN Clinical Practice Guidelines in Oncology™

# **Genetic/Familial High-Risk Assessment: Breast and Ovarian**

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This manuscript is being updated to correspond with the newly updated algorithm.

**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.

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical\\_trials/physician.html](#)

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

See [NCCN Categories of Evidence and Consensus](#)

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## Summary of the Guidelines updates

Summary of the changes in the 1.2009 version of the Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer guidelines from the 1.2008 version include:

### Genetic/Familial High-Risk Assessment:

#### BR/OV-1

- Criteria for further risk evaluation, 3rd bullet, a combination of breast cancer with one or more of the following, “diffuse gastric cancer” was added.
- Footnotes ‘d’ and ‘e’ are new to the page.

### Hereditary Breast and Ovarian Cancer:

#### HBOC-1

- The diagnoses of “fallopian tube cancer and primary peritoneal cancer” were added to ovarian cancer as a criteria for testing.
- For a personal history of breast cancer + one or more of the following:
  - Diagnosed age  $\leq 40$  y was changed to  $\leq 45$  y
  - A separate bullet for two breast primaries was added, “Two breast primaries, when first breast cancer diagnosis occurred prior to age 50”
- The qualifying criteria for males with breast cancer, “ $\geq 1$  close male blood relative with breast cancer” and “ $\geq 1$  close female blood relative with breast or epithelial ovarian cancer” were removed.
- Footnote ‘e’ is new to the page.

#### HBOC-2

- Footnote ‘h’ was modified by adding, “If no living family member with breast or ovarian cancer, consider testing family members affected with cancers thought to be related to BRCA1/BRCA2 eg, prostate, pancreas, or melanoma.”
- Footnote ‘l’ is new to the page.

#### HBOC-A 1 of 2

- Footnotes ‘5’ and ‘7’ are new to the page.

#### HBOC-A 2 of 2

- “Reproductive options” section and the respective footnotes are new to HBOC syndrome management.
- Risk to relatives bullets were clarified by separating into, “Advise about possible inherited cancer risk to relatives, options for risk assessment, and management” and “Recommend genetic counseling and consideration of genetic testing for at-risk relatives.” (Also for [LIFR-A](#) and [COWD-A](#))
- Footnote 8 was modified by removing “gastric cancer” and adding ‘prostate cancer’ to the list of cancers of which some families have an increased incidence.

### Li-Fraumeni Syndrome:

#### LIFR-1

- A new criteria, “Early onset breast cancer: Individual with breast cancer  $< 30$  y with a negative BRCA1/BRCA2 test especially if there is also a family history of sarcoma, brain cancer, or adrenocortical cancer” was added to the Li-Fraumeni syndrome testing criteria.
- “Colon cancer” was added to “Cancers associated with Li-Fraumeni syndrome”.

#### LIFR-2

- For genetic testing when a deleterious familial TP53 mutation is known, the following categories were added, “category 2A for adults; category 2B for children.”

#### LIFR-A

- Other cancer risks, “Discuss option to participate in novel imaging technologies such as PET scan, abdominal ultrasound, and brain MRI” was added to Li-Fraumeni syndrome management.

### Cowden Syndrome:

#### COWD-A

- Recommendation regarding renal cell screening was removed.
- Footnote ‘3’ is new to the page.

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**CRITERIA FOR FURTHER RISK EVALUATION<sup>a</sup>**

- One or more of the following:
- Early-age-onset breast cancer<sup>b</sup>
  - Two breast primaries<sup>c</sup> or breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual
  - or
  - Two or more breast primaries<sup>c</sup> or breast and ovarian/fallopian tube/primary peritoneal cancers in close relative(s) 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<sup>d</sup>, dermatologic manifestations<sup>e</sup> or leukemia/lymphoma on the same side of family
  - Member of a family with a known mutation in a breast cancer susceptibility gene<sup>f</sup>
  - Populations at risk<sup>f</sup>
  - Any male breast cancer
  - Ovarian/fallopian tube/primary peritoneal cancer

Referral to cancer genetics professional recommended

**ASSESSMENT**

Patient needs and concerns:

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

Detailed family history:

- Expanded pedigree to include first-, second-, and third-degree relatives (parents, children, siblings, aunts, uncles, grandparents, great-grandparents, nieces, nephews, grandchildren, first cousins)
- 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 (eg, history of radiation therapy)
- Reproductive history
- Hormone use
- Previous breast biopsies

Focused physical exam (refer to specific syndrome):

- Breast/ovarian
- Head circumference
- Dermatologic<sup>e</sup>,
- Thyroid
- including oral mucosa

See Testing Criteria for [Hereditary Breast/Ovarian Syndrome \(HBOC-1\)](#)

[Li-Fraumeni Syndrome \(LIFR-1\)](#)

[Cowden Syndrome \(COWD-1\)](#)

<sup>a</sup>The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

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

<sup>c</sup>Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

<sup>d</sup>For lobular breast cancer and diffuse gastric cancer, CDH1 gene testing can be considered.

<sup>e</sup>For dermatologic manifestations, [see COWD-1](#).

<sup>f</sup>For populations at risk, requirements for inclusion may be lessened (eg, women of Ashkenazi Jewish descent with breast or ovarian cancer at any age.)

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HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA<sup>a,b</sup>

- Individual from a family with a known BRCA1/BRCA2 mutation
- Personal history of breast cancer<sup>c</sup> + one or more of the following:
  - ▶ Diagnosed age  $\leq 45$  y
  - ▶ Diagnosed age  $\leq 50$  y<sup>a</sup> with  $\geq 1$  close blood relative with breast cancer  $\leq 50$  y and/or  $\geq 1$  close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer
  - ▶ Two breast primaries<sup>d</sup> when first breast cancer diagnosis occurred prior to age 50
  - ▶ Diagnosed at any age, with  $\geq 2$  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<sup>e</sup>/fallopian tube/primary peritoneal cancer
  - ▶ For an individual of ethnicity associated with higher mutation frequency (eg, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required<sup>f</sup>
- Personal history of epithelial ovarian<sup>e</sup>/fallopian tube/primary peritoneal cancer
- Personal history of male breast cancer
- Family history only—Close family member<sup>b</sup> meeting any of the above criteria

Criteria  
met→ [See Follow-up  
\(HBOC-2\)](#)Criteria  
not met→ Refer to [NCCN  
Breast Cancer  
Screening and  
Diagnosis  
Guidelines](#)

<sup>a</sup>One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further professional evaluation. Individuals with limited family history, such as fewer than 2 first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of 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.)

<sup>b</sup>When investigating family histories for HBOC, the maternal and paternal sides should be considered independently. Close relatives include first-, second-, and third-degree relatives. Early onset breast cancer or epithelial ovarian/fallopian tube/primary peritoneal cancers at any age also increases suspicion of HBOC. Other malignancies reported in some families with HBOC include prostate, pancreatic, and melanoma.

<sup>c</sup>For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

<sup>d</sup>Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

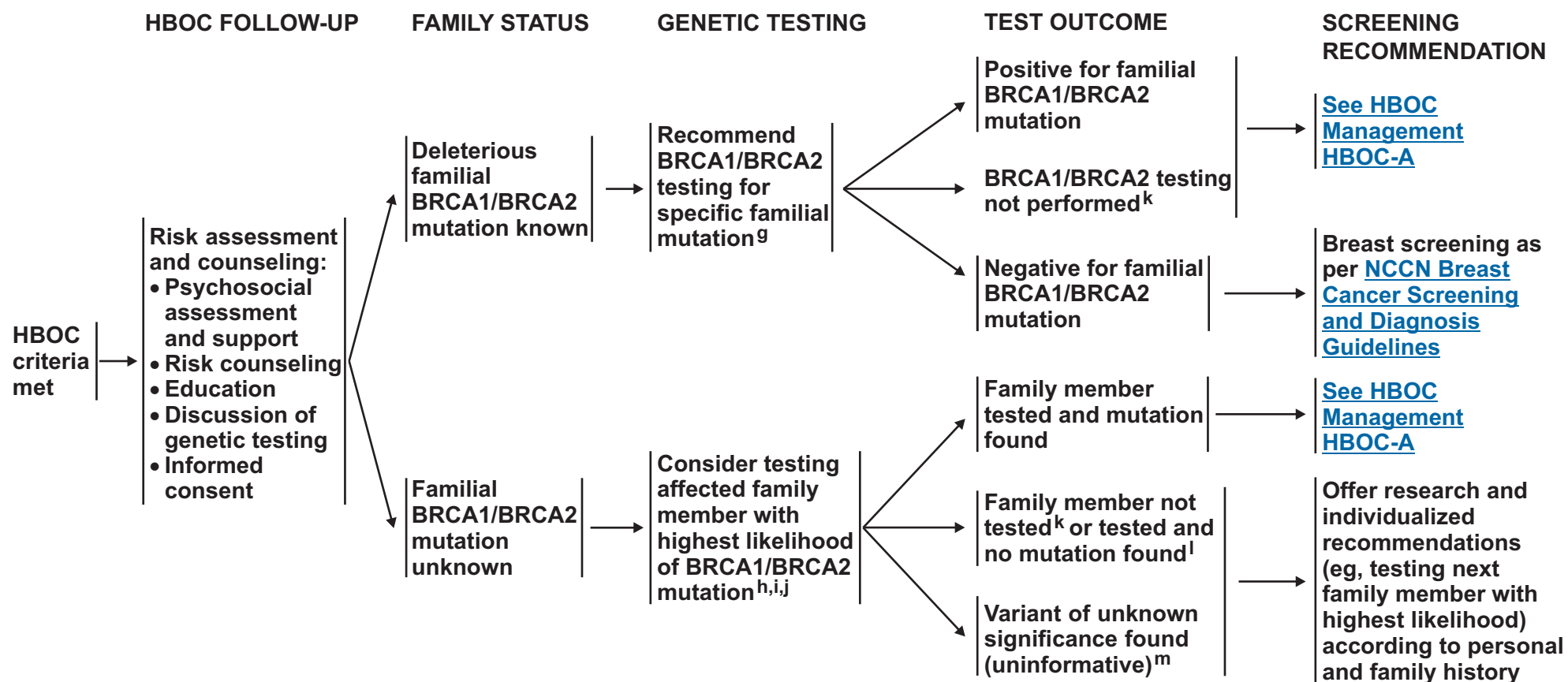
<sup>e</sup>Ovarian cancer is a component tumor of hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome, be attentive for clinical evidence of this syndrome. [See NCCN Colorectal Cancer Screening Guidelines.](#)

<sup>f</sup>Testing for founder-specific mutation(s), if available, should be performed first. Full sequencing may be considered if other HBOC criteria met.

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[Back to Assessment  
\(see BR/OV-1\)](#)



<sup>g</sup>If Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.

<sup>h</sup>If more than one affected, consider: youngest age at diagnosis, bilateral disease, multiple primaries, ovarian cancer, most closely related to the proband/patient/consultand. If no living family member with breast or ovarian cancer, consider testing family members affected with cancers thought to be related to BRCA1/BRCA2 eg, prostate, pancreas, or melanoma.

<sup>i</sup>Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

<sup>j</sup>BRCA1/BRCA2 testing: For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations, consider

full sequence testing based on assessment of individual and family history. 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 who have no known familial mutation, full sequence testing is the approach, if testing is done.

<sup>k</sup>Genetic testing may not be performed due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.

<sup>l</sup>If individual affected with breast cancer is < 30 y, especially if there is also a family history of sarcoma, brain cancer, or adrenocortical cancer, consider p53 gene testing.

<sup>m</sup>Consider other efforts to define functional impact of variant. Testing for variant of unknown significance should not be used for clinical purposes and is not recommended for unaffected relatives at risk (except for research purposes).

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## HBOC SYNDROME MANAGEMENT (1 of 2)

**WOMEN**

- Breast self-exam (BSE) training and education and regular monthly BSE starting at age 18 y.
- Clinical breast exam, semiannually,<sup>1</sup> starting at age 25 y.
- Annual mammogram and breast MRI<sup>2</sup> screening starting at age 25 y, or individualized based on earliest age of onset in family<sup>3</sup>
- 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<sup>4,5</sup> ideally between 35 and 40 y, or upon completion of child bearing, or individualized based on earliest age of onset of ovarian cancer in the family. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, and possible short term hormone replacement therapy (HRT), and related medical issues.
- For those patients who have not elected risk-reducing salpingo-oophorectomy, concurrent transvaginal ultrasound + CA-125<sup>6</sup>, 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 discussing risks and benefits<sup>7</sup> ([See NCCN Breast Cancer Risk Reduction Guidelines](#)).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies and more frequent screening intervals).

[Continued on next page](#)

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>The appropriateness of imaging scheduling is still under study.

<sup>4</sup>Given the high rate of occult disease, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes.

<sup>5</sup>There are insufficient data to distinguish a difference in degree of protection afforded by risk-reducing salpingo-oophorectomy between BRCA1 and BRCA2 gene mutation carriers.

<sup>6</sup>There are data that annual transvaginal ultrasound and CA-125 are not effective strategies for screening for ovarian cancer in high risk women. There are limited data regarding the effectiveness of a six month screening interval, thus until such data are available it is reasonable to consider this approach in high risk women, especially in the context of a clinical research setting.

<sup>7</sup>OCP for contraception is acceptable; however, the risk/benefit ratio is uncertain because of contradictory evidence about increasing breast cancer risk.

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## HBOC MANAGEMENT (2 of 2)

**MEN**

- Breast self-exam training and education and regular monthly BSE.
- Clinical breast exam, semi-annually.
- Consider baseline mammogram; annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study.
- Adhere to screening guidelines for prostate cancer ([See NCCN Prostate Cancer Early Detection Guidelines](#)).

**MEN and WOMEN**

- Education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene mutations.<sup>8</sup>
- Refer to other NCCN guidelines for other cancer screening<sup>9</sup> ([See NCCN Guidelines for Detection, Prevention, & Risk Reduction of Cancer](#)).

**RISK TO RELATIVES**

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

**REPRODUCTIVE OPTIONS**

- Advise about options for assisted reproduction, including pre-implantation genetic diagnosis, for couples expressing the desire that their offspring not carry a familial BRCA mutation. Discussion should include known risks and benefits of these technologies.<sup>10</sup>
- For reproductive age carriers of BRCA2 mutations, discussion of risk of the rare (recessive) Fanconi anemia/brain tumor phenotype in offspring of populations with an increased population frequency of founder mutations.<sup>11</sup>

<sup>8</sup>Some families also have an increased incidence of prostate cancer, pancreatic cancer, and melanoma.

<sup>9</sup>Consider full body skin exam for melanoma and investigational protocols for pancreatic cancer.

<sup>10</sup>Offit K, Sagi M, Hurley K. Preimplantation genetic diagnosis for cancer syndromes: a new challenge for preventive medicine. JAMA 2006;296:2727-2730.

<sup>11</sup>Offit K, Levrn O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548-1551.

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**LI-FRAUMENI SYNDROME TESTING CRITERIA<sup>a</sup>**

**Classic Li-Fraumeni Syndrome Criteria:**

- Member of kindred with a known TP53 mutation
- Combination of an individual diagnosed < age 45 y with a sarcoma<sup>b</sup>  
*AND*  
A first-degree relative diagnosed < age 45 y with cancer  
*AND*  
An additional first- or second-degree relative in the same lineage with cancer diagnosed < age 45 y, or a sarcoma at any age

**Li-Fraumeni-Like Syndrome Criteria:**

- Combination of an individual diagnosed with a childhood tumor or sarcoma<sup>b</sup>, brain tumor, or adrenocortical carcinoma diagnosed < age 45  
*AND*  
A first- or second-degree relative with a typical Li-Fraumeni Syndrome tumor at any age  
*AND*  
Another first- or second-degree relative with cancer diagnosed < age 60 y

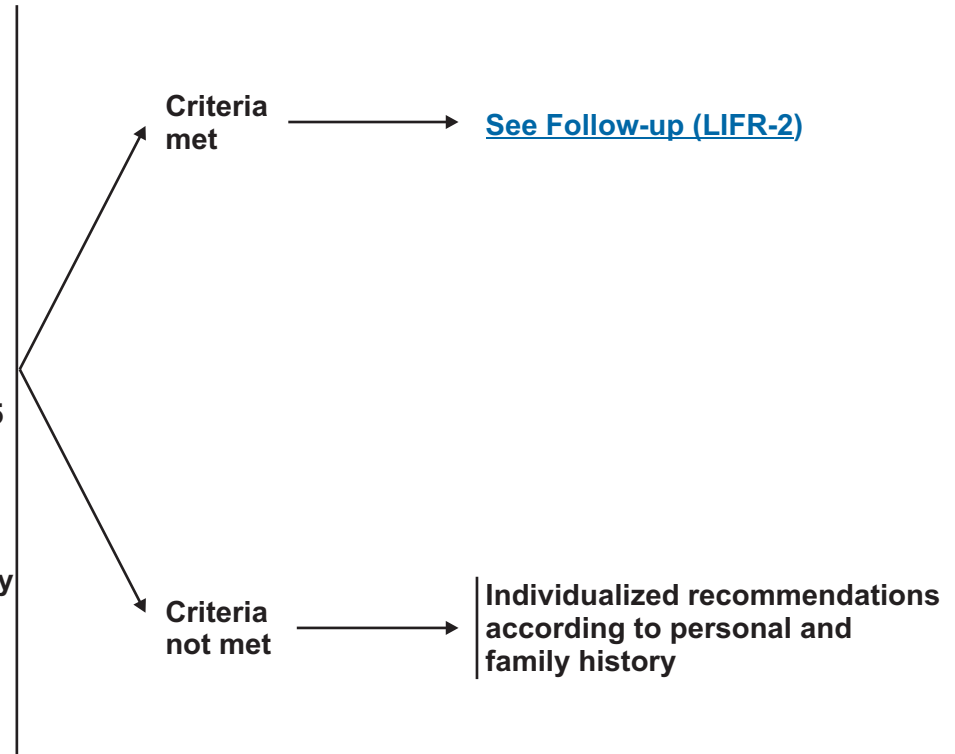
**Early onset breast cancer:**

- Individual with breast cancer < 30 y with a negative BRCA1/BRCA2 test especially if there is also a family history of sarcoma, brain cancer, or adrenocortical cancer<sup>c</sup>

**Cancers associated with Li-Fraumeni syndrome include but are not limited to:**

- Premenopausal breast cancer
- Bone and soft tissue sarcomas
- Acute leukemia
- Brain tumor
- Adrenocortical carcinoma
- Colon cancer
- Early onset of other adenocarcinomas, or other childhood cancers

**FOLLOW-UP**

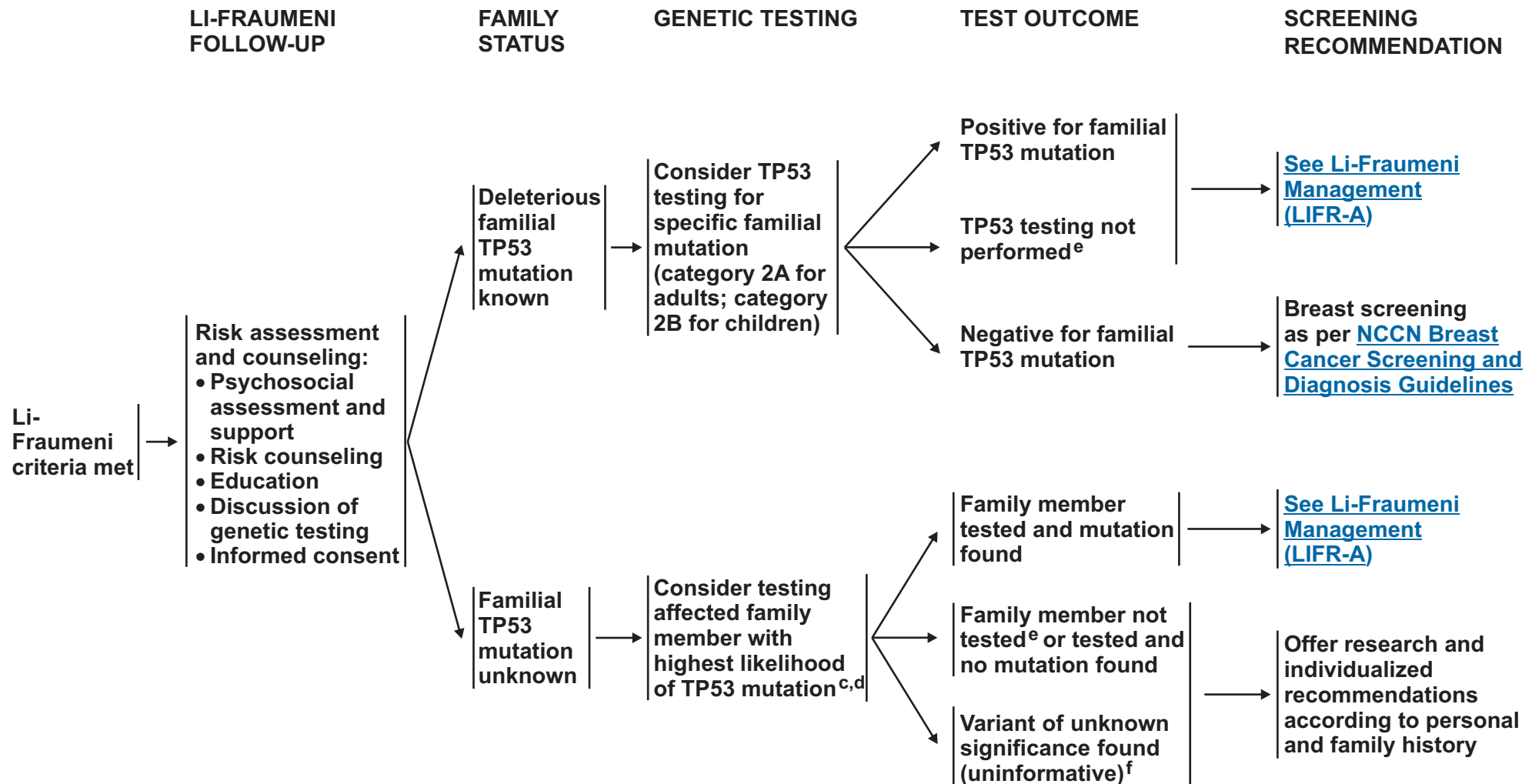


<sup>a</sup>Adapted from: Varley JM, Evans DGR, Birch JM: Li-Fraumeni syndrome—A molecular and clinical review. Br J Cancer. 1997;76:1-14, by permission of Nature Publishing Group.

<sup>b</sup>Ewing sarcoma is less likely to be related to Li-Fraumeni syndrome than other types of sarcomas.

<sup>c</sup>Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: Clinical characteristics of families with p53 germline mutations. J Clin Oncol 2009;27:1-11.

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<sup>c</sup>Youngest age at diagnosis, bilateral disease, multiple primaries, sarcoma at age < 45 y.

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

<sup>e</sup>Genetic testing may not be performed due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.

<sup>f</sup>Consider other efforts to define functional significance of mutations. Testing for variant of unknown significance should not be used for clinical purposes and is not recommended for unaffected relatives at risk (except for research purposes).

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## LI-FRAUMENI SYNDROME MANAGEMENT

**BREAST CANCER RISK**

- Breast self-exam (BSE) training and education and regular monthly BSE starting at age 18 y
- 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
- Annual mammogram and breast MRI screening starting at age 20-25 y, or individualized based on earliest age of onset in family<sup>1,2</sup>
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, degree of cancer risk, and reconstruction options

**OTHER CANCER RISKS**

- Address limitations of screening for many cancers associated with Li-Fraumeni syndrome: Because of the remarkable risk of additional primary neoplasms, screening may be considered for cancer survivors with Li-Fraumeni syndrome and a good prognosis from their prior tumor(s)
- Discuss option to participate in novel imaging technologies such as PET scan, abdominal ultrasound, and brain MRI<sup>3</sup>
- Pediatricians should be apprised of the risk of childhood cancers in affected families
- Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors: include careful skin and neurologic examinations
- Consider colonoscopy every 2-5 y starting no later than 25 y
- 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.

<sup>1</sup>The appropriateness of imaging scheduling is still under study.

<sup>2</sup>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.

<sup>3</sup>Some centers are evaluating novel imaging techniques as investigational tools.

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**COWDEN SYNDROME TESTING CRITERIA<sup>a</sup>**

**FOLLOW-UP**

**Operational diagnosis in an individual**

- Any single pathognomonic criterion:
  - ▶ Mucocutaneous lesions alone if there are:
    - ◊ six or more facial papules, of which three or more must be trichilemmoma, or
    - ◊ cutaneous facial papules and oral mucosal papillomatosis, or
    - ◊ oral mucosal papillomatosis and acral keratoses, or
    - ◊ six or more palmoplantar keratoses
- Two or more major criteria (one must be macrocephaly) or
- One major and ≥ three minor criteria or
- ≥ Four minor criteria

**Operational diagnosis for individuals in a family where one relative is diagnostic for Cowden syndrome. The individual must also have one or more of the following:**

- A pathognomonic criterion
- Any one major criteria with or without minor criteria
- Two minor criteria
- History of Bannayan-Riley-Ruvalcaba syndrome

Criteria met

→ [See Follow-up \(COWD-2\)](#)

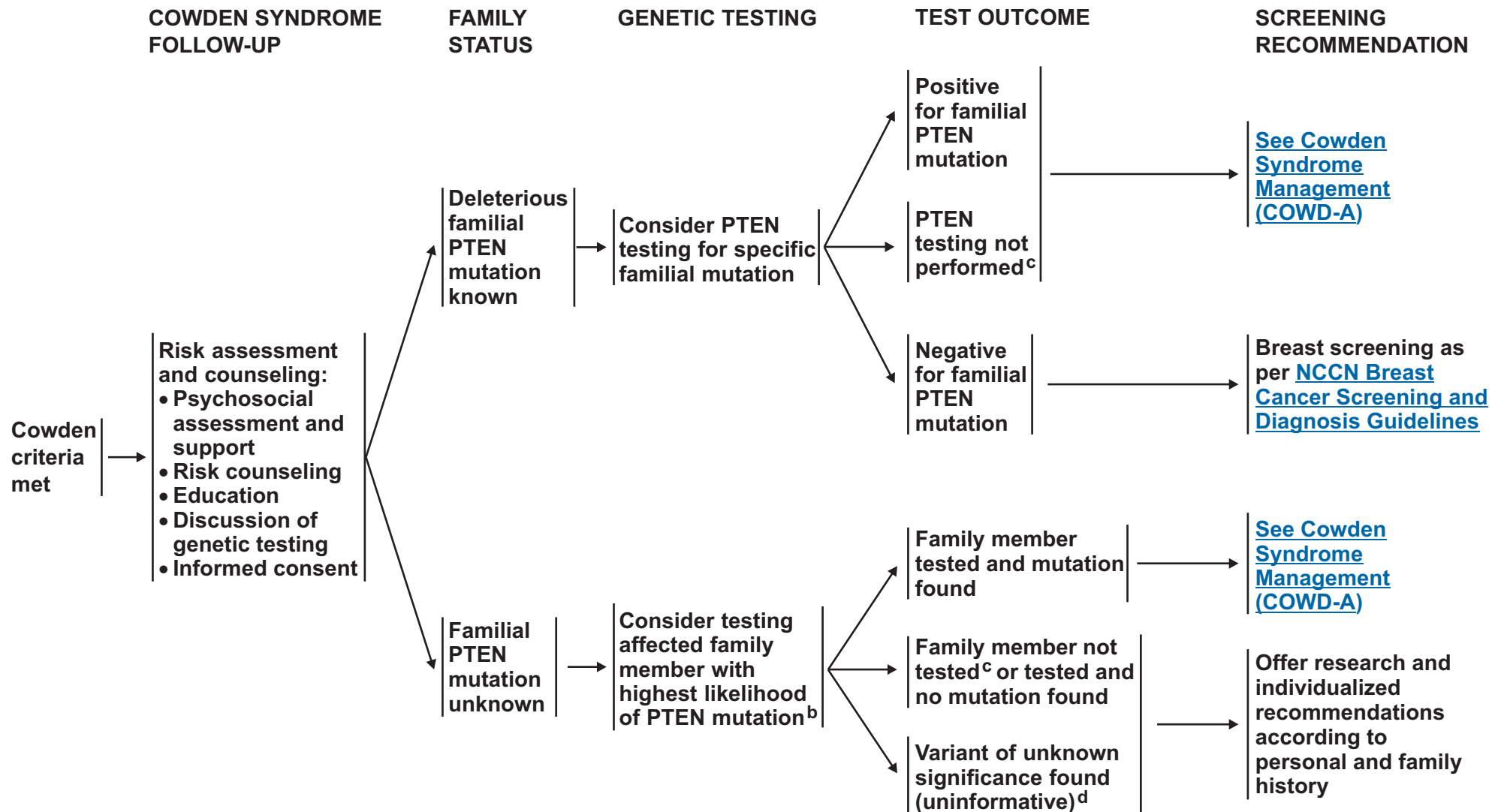
Criteria not met

→ Individualized recommendations according to personal and family history

<p><b><u>Pathognomonic criteria:</u></b></p> <ul style="list-style-type: none"> <li>• Adult Lhermitte-Duclos disease (LDD) (cerebellar tumors)</li> <li>• Mucocutaneous lesions                             <ul style="list-style-type: none"> <li>▶ Trichilemmomas, facial</li> <li>▶ Acral keratoses</li> <li>▶ Papillomatous papules</li> </ul> </li> </ul>	<p><b><u>Major criteria:</u></b></p> <ul style="list-style-type: none"> <li>• Breast cancer</li> <li>• Non-medullary thyroid cancer</li> <li>• Macrocephaly (megalencephaly) (ie, ≥ 97th percentile)</li> <li>• Endometrial cancer</li> </ul>	<p><b><u>Minor criteria:</u></b></p> <ul style="list-style-type: none"> <li>• Other thyroid lesions (eg, adenoma, multinodular goiter)</li> <li>• Mental retardation (ie, IQ ≤ 75)</li> <li>• GI hamartomas</li> <li>• Fibrocystic disease of the breast</li> <li>• Lipomas</li> <li>• Fibromas</li> <li>• GU tumors (especially renal cell carcinoma)</li> <li>• GU structural manifestations</li> <li>• Uterine fibroids</li> </ul>
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<sup>a</sup>Adapted from Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;37:828-830, with permission from the BMJ Publishing Group.

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

<sup>c</sup>Genetic testing may not be pursued due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.

<sup>d</sup>Consider other efforts to define functional significance of mutations. Testing for variant of unknown significance should not be used for clinical purposes and is not recommended for unaffected relatives at risk (except for research purposes).

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## COWDEN 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 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 is earlier)<sup>1, 2</sup>
- For endometrial cancer screening,<sup>3</sup> consider participation in a clinical trial to determine the effectiveness and necessity of screening modalities.
- Discuss option of risk-reducing mastectomy 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.

<sup>1</sup>The appropriateness of imaging scheduling is still under study.

<sup>2</sup>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.

<sup>3</sup>One study demonstrated a 5-10% risk of endometrial cancer in Cowden syndrome patients. Surveillance screening and surgical intervention should be on an individual basis.

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

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

## Discussion

This manuscript is being updated to correspond with the newly updated algorithm. Last updated 12/14/05.

### NCCN Categories of Evidence and Consensus

**Category 1:** The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

**Category 2A:** The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

**Category 2B:** The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

**Category 3:** The recommendation is based on any level of evidence but reflects major disagreement.

**All recommendations are category 2A unless otherwise noted.**

### Overview

Family studies have long documented an increased risk of several forms of cancer among first-degree relatives (ie, parents, siblings, and children) and second-degree relatives (ie, grandparents, aunts or uncles, grandchildren, and nieces or nephews) of affected individuals. Hereditary patterns of cancer are often characterized by early age at onset, high penetrance, bilaterality in paired organs, vertical transmission through either parent, and an association with other types of tumors.<sup>1,2</sup>

Recent advances in molecular genetics have identified a number of genes associated with inherited susceptibility to cancer and have provided a means to begin identifying individuals and families with an increased risk of cancer. This rapid expansion of knowledge about cancer genetics has implications for all aspects of cancer management, including prevention, screening, and treatment.

These guidelines are specifically for hereditary breast/ovarian cancer syndrome (HBOC), Li-Fraumeni syndrome, and Cowden syndrome. The guidelines were developed with an acute awareness of the preliminary nature of much of our knowledge regarding the clinical application of the rapidly emerging field of molecular genetics, and with an appreciation for the need for flexibility when applying these guidelines to individual families.

### Hereditary Patterns of Breast Cancer

Breast cancer is the most prevalent type (32% of all new cancer cases) of cancer in women in the United States and the second leading cause of the country's cancer deaths.<sup>3</sup> Age-adjusted incidence rates for breast cancer had risen steadily during the past several decades but during the last 5 years have begun to decline. After decades of remaining stable, mortality rates have shown a modest decline since 1989, particularly among women aged 50 or younger.<sup>3</sup>

Epidemiologic studies have identified several risk factors for breast cancer, including a family history of the disease. Cross-sectional and case-control studies have clearly documented a two- to fourfold increase in the risk of breast cancer among women with one or more first-degree relatives with the disease.<sup>4</sup>

About 5-10% of all cancers are related to specific gene aberrations that are passed down in a family. Specific patterns of hereditary breast cancer exist in some families and are linked to BRCA1 and BRCA2 susceptibility genes, which are responsible for hereditary breast cancer and some hereditary ovarian cancers. The magnitude of the risk increases with the number of affected relatives in the family, the closeness of the relationship, and the age at which the affected relative was diagnosed.<sup>5,6</sup> The younger the age at diagnosis, the more likely it is that a genetic component is present.

When assessing a family history for a hereditary pattern, the equal likelihood of paternal or maternal transmission of a gene that predisposes to breast cancer must also be kept in mind.

Studies of families with a hereditary pattern of breast cancer have also revealed an association with ovarian cancer among some individuals with a genetic predisposition for breast cancer. Families in which both breast and ovarian cancers are present in the same lineage have a significantly increased likelihood of carrying a cancer-predisposing mutation.<sup>7,8</sup>

### Hereditary Breast/Ovarian Cancer Syndrome

Several genes associated with hereditary breast cancer have been identified. In 1990, a susceptibility gene for breast cancer, BRCA1, was mapped by genetic linkage to the long arm of chromosome 17, in the interval 17q12-21.<sup>9</sup> The linkage between breast cancer and genetic markers on chromosome 17q was soon confirmed by others, and evidence for the coincident transmission of both breast and ovarian cancer susceptibility in linked families was observed.<sup>2</sup>

Alterations in this highly penetrant gene are now thought to account for 45% of multiple cases of site-specific breast cancer and up to 90% of families with both breast and ovarian cancer.<sup>10</sup>

A second breast cancer gene, BRCA2, was subsequently localized to the long arm of chromosome 13 and is thought to account for approximately 35% of multiple-case breast cancer families. This gene is also associated with male breast cancer and, possibly, prostate and pancreatic cancers.<sup>11-13</sup>

Although the exact functions of BRCA1 and BRCA2 and their role in breast carcinogenesis are not completely known, it appears that they may not only function as tumor-suppressor genes but also play a role in DNA repair.<sup>14-16</sup>

The overall prevalence of disease-related mutations in BRCA1 has been estimated as 1 in 800. However, a number of founder effects have been observed, 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 185delAG and 5382insC mutations in BRCA1 and of the 6174delT mutation in BRCA2 approximates 1 in 50. These mutations may account for up to 25% of early-onset breast cancers and up to 90% of early onset cancers in families with both breast and ovarian cancers.<sup>17,18</sup> Similar founder mutations have been identified in the Netherlands, Sweden, Hungary, and Iceland.<sup>19,20</sup>

Estimates of penetrance (ie, disease expression in mutation carriers) range from a 36% to 85% lifetime risk for breast cancer and from a 16% to 60% lifetime risk for ovarian cancer, depending upon the population studied. At present, it is unclear whether penetrance is related to the specific mutation identified in a family or whether additional factors, either genetic or environmental, affect disease expression. It is generally accepted, however, that carriers of mutations in BRCA1 or BRCA2 have an excessive risk for both breast and ovarian cancer that warrants consideration of more intensive preventive and screening strategies. A recent literature review has shown that the male carriers of mutations in BRCA1 and BRCA2 genes also have a greater risk for cancer susceptibility. Testing criteria for men are similar to the genetic testing criteria for women BRCA1 and BRCA2 carriers.<sup>21</sup>

### Li-Fraumeni Syndrome

Breast cancer is also a component of the rare Li-Fraumeni syndrome, in which germline mutations in the p53 gene (TP53) on the short arm of chromosome 17 have been documented.<sup>22</sup> The tumor suppressor gene p53 mutation is observed in 77% of Li-Fraumeni syndrome

families.<sup>23</sup> Discovery of the P53 gene occurred in 1979 and it was first identified as a protein with an important role in cell cycle regulation after genotoxic stress. The protein product of the tumor suppressor p53 gene is located in the cell nucleus and binds directly to DNA. This is a major protein, which plays an important role by stopping cell progression in response to DNA damage or genotoxic stress. The p53 protein detects DNA damage and activates other genes to either repair the DNA or signal programmed cell death (apoptosis). This is a critical role of the p53 gene in cell growth regulation which prevents cells from uncontrolled dividing and developing into tumors caused by mutated DNA. This syndrome is characterized by premenopausal breast cancer in combination with childhood sarcomas, brain tumors, leukemias, adrenocortical carcinomas, and lung cancer.<sup>24</sup> The proband with sarcoma is usually diagnosed before age 45 in a family with Li-Fraumeni syndrome. The syndrome is also characterized by both multiple tumors in the same individuals and clustering of tumors within the same family. Inheritance is autosomal-dominant, with a penetrance of at least 50% by age 50. Although highly penetrant, the Li-Fraumeni gene is thought to account for less than 1% of all breast cancers.

### Cowden Syndrome

Cowden syndrome was first described by doctors Lloyd KM and Dennis M in 1963 and named after Rachel Cowden, the first patient to show signs of the disease. Cowden syndrome is a rare disease with an autosomal-dominant pattern of inheritance. It is one of the 50 cancer-related genodermatoses that is characterized by skin manifestations and an excess of breast cancer, gastrointestinal malignancies, genitourinary, and by both benign and malignant thyroid disease.<sup>25</sup> Major criteria for diagnosing Cowden syndrome include thyroid cancer, especially follicular thyroid carcinoma, macrocephaly, cerebellar tumors, endometrial cancer, and breast cancer. Additional

major criteria also include lesions of the skin and oral mucosa, including multiple facial trichilemmomas, acral keratoses, and papillomatous papules. These criteria are found in >90% cases of the Cowden syndrome.<sup>26</sup> Minor criteria include other thyroid lesions, such as adenoma and multinodular goiter; genitourinary tumors, especially renal cell carcinoma; gastrointestinal hamartomas; lipomas; fibromas; mental retardation; and fibrocystic disease of the breast. The diagnosis of the Cowden's syndrome is made when a patient has a combination of pathognomonic major and minor criteria.

Germline mutations in the PTEN gene (protein tyrosine phosphatase with homology to tensin) located on chromosome 10q23 are responsible for this syndrome and have been observed in 80% of probands with Cowden's syndrome.<sup>27</sup> The PTEN acts as the tumor-suppressor gene and is the important regulation protein in cell growth, cell cycle control, apoptosis, and proliferation. Complete loss of PTEN function and inactivation of the p53 gene is associated with development of tumors in Cowden's syndrome.<sup>26,27</sup> Lifetime estimates for breast cancer among women with Cowden syndrome range from 25% to 50%. Like other forms of hereditary breast cancer, Cowden syndrome occurs at a young age and may be bilateral.<sup>28</sup>

### Assessment

Characteristics of hereditary breast cancer include breast cancer prior to age 40; multiple cases of breast and/or ovarian cancer in the same individual or close blood relatives, either maternal or paternal; a family member with a known mutation in a breast cancer susceptibility gene; or a clustering of breast cancer with other cancers indicative of Li-Fraumeni syndrome or Cowden syndrome.

Characteristics indicative of hereditary breast/ovarian cancer syndrome in individuals with a personal history of breast cancer

include onset of the disease at an early age, Ashkenazi Jewish ancestry, any male breast cancer, and a family history of breast and/or ovarian cancer. Individuals who have only a family history of breast and/or ovarian cancer may also be at risk. For this reason, risk assessment and counseling are considered to be integral components of genetic screening for hereditary breast cancer.

The first step in this process is the evaluation of the family history for patterns suggestive of an inherited breast cancer syndrome. Family history is an important component for cancer risk assessment.<sup>29,30</sup> The primary assessment is broad and flexible so as not to exclude from further evaluation individuals whose knowledge of their family history may be incomplete or inaccurate. Because of the high prevalence of breast cancer in the population, and because of the anxiety felt by those with a self-perceived high risk of breast cancer, individuals who do not meet these broad criteria should still be considered for more generalized cancer risk counseling to accurately determine their risk and to offer screening and general prevention recommendations.

For individuals who meet one or more of the inclusion criteria, further in-depth assessment is warranted. Ideally, the patient should be referred to a team with expertise in the management of cancer genetics. The first step in evaluating a woman's risk for hereditary breast cancer is to assess her concerns and reasons for seeking counseling and to guarantee that her personal needs and priorities will be met 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.<sup>31</sup> This is a situation that can interfere with the adoption of appropriate health behaviors. In addition, the patient's knowledge about the benefits, risks, and limitations of genetic testing should be

assessed in addition to the patient's goals. A positive, supportive interaction with the counseling team is an important determinant of ultimate satisfaction with the counseling process and of adherence to recommended health behaviors.

### Family History

A detailed family history is the cornerstone of effective genetic counseling. The family history is 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. Unaffected family members, both living and deceased, are included, as their histories also provide information about the magnitude of genetic risk.

Information collected includes cancer diagnoses by primary site, age at diagnosis, bilaterality (when appropriate), and current age or age at death. Whenever possible, cancer diagnoses in the family are verified by obtaining medical records, pathology reports, or death certificates. This is particularly important in the case of a report of an “abdominal” cancer in a female relative - a situation in which cancers of the cervix, uterus, ovary, and/or colon are often confused.

### Pedigree

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, early deaths in family members (which precludes the possibility that they will develop adult diseases), prophylactic surgeries that remove an organ from

subsequent risk of cancer (eg, hysterectomy for uterine fibroids in which the ovaries are also removed), and incomplete information about the health of other family members.

### 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 of breast cancer. A history of previous breast biopsies, especially those in which the pathology revealed atypical hyperplasia or lobular carcinoma in situ (LCIS), is associated with an increased risk of breast cancer, especially in the setting of a positive family history.<sup>32,33</sup> Pathologic verification of these diagnoses is encouraged. Carcinogen exposure history (radiation therapy, etc.) should also be included in the patient's assessment. When taking the medical history, the clinician should also be alert to the physical manifestations of Cowden syndrome, especially skin conditions.

Reproductive variables are important determinants of risk for both breast and ovarian cancer, suggesting a significant contribution of hormones to the etiology of these cancers. This possible link is supported by the increased breast cancer risk seen among women who have had prolonged exposure to exogenous estrogens and progestins and the reduction in risk for ovarian cancer observed among women who report using oral contraceptives.<sup>34-38</sup>

### Age

Age of the proband is also an important, although complex, component in determining risk for hereditary breast cancer. The average age of onset of hereditary breast cancer is significantly younger than that of sporadic breast cancer.<sup>15</sup> Therefore, the older an unaffected

woman becomes, the less likely she is to carry a disease-related mutation. However, there are well-documented families, particularly those with mutations in the BRCA2 gene, who present with postmenopausal breast cancer. Age cannot, therefore, be considered an absolute guide to determining risk of hereditary breast cancer.

### Women Not Meeting Inclusion Criteria

Women with a family history of breast cancer who do not meet the criteria for one of the hereditary breast cancer syndromes are still considered to be at moderately increased risk. The guidelines recommend that these women undergo recommendations of the [NCCN Breast Cancer Screening and Diagnosis Guidelines](#).

### Hereditary Breast/Ovarian Cancer Syndrome

#### Risk Counseling

Women who meet the criteria for hereditary breast/ovarian cancer syndrome should be offered the opportunity to participate in genetic counseling delivered by a team of trained health professionals. Genetic counseling for breast/ovarian cancer relies on education, risk assessment, and risk management to help individuals and their families cope with a disorder or heightened risk of a disorder. The specific goals of the counseling process are to 1) provide accurate information on the genetic, biological, and environmental factors related to the individual's risk of disease; 2) provide a sufficient understanding of the genetic basis of breast/ovarian cancer to assist in decisions regarding genetic testing; 3) formulate appropriate options and recommendations for prevention and screening; and 4) offer psychosocial support to facilitate adjustment to an altered risk perception and to promote adherence to the recommended actions.

Counseling for hereditary breast/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 interaction among shared environmental, reproductive, and genetic factors in family members with respect to determining breast/ovarian cancer risk is explored. 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.

### Genetic Testing

The selection of appropriate candidates for genetic testing is based on the personal and familial characteristics that determine the individual's prior probability of being a mutation carrier, and on the psychosocial degree of readiness of the person to receive genetic test results. Statistical models based on personal and family history characteristics have been developed to estimate a person's chance of having a BRCA1 or BRCA2 mutation.<sup>8,39,40</sup> Although these models are limited by the characteristics of the populations from which they are derived, and they have not yet been validated, they are being used by some insurance carriers to determine eligibility for coverage of the costs of genetic testing. Thus, these models may aid the counselor and the proband in making genetic testing decisions. The potential benefits, limitations, and risks of genetic testing are also important considerations in the decision-making process.

Next, the counselor reviews the distinctions between true-positive, true-negative, indeterminate, and inconclusive test results ([Table 1](#)), as well as the technical limitations of the testing process. A clear distinction is made between the probability of being a mutation carrier and the probability of developing cancer. The probabilistic nature of genetic test results and the potential implications for other family members must also be discussed.

The ultimate decision to proceed with genetic testing is based upon multiple factors, including level of risk, cost considerations, and the perceived risk-benefit ratio. A commonly cited reason for not proceeding with genetic testing is the fear of insurance discrimination,<sup>41</sup> despite the fact that no cases of insurance coverage being lost or denied on the basis of genetic predisposition for cancer have been reported. Many women feel that they are already doing everything they can to minimize their risk of developing breast cancer, and others fear the emotional toll of finding out that they are a mutation carrier, especially if they have children who would be at risk of inheriting the mutation. For those who choose not to proceed with testing, the counseling team tailors recommendations for primary and secondary prevention to the personal and family history.

**Mutation Status Known:** 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 BRCA1 or BRCA2. If the patient is of Ashkenazi Jewish descent, testing should be performed for all three founder mutations. A negative test result in that case is considered a “true-negative,” and breast cancer screening recommendations are the same as those for the general population (see the [NCCN Breast Cancer Screening and Diagnosis Guidelines](#)).

If the same mutation is found in additional family members, a more intensive management strategy is warranted (see “Medical Management” below). First-degree relatives of individuals with a known deleterious mutation who choose not to undergo genetic testing are considered to have a 50% risk of carrying that mutation and should also consider more intensive medical management. For

individuals, whose family histories are consistent with a pattern of hereditary breast/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.

**Mutation Status Unknown:** For the majority of families in whom mutation status is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual is most likely to test positive. If the patient is of Ashkenazi Jewish ancestry, testing for the three common mutations is performed first. If the results of these tests are negative, full sequencing of BRCA1 and BRCA2 may be considered. Full sequence testing is recommended for patients of non-Ashkenazi Jewish ancestry. A more intensive management strategy is warranted if a mutation is found in that individual. If there are no affected individuals available or willing to undergo testing, research and individualized recommendations for management are based on the personal and family history.

The testing of unaffected family members may be considered when no affected member is available. A negative test result in this case, however, is considered indeterminate (see [Table 1](#)) and does not provide the same level of information as when there is a known deleterious mutation in the family.

Another counseling dilemma is posed by the finding of a variant or mutation of unknown significance - a mutation that may actually represent a benign polymorphism unrelated to increased breast cancer risk. The individual must be counseled in such a situation, because additional information about that specific mutation will be needed before its significance can be understood.

### Medical Management

Recommendations for the medical management of hereditary breast/ovarian cancer syndrome are based on an appreciation of the early onset of disease, the increased risk of ovarian cancer, and the risk for male breast cancer in BRCA carriers. The phenotypic expression of hereditary breast and ovarian cancer is just beginning to be defined. Medullary histology has been found to be more common in BRCA1 carriers than in control populations, although the histologic patterns of BRCA2-related disease appear to be more heterogeneous.<sup>42,43</sup> Breast cancer patients who are carriers of BRCA1 mutations are also more likely to have high-grade tumors, with high mitotic rates, high proliferative fractions, and lower estrogen-receptor scores.<sup>44-46</sup>

Survival data are very preliminary, but two studies from Europe suggest that survival among breast cancer patients who are BRCA1 carriers is similar to or worse than that of controls. These studies also showed that BRCA1 carriers have a significantly increased risk of contralateral breast cancer.<sup>47,48</sup>

An excess of serous histology was found in one study of BRCA1-related ovarian cancers.<sup>46</sup> Survival has been reported to be superior among women with hereditary ovarian cancer, although studies are preliminary and need further follow-up.<sup>49,50</sup>

### Screening Recommendations

The current recommendations for the screening of women at risk for hereditary breast/ovarian cancer are based upon the best available evidence<sup>51</sup> and will likely change as more data on the specific features of BRCA1- and BRCA2-related disease become available. All patients should be advised of potential risks to family members,

and made aware of the availability of genetic counseling for them. In addition, patients should be educated regarding signs and symptoms of cancers associated with BRCA mutations. The emphasis is on initiating screening considerably earlier than standard recommendations as a reflection of the early age of onset seen in hereditary breast/ovarian cancer. Training in breast self-examination with regular monthly practice should begin at age 18, and semiannual clinical breast examinations should begin by age 25. The woman should begin having annual mammograms and breast MRI screening at age 25 or on an individualized timetable based on the earliest age of cancer onset in family members.<sup>52-55</sup>

For patients, who have not elected ovarian cancer risk reducing surgery, concurrent transvaginal ultrasound and CA-125 determination should be performed every 6 months, starting at ages 35 or 5-10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family, for the early detection of ovarian cancer. Investigational imaging and screening studies may be considered for this population. The panel also recommends consideration of breast cancer and ovarian cancer chemoprevention studies.

### **Risk reducing Mastectomy/Oophorectomy**

A recent study reported close to a 90% reduction in the incidence of breast cancer among women with a family history who underwent prophylactic mastectomy. A similar risk reduction was reported among women with BRCA1 and BRCA2 mutations.<sup>56,57</sup> This is an option considered by some women, especially those who have already been diagnosed with cancer in one breast or those who have had to undergo multiple breast biopsies for abnormal clinical or mammographic findings.

Risk reducing salpingo oophorectomy may be considered by women with a family history that includes ovarian cancer, particularly in view

of the lack of a standard approach to screening. The ideal age to perform this procedure is between 35 to 40 years of age or upon completion of child bearing period, after 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. Two recent studies support the role of risk reducing salpingo oophorectomy. The hazard ratio for ovarian cancer for women who underwent prophylactic surgery compared to those who chose surveillance was 0.15 and 0.04 respectively.<sup>58,59</sup> These women should be counseled about the potential for the subsequent development of peritoneal carcinomatosis, which has been reported up to 15 years following risk reducing oophorectomy,<sup>60,61</sup> and about the medical management of surgically induced menopause. Risk reducing oophorectomy in known BRCA1 carriers has been shown to reduce the risk of subsequent breast cancer by nearly 50%.<sup>62</sup>

### **Male BRCA Carriers**

Men testing positive for a BRCA mutation should have a semiannual clinical breast examination, undergo training in breast self-examination with regular monthly practice. Baseline mammography should be considered, followed by annual screening with mammography for those men with gynecomastia or parenchymal/glandular breast density on baseline study. Involvement in population screening guidelines for prostate cancer is recommended. All strategies for risk reduction among members of hereditary breast/ovarian cancer families should be discussed in the context of their known efficacy, the risks involved, and potential psychological implications.

### **Li-Fraumeni Syndrome**

The approach to families with other hereditary breast cancer syndromes, such as Li-Fraumeni syndrome, reflects that of

hereditary breast/ovarian cancer in many ways. However, there are some syndrome-specific differences with regard to assessment and management. In the case of Li-Fraumeni syndrome, there are multiple associated cancers, both pediatric and adult, that should be reflected in the expanded pedigree. Cancers associated with Li-Fraumeni include but are not limited to premenopausal breast cancer, bone and soft tissue sarcomas, acute leukemia, brain tumor, adrenocortical carcinoma, unusually early onset of other adenocarcinomas, or other childhood cancers.<sup>63</sup> Verification of these sometimes very rare cancers is particularly important.

If a familial mutation is known, the clinician should consider TP53 testing for specific familial mutations. If the familial mutation is unknown, consider testing the affected family member with the highest likelihood of a mutation. Follow Li-Fraumeni syndrome management or individualized recommendations depending on the test results. This would be the individual with the youngest age at diagnosis or bilateral disease or multiple primaries. Individuals who tested positive for a TP53 mutation may have greater distress than anticipated, so provisions for supportive interventions should be provided.<sup>64</sup>

Management of Li-Fraumeni syndrome should address the limitations of screening for the many cancers associated with it. For those at risk for breast cancer, training and education in breast self-examination (BSE) should start at age 18, with the patient performing regular self-examination on a monthly basis. It is recommended that breast cancer surveillance for families with Li-Fraumeni syndrome begin between the ages of 20 and 25 or 5 to 10 years before the earliest known breast cancer in the family (whichever is earlier) because of the very early age of onset seen in these families. Annual mammograms and breast MRI screening

should begin at ages 20 to 25 or be individualized, based on earliest age of onset in the family.<sup>65</sup> Options for risk reducing mastectomy should be discussed on a case-by-case basis. This discussion should include counseling regarding the degree of protection the procedure offers, the degree of cancer risk, and the patient's reconstruction options. The option to participate in investigational breast imaging, such as novel imaging technologies and more frequent screening intervals, should also be discussed.

Many of the other cancers associated with germline mutations in TP53 do not lend themselves to early detection. Thus, additional recommendations are general and include annual comprehensive physical examinations starting at age 20 to 25 years among family members who have survived one cancer where there is a high index of suspicion for second malignancies. Clinicians should address screening limitations for other cancers associated with the Li-Fraumeni syndrome. Education regarding signs and symptoms of cancer is important. Patients should be advised about the risk to relatives, and genetic testing for relatives should be discussed. 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 of childhood cancers in affected families.

### **Cowden Syndrome**

The assessment of individuals suspected of having Cowden syndrome incorporates both a history of the benign conditions associated with the syndrome and a targeted physical examination, including the skin and oral mucosa, breast, and thyroid gland. These criteria include pathognomonic criteria, and both major and minor criteria and describe the combinations of these that establish the diagnosis. The PTEN gene (protein tyrosine phosphatase with

homology to tensin) is associated with Cowden syndrome and has recently become available for routine testing of appropriate family members. In families in whom a deleterious mutation has been found, the identification of the phenotype pathognomonic for the syndrome can take the place of genetic testing in additional family members.<sup>66,67</sup>

A patient with known familial PTEN mutation should proceed to Cowden syndrome management if tested positive. Routine breast screening is recommended if the patient's test is negative for familial PTEN mutation with a known familial PTEN mutation. Individualized recommendations should be offered to a patient who tests negative for PTEN mutation if the familial PTEN mutation is unknown.

A patient should proceed to Cowden syndrome management if the affected family member is tested and the PTEN mutation is found. Individualized approach based upon personal and family history is recommended if the affected family member has not been tested for PTEN mutation or tested and no mutation has been found, or variant of unknown significance has been found in a family with an unknown familial PTEN mutation.

Current medical management recommendations focus on primary and secondary prevention options for breast cancer and on annual physical examinations, starting at age 18, to detect skin changes and to monitor the thyroid gland for abnormalities. The annual examination for men and women should include urinalysis and renal ultrasound (where there is a history of renal cancer). Annual urine cytology should also be considered. A baseline thyroid ultrasound should be performed at age 18 and considered annually thereafter. Annual dermatological examination should also be considered. Education regarding the signs and symptoms of cancer is important; patients should also be advised about the risk to relatives, and genetic testing should be suggested. Options for prophylactic mastectomy should be

discussed on a case-by-case basis. This discussion should include counseling regarding the degree of protection the procedure offers, the degree of cancer risk, and the patient's reconstruction options.

Both men and women should have a clinical breast examination, beginning at age 25 or 5-10 years earlier than the earliest known breast cancer in the family. In addition, women should have training in breast self-examination, with regular monthly practice beginning at age 18. Women should also have an annual mammogram and breast MRI screening starting at ages 30-35, or 5 to 10 years earlier than the earliest known breast cancer in the family (but not earlier than age 25). In addition, premenopausal women should undergo annual blind endometrial aspiration biopsies starting at ages 35 to 40 or 5 years before the earliest case of endometrial cancer in the family. Postmenopausal women should receive an annual endometrial ultrasound.

**Table 1: Genetic Test Results to Determine the Presence of a Cancer-Predisposing Gene**

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

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