Genetic/Familial High-Risk Assessment: Breast

Version 1.2002
NCCN Genetic/Familial High-Risk Assessment: Breast Panel Members

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INCLUSION CRITERIA\textsuperscript{a}

One or more of the following:

- Early-age-onset breast cancer (age ≤ 40 yr)
- Breast and ovarian cancer in the same individual or close blood relatives on same side of family (maternal or paternal)
- Clustering of breast cancer with male breast cancer, thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, brain tumors, dermatologic manifestations and/or leukemia/lymphoma in the same family
- Member of a family with a known mutation in a breast cancer susceptibility gene
- Populations at risk\textsuperscript{b}

\textsuperscript{a}HBOC syndrome may include families with only breast cancer or only ovarian cancer.

\textsuperscript{b}For populations at risk, requirements for inclusion may be lessened (e.g., women of Ashkenazi Jewish descent with breast or ovarian cancer at < 50 years of age).

\textbf{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.
SECONDARY ASSESSMENT

Inclusion criteria met

Referral to cancer genetics professional recommended

Patient needs:
- Patient concerns
- Knowledge of genetic testing, including benefits, risks, and limitations
- Goals

Detailed family history: a
- 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 onset
- Medical record documentation of cancer strongly encouraged

Detailed medical and surgical history: a
- Any personal cancer history
- Age
- Reproductive history
- Hormone use
- Previous breast biopsies, especially LCIS or atypical hyperplasia
- Pathology verification of cancers strongly encouraged

Criteria not met a
See Follow-up (HBOC-2)

Criteria met a
See Follow-up (HBOC-2)

aSee HBOC Criteria (HBOC-A).

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.
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NCCN® Practice Guidelines in Oncology – v.1.2002

Hereditary Breast and/or Ovarian Cancer

FOLLOW-UP

- Initiate screening mammography at age 40 yr or 5-10 yr prior to earliest breast cancer in family (but not before age 25 yr)
- Clinical breast exam
- Training in breast self-exam
- Pelvic exam

Genetic testing not pursued due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.

BRCA1/BRCA2 testing: If patient is of Ashkenazi Jewish descent, test three common mutations first. Then, if negative, consider full sequence testing based on assessment of individual and family history. If patient is non-Ashkenazi Jewish, test full sequence.

See HBOC Criteria (HBOC-A).

Criteria not met:
- Genetic testing not pursued

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

Deleterious familial mutation known
- See Screening Recommendation (HBOC-3)

Familial mutation unknown
- See Screening Recommendation (HBOC-3)

See HBOC Management (HBOC-B)

See Screening Recommendation (HBOC-3)
### Hereditary Breast and/or Ovarian Cancer

**FAMILY STATUS**

<table>
<thead>
<tr>
<th>Deleterious familial mutation known</th>
<th>Consider BRCA1/BRCA2 testing for specific familial mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial mutation unknown</td>
<td>Consider BRCA1/BRCA2 testing for affected family member with highest likelihood of mutation</td>
</tr>
</tbody>
</table>

**TEST OUTCOME**

- Positive for BRCA1/BRCA2 mutation
  - See HBOC Management (HBOC-B)
- BRCA1/BRCA2 testing not performed
  - Routine breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines
- Negative for BRCA1/BRCA2 mutation
  - See HBOC Management (HBOC-B)
- Affected family member tested and mutation found
  - See HBOC Management (HBOC-B)
- Affected family member not tested or tested and no mutation found
  - Individualized recommendations according to personal and family history
- Mutation of unknown significance found (uninformative)

**SCREENING RECOMMENDATION**

- Testing of unaffected family members when no affected member is available may be considered. Significant limitations of interpreting test results should be discussed.
- Consider other efforts to define functional significance of mutations.

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HBOC CRITERIA\textsuperscript{g,h}

- Member of known BRCA1/BRCA2 kindred

- Personal history of breast cancer + one or more of the following:
  - Diagnosed age $\leq 40$ yr, with or without family history
  - Diagnosed age $\leq 50$ yr or bilateral, with $\geq 1$ close blood relative with breast cancer or $\geq 1$ close blood relative with ovarian cancer
  - Diagnosed at any age, with $\geq 2$ close blood relatives with ovarian cancer at any age, or breast cancer, especially if $\geq 1$ woman is diagnosed before age 50 yr or has bilateral disease
  - Close male blood relative has breast cancer
  - Personal history of ovarian cancer
  - If of Ashkenazi Jewish descent and diagnosed age $\leq 50$ yr, no additional family history required, or at any age if history of breast and/or ovarian cancer in close blood relative

- Personal history of ovarian cancer + one or more of the following:
  - $\geq 1$ close blood relative with ovarian cancer
  - $\geq 1$ close female blood relative with breast cancer at age $\leq 50$ yr or bilateral breast cancer
  - $\geq 2$ close blood relatives with breast cancer
  - $\geq 1$ close male blood relative with breast cancer
  - If of Ashkenazi Jewish descent, no additional family history is required

- Personal history of male breast cancer + one or more of the following:
  - $\geq 1$ close male blood relative with breast cancer
  - $\geq 1$ close female blood relative with breast or ovarian cancer
  - If of Ashkenazi Jewish descent, no additional family history is required

- Family history only—Close family member meeting any of the above criteria

\textsuperscript{g}Criteria suggestive of hereditary breast/ovarian cancer syndrome that warrant further professional evaluation.

\textsuperscript{h}When investigating family histories for HBOC, all close relatives on the same side of the family should be included. Close relatives include first-, second-, and third-degree relatives.
HBOC MANAGEMENT

WOMEN

- Training in breast self-exam and monthly BSE starting at age 18 yr
- Clinical breast exam, semiannually, starting at age 25 yr
- Annual mammogram starting at age 25 yr, or individualized based on early age of onset in family
- Discuss option of prophylactic mastectomy on case-by-case basis and counsel regarding degree of protection and reconstruction options
- Transvaginal ultrasound with color doppler + CA-125 + pelvic exam, every 6 mo starting at age 30-40 yr and done concurrently
- Discuss option of prophylactic oophorectomy on case-by-case basis, including discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, and management of menopausal symptoms and related medical issues
- Consider chemoprevention options (category 1, see NCCN Breast Cancer Risk Reduction Guidelines)
- Education regarding signs and symptoms of cancer
- Consider investigational breast imaging studies, when available (e.g., novel imaging technologies and more frequent screening intervals)

MEN

- Breast self-exam training and regular monthly practice for BRCA carriers
- Clinical breast exam for BRCA carriers
- Consider annual mammogram for BRCA carriers
- Refer to other NCCN guidelines for other cancer screening
- Education regarding signs and symptoms of cancer

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## Li-Fraumeni Syndrome

### SECONDARY ASSESSMENT

<table>
<thead>
<tr>
<th>Inclusion criteria met</th>
<th>Referral to cancer genetics professional recommended</th>
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<td><strong>Patient needs:</strong></td>
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<td>• Patient concerns</td>
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<tr>
<td>• Knowledge of genetic testing, including benefits, risks, and limitations</td>
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<td>• Goals</td>
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<tr>
<td><strong>Detailed family history:</strong></td>
<td></td>
</tr>
<tr>
<td>• Expanded pedigree to include first-, second-, and third-degree relatives (parents, children, siblings, aunts, uncles, grandparents, great-grandparents, nieces, nephews, grandchildren, first cousins)</td>
<td></td>
</tr>
<tr>
<td>• Types of cancer</td>
<td></td>
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<td>• Bilaterality</td>
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<td>• Age at onset</td>
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<tr>
<td>• Medical record documentation of cancer strongly encouraged</td>
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<td><strong>Detailed medical and surgical history:</strong></td>
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<tr>
<td>• Any personal cancer history</td>
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<tr>
<td>• Pathology verification of cancers strongly encouraged</td>
<td></td>
</tr>
</tbody>
</table>

**Criteria not met**

- [See Follow-up (LIFR-2)]

**Criteria met**

- [See Follow-up (LIFR-2)]

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*See Li-Fraumeni Criteria (LIFR-A).*

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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.
Li-Fraumeni Syndrome

FOLLOW-UP

Criteria not met\textsuperscript{a} → Individualized recommendations according to personal and family history

Criteria met\textsuperscript{a} →

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

FAMILY STATUS

Genetic testing not pursued\textsuperscript{b} →

See Li-Fraumeni Management (LIFR-B)

Familial TP53 mutation known

See Screening Recommendation (LIFR-3)

Familial TP53 mutation unknown

See Screening Recommendation (LIFR-3)

\textsuperscript{a}See Li-Fraumeni Criteria (LIFR-A).

\textsuperscript{b}Genetic testing not pursued due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.

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.
### Li-Fraumeni Syndrome

<table>
<thead>
<tr>
<th>FAMILY STATUS</th>
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<th>SCREENING RECOMMENDATION</th>
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<td>Consider TP53 testing for specific familial mutations</td>
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<tr>
<td></td>
<td>Positive for TP53 mutation</td>
<td>See Li-Fraumeni Management (LIFR-B)</td>
</tr>
<tr>
<td></td>
<td>Negative for TP53 mutation</td>
<td>Routine breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines</td>
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<tr>
<td></td>
<td>Not tested</td>
<td>See Li-Fraumeni Management (LIFR-B)</td>
</tr>
<tr>
<td>Familial TP53 mutation unknown</td>
<td>Consider testing affected family member with highest likelihood of TP53 mutation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive for TP53 mutation</td>
<td>See Li-Fraumeni Management (LIFR-B)</td>
</tr>
<tr>
<td></td>
<td>Negative for TP53 mutation or not tested</td>
<td>Individualized recommendations according to personal and family history</td>
</tr>
</tbody>
</table>

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.

© Youngest age at diagnosis, bilateral disease, multiple primaries, or relative with sarcoma at age < 45 yr.
LI-FRAUMENI CRITERIA

Classic Li-Fraumeni Syndrome Criteria:

- Member of kindred with a known positive TP53 mutation
- A proband diagnosed under age 45 yr with a sarcoma, and having a first-degree relative diagnosed under age 45 yr with any cancer and an additional first- or second-degree relative in the same lineage with any cancer diagnosed under age 45 yr, or a sarcoma at any age

Li-Fraumeni-Like Syndrome Criteria

A proband with:
- Any childhood tumor or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed under 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 any cancer diagnosed under the age of 60

Cancers associated with Li-Fraumeni syndrome include but are not limited to:
- Acute leukemia
- Premenopausal breast cancer
- Brain tumor
- Adrenocortical carcinoma
- Bone and soft tissue sarcomas
- Unusually early onset of other adenocarcinomas, or other childhood cancers.


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LI-FRAUMENI MANAGEMENT

BREAST CANCER RISK

- Address limitations of screening for many cancers associated with Li-Fraumeni Syndrome

- Training and education in breast self-exam and regular monthly BSE starting at age 18 yr

- Semiannual clinical breast exam starting at age 20-25 yr, or 5-10 yr before the earliest known breast cancer in the family (whichever is earlier)

- Annual mammogram starting at age 20-25 yr, or individualized based on early age of onset in family

- Discuss options for prophylactic mastectomy on case-by-case basis and counsel regarding degree of protection, degree of cancer risk, and reconstruction options

- Discuss option to participate in investigational breast imaging when available (e.g., novel imaging technologies and more frequent screening intervals)

- Pediatricians should be apprised of the risk of childhood cancers in affected families

OTHER CANCER RISK MANAGEMENT

- Annual comprehensive physical exam starting at age 20-25 yr with high index of suspicion for rare cancers and second malignancies in cancer survivors

- Target surveillance based on individual family histories

- Education regarding signs and symptoms of cancer

\( ^d \) Many centers are employing alternative imaging techniques such as ultrasound and MRI.
Cowden Syndrome

SECONDARY ASSESSMENT

Patient needs:
- Patient concerns
- Knowledge of genetic testing, including benefits, risks, and limitations
- Goals

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

Detailed medical and surgical history, including development history and history of:
- Pathologically confirmed LCIS or atypical hyperplasia
- Trichilemmomas, facial
- Acral keratoses
- Mucosal lesions
- Age at onset
- Documentation of benign conditions associated with cancer phenotypes
- Medical record documentation of cancer strongly encouraged
- History of Bannayan-Riley-Ruvalcaba syndrome

Focused physical exam:
- Oral exam
- Dermatologic exam
- Breast exam
- Thyroid exam
- Head circumference

Criteria met\(^a\) \rightarrow See Follow-up (COWD-2)

Inclusion criteria met \rightarrow Referral to cancer genetics professional recommended

Criteria not met\(^a\) \rightarrow See Cowden Syndrome Criteria (COWD-A)

\(^a\) See Cowden Syndrome Criteria (COWD-A)

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.
### Cowden Syndrome

#### FOLLOW-UP

- **Criteria not met**
  - Individualized recommendations according to personal and family history

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

#### FAMILY STATUS

- Genetic testing not pursued
  - See Cowden Syndrome Management (COWD-B)

- Familial PTEN mutation known
  - See Screening Recommendations (COWD-3)

- Familial PTEN mutation unknown
  - See Screening Recommendations (COWD-3)

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**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.

---

*a See Cowden Syndrome Criteria (COWD-A).*

*b Genetic testing not pursued due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.*
Cowden Syndrome

**FAMILY STATUS**

- Familial PTEN mutation known
  - Consider PTEN testing for specific family mutation
    - Positive for PTEN mutation: See Cowden Syndrome Management (COWD-B)
    - Negative for PTEN mutation: Routine breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines
    - Not tested: See Cowden Syndrome Management (COWD-B)

- Familial PTEN mutation unknown
  - Consider testing affected family member with highest likelihood of PTEN mutation
    - Positive for PTEN mutation: See Cowden Syndrome Management (COWD-B)
    - Negative for PTEN mutation: Offer research and individualized recommendations according to personal and family history

**TEST OUTCOME**

- Positive for PTEN mutation
- Negative for PTEN mutation
- Not tested

**SCREENING RECOMMENDATION**

- See Cowden Syndrome Management (COWD-B)
- Routine breast screening as per NCCN Breast Cancer Screening and Diagnosis Guidelines
- See Cowden Syndrome Management (COWD-B)

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COWDEN SYNDROME CRITERIA

Pathognomonic criteria:
- Mucocutaneous lesions
  - Trichilemmomas, facial
  - Acral keratoses
  - Papillomatous papules
  - Mucosal lesions

Major criteria:
- Breast cancer
- Thyroid cancer, especially follicular thyroid carcinoma
- Macrocephaly (mealocephaly) (i.e., ≥ 95th percentile)
- Lhermitte-Duclos disease (LDD) (cerebellar tumors)
- Endometrial cancer

Minor criteria:
- Other thyroid lesions (e.g., adenoma, multinodular goiter)
- Mental retardation (i.e., IQ ≤ 75)
- GI hamartomas
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- GU tumors (especially renal cell carcinoma)

Operational diagnosis in an individual:
- 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
  - palmarplantar keratoses, six or more
- Two major criteria but one must include macrocephaly or LDD, or
- One major and three minor criteria, or
- Four minor criteria

Operational diagnosis in a family where one individual is diagnostic for Cowden syndrome:
- The pathognomonic criteria
- Any one major criteria with or without minor criteria
- Two minor pathognomonic criteria

COWDEN SYNDROME MANAGEMENT

WOMEN

- Training and education in breast self-exam and regular monthly BSE starting at age 18 yr
- Annual mammography starting at age 30-35 yr or 5-10 yr earlier than earliest known breast cancer in the family (not before age 25 yr) (whichever is earlier)
- Annual clinical breast exam starting at age 25 yr or 5-10 yr earlier than earliest known breast cancer in the family
- Discuss options for prophylactic mastectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.
- Blind endometrial suction biopsies annually for premenopausal women starting at age 35-40, or 5 yr before earliest diagnosis of endometrial cancer, and annual endometrial ultrasound in postmenopausal women.

MEN AND WOMEN

- Annual comprehensive physical exam starting at age 18 yr or 5 yr younger than the youngest age of diagnosis of a component cancer in the family (whichever is younger), with particular attention to breast and thyroid exam
- Annual urinalysis; consider annual urine cytology
- Baseline thyroid ultrasound at age 20 yr, and consider annually thereafter
- Education regarding the signs and symptoms of cancer
Manuscript

NCCN Categories of Consensus

**Category 1:** There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

**Category 2A:** There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 2B:** There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 3:** There is major NCCN disagreement that the recommendation is appropriate.

**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 (i.e., parents, siblings, and children) and second-degree (i.e., grandparents, aunts or uncles, grandchildren, and nieces or nephews) relatives 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.¹,²

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, 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 of cancer in women in the United States and the second leading cause of the country's cancer deaths. Age-adjusted incidence rates for breast cancer have risen steadily during the past several decades. After decades of remaining stable, mortality rates have shown a modest decline since 1989, particularly among women ages 50 or younger.³

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 risk of breast cancer among women with one or more first-degree relatives with the disease.⁴

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.⁵,⁶ The younger the age at diagnosis, the more likely a genetic component is present. When assessing a family history for a hereditary pattern, the possibility of
paternal 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.\(^7,8\)

**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.\(^9\) 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.\(^2\)

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.\(^10\)

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.\(^11,12\)

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.\(^13,14\)

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 families with both breast and ovarian cancers.\(^15,16\)

Similar founder mutations have been identified in populations in the Netherlands and Iceland.\(^17,18\)

Estimates of penetrance (i.e., 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 strategies.

**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.\(^19\) This syndrome is characterized by premenopausal breast cancer in combination with childhood sarcomas, brain tumors, leukemias, lymphomas, adrenocortical carcinomas, and lung cancer.\(^20\) 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 is one of the 50 cancer-related genodermatoses that, in addition to skin manifestations, is characterized by an excess of breast cancer, gastrointestinal malignancies, and thyroid disease—both benign and malignant. 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 facial trichilemmomas, acral keratoses, and papillomatous papules. 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.

Germline mutations in the PTEN gene (protein tyrosine phosphatase with homology to tensin) located on chromosome 10q23 are responsible for this syndrome. 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.

**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, and a family history of breast and/or ovarian cancer (HBOC-A). 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. 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. 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 onset, 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 (e.g., polycystic ovary disease) 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 (e.g., 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. Pathologic verification of these diagnoses is strongly encouraged. 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 the reduction in risk for ovarian cancer observed among women who report using oral contraceptives.

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. 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. These women are urged to begin annual mammography at age 40 or 5 to 10 years prior to the earliest breast cancer in the family (although not before age 25). Annual clinical breast and pelvic examinations, as well as training in breast self-examination, are also encouraged.

**Hereditary Breast/Ovarian Cancer Syndrome**

**Risk Counseling**

Women who meet the criteria for hereditary breast/ovarian cancer syndrome (HBOC-A) 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. 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, 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. 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 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 and HBOC-B). 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, on both the maternal and paternal sides, are consistent with a pattern of hereditary breast/ovarian cancer, 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 should proceed. If a mutation is found in that individual, additional family members can then be tested specifically for that mutation, as described above. If there are no affected individuals available or willing to undergo testing, 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 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 (HBOC-B). 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. 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, and to lack an in situ component.

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.

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

**Screening Recommendations**

The current recommendations for the screening of women at risk for hereditary breast/ovarian cancer are based upon the best available evidence and will likely change as more data on the specific features of BRCA1- and BRCA2-related disease become available. 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 clinical breast examinations, either annual or semiannual, should begin by age 25. The woman should begin having annual mammograms at age 25 or on an individualized time table based on the age of cancer onset in family members. The combination of a pelvic examination, CA 125 determination, and transvaginal ultrasound, done concurrently for the early detection of ovarian cancer should be performed every 6 to 12 months starting at ages 30 to 40.

**Prophylactic 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. 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.

Prophylactic 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. Two recent studies...
support the role of prophylactic 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.\textsuperscript{43,44} These women should be counseled about the potential for the subsequent development of peritoneal carcinomatosis, which has been reported up to 15 years following prophylactic oophorectomy,\textsuperscript{45} and about the medical management of surgically induced menopause. Prophylactic oopherectomy in known BRCA1 carriers has been shown to reduce the risk of subsequent breast cancer by nearly 50%.\textsuperscript{46}

**Male BRCA Carriers**

Men testing positive for a BRCA mutation should consider annual screening with mammography and clinical breast examination. 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 (\textsuperscript{LIFR-A}). Cancers associated with Li-Fraumeni include acute leukemia, brain tumor, adrenocortical carcinoma, and bone and soft-tissue sarcomas, as well as lung cancer and premenopausal breast cancer. 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. This would be the individual with the youngest age at diagnosis or bilateral disease or multiple primaries.

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 should begin at ages 20 to 25, or be individualized based on early age of onset in the family. 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. 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 (\textsuperscript{LIFR-B}). Education regarding signs and symptoms of cancer is important. 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 is expanded to incorporate 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 \(\text{COWD-A}\). These criteria include 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.\(^{47}\)

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 \(\text{COWD-B}\). The annual examination for men and women should include urinalysis, and the clinician should consider annual urine cytology. A baseline thyroid ultrasound should be performed at age 20 and considered annually thereafter. Both men and women should have a clinical breast examination, beginning at age 25. 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 starting at ages 30 to 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 suction biopsies starting at ages 35 to 40 or 5 years before the earliest case of endometrial cancer. Postmenopausal women should receive an annual endometrial ultrasound.
**Table 1**

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

<table>
<thead>
<tr>
<th>Result</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>True-positive</td>
<td>The person is a carrier of an alteration in a known cancer-predisposing gene.</td>
</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</td>
<td>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.</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>The person is a carrier of an alteration in a gene that currently has no known significance.</td>
</tr>
</tbody>
</table>
References


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