National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Genetic/Familial High-Risk Assessment: Breast and Ovarian

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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

Summary of the Guidelines updates

Summary of the changes in the 1.2010 version of the Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer guidelines from the 1.2009 version include:

Genetic/Familial High-Risk Assessment:

BR/OV-1

- **Footnote g, "A genetic counselor and/or medical geneticist should be involved early in counseling patients who potentially meet criteria for an inherited syndrome. Genetic counseling is advised when genetic testing is offered and often after results are disclosed" is new to the page. (Also footnote 'h' on HBOC-2)**

BR/OV-2

- **"Pedigree: first-, second-, and third-degree relatives of proband" is new to the guidelines.**

Hereditary Breast and Ovarian Cancer:

HBOC-1

- **Family history only was separated into "First- or second-degree blood relative meeting any of the above criteria" and "Third-degree blood relative with ≥ 2 close blood relatives with breast and/or ovarian cancer (at least one close blood relative with breast cancer ≤ 50 y)".**
- **For a personal history of breast cancer, the following examples of founder populations, "Icelandic, Swedish, Hungarian" were moved to footnote g, "Examples of other founder populations include Icelandic, Swedish, Hungarian, and Dutch."**
- **Footnote 'b' was modified by adding "Individuals with early-onset (≤ 40 y), triple negative breast cancer may consider BRCA1/2 mutation testing. (Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 2009;9:86)".**

HBOC-2

- **Footnote i, "Certain mutations (ie, large rearrangements) are not detectable by the primary sequencing assay and supplementary testing may be necessary" is new to the page. (Also footnote 'h' for COWD-2)**
- **Footnote 'o' was modified by adding, "Consider referral to research studies that aim to define functional impact of variant." (Also footnote 'f' for LIFR-2 and footnote 'i' for COWD-2)**

HBOC-A 1 of 2

- **HBOC management for women, 6th bullet was modified by adding "consider" to "For those patients who have not elected risk-reducing salpingo-oophorectomy, *conside*r concurrent transvaginal ultrasound + CA-125..."**
- **Footnote '2' was modified by adding, "Breast MRI is performed preferably day 1-15 of menstrual cycle for premenopausal women."**
- **Footnote 4, a reference regarding the role of serial sectioning in the detection of occult malignancy and a link to the "College of American Pathologists, Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary" were added.**
- **Footnote 6, was modified, "Data suggest that oral contraceptives (OC) reduce ovarian cancer risk in BRCA mutation carriers. The risk/benefit ratio is uncertain because of contradictory evidence about OC increasing breast cancer risk; however, OC use for contraception is acceptable" and a reference was added.**

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Summary of the Guidelines updates (continued)

Summary of the changes in the 1.2010 version of the Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer guidelines from the 1.2009 version include:

Li-Fraumeni Syndrome:

LIFR-A

- **Breast cancer risk, 3rd bullet was modified by adding "or" to "annual mammogram and/*or* breast MRI".**
- **Other cancer risks, 5th bullet was modified by adding, "Discuss option to participate in novel *screening approaches* using technologies such as PET scan, abdominal ultrasound, and brain MRI *within clinical trials when possible."***

Cowden Syndrome:

COWD-1

- **Cowden syndrome testing criteria have been extensively revised.**
- **Footnotes 'a' through 'f' are new to the page.**

COWD-A

- **Women, 4th bullet, the management for endometrial cancer screening was modified by adding, "*encourage patient education and prompt response to symptoms*...".**
- **Women, 5th bullet was modified, "Discuss option of risk-reducing mastectomy *and hysterectomy* on case-by-case basis..."**
- **Footnote '3' was revised as, "There are limited data regarding the lifetime risk of endometrial cancer in Cowden syndrome" from "One study demonstrated a 5-10% risk of endometrial cancer in Cowden syndrome patients."**

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Breast and/or Ovarian Genetic Assessment

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CRITERIA FOR FURTHER RISK EVALUATION[a]

One or more of the following:

- Early-age-onset breast cancer[b]
- Two breast primaries[c] or breast and ovarian/fallopian tube/primary peritoneal cancer in a single individual
  or
  Two or more breast primaries[c] 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,[d] dermatologic manifestations[e] or leukemia/lymphoma on the same side of family
- Member of a family with a known mutation in a breast cancer susceptibility gene
- Populations at risk[f]
- Male breast cancer
- Ovarian/fallopian tube/primary peritoneal cancer

→ Referral to cancer genetics professional recommended[g] →

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) (See BR/OV-2)
- 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
- Dermatologic,[e] including oral mucosa
- Head circumference
- Thyroid

→ See Testing Criteria for Hereditary Breast/Ovarian Syndrome (HBOC-1)

Li-Fraumeni Syndrome (LIFR-1)

Cowden Syndrome (COWD-1)

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

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

[c] Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

[d] For lobular breast cancer and diffuse gastric cancer, CDH1 gene testing can be considered.

[e] For dermatologic manifestations, see COWD-1.

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

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

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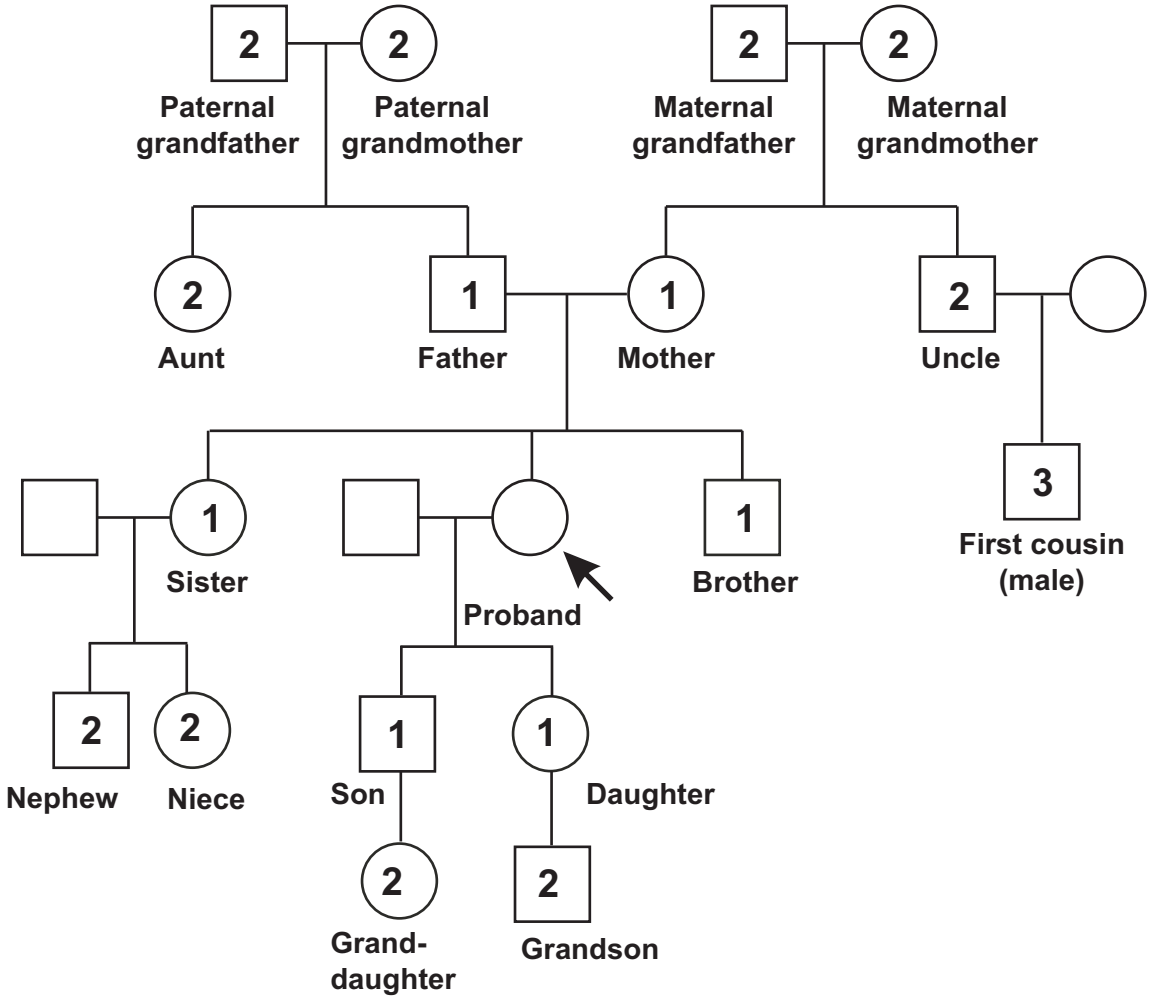
PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND[h]



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

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HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA[a,b]

- **Individual from a family with a known BRCA1/BRCA2 mutation**

- **Personal history of breast cancer[c] + one or more of the following:**
  - **Diagnosed age ≤ 45 y**
  - **Diagnosed age ≤ 50 y[b] with ≥ 1 close blood relative[d] with breast cancer ≤ 50 y and/or ≥ 1 close blood relative[d] with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age**
  - **Two breast primaries[e] when first breast cancer diagnosis occurred prior to age 50**
  - **Diagnosed at any age, with ≥ 2 close blood relatives[d] with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age**
  - **Close male blood relative[d] with breast cancer**
  - **Personal history of epithelial ovarian[f]/fallopian tube/primary peritoneal cancer**
  - **For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[g]**

- **Personal history of epithelial ovarian[f]/fallopian tube/primary peritoneal cancer**

- **Personal history of male breast cancer**

- **Family history only:**
  - **First- or second-degree blood relative meeting any of the above criteria**
  - **Third-degree blood relative with breast cancer and/or ovarian[f]/fallopian tube/primary peritoneal cancer with ≥ 2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤ 50 y) and/or ovarian cancer**

HBOC criteria met → **See Follow-up (HBOC-2)**

HBOC criteria not met → **See NCCN Breast Cancer Screening and Diagnosis Guidelines**

[a] One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further professional evaluation. When investigating family histories for HBOC, the maternal and paternal sides should be considered independently. Early onset breast cancer and/or epithelial ovarian/fallopian tube/primary peritoneal cancers at any age also increases suspicion of HBOC. Other malignancies reported in some families with HBOC include prostate, pancreatic, and melanoma.

[b] Other considerations: Individuals with limited family history, such as 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 a familial mutation (Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and BRCA gene mutation status in single cases of breast cancer. JAMA 2007;297:2587-2595.) Individuals with early-onset (≤ 40 y), triple negative breast cancer may consider BRCA1/2 mutation testing. (Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 2009;9:86)

[c] For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

[d] Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-2)

[e] Two breast primaries including bilateral disease or cases where there are two or more clearly separate ipsilateral primary tumors.

[f] 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.

[g] Testing for Ashkenazi Jewish founder-specific mutation(s), should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. Examples of other founder populations include Icelandic, Swedish, Hungarian, and Dutch.

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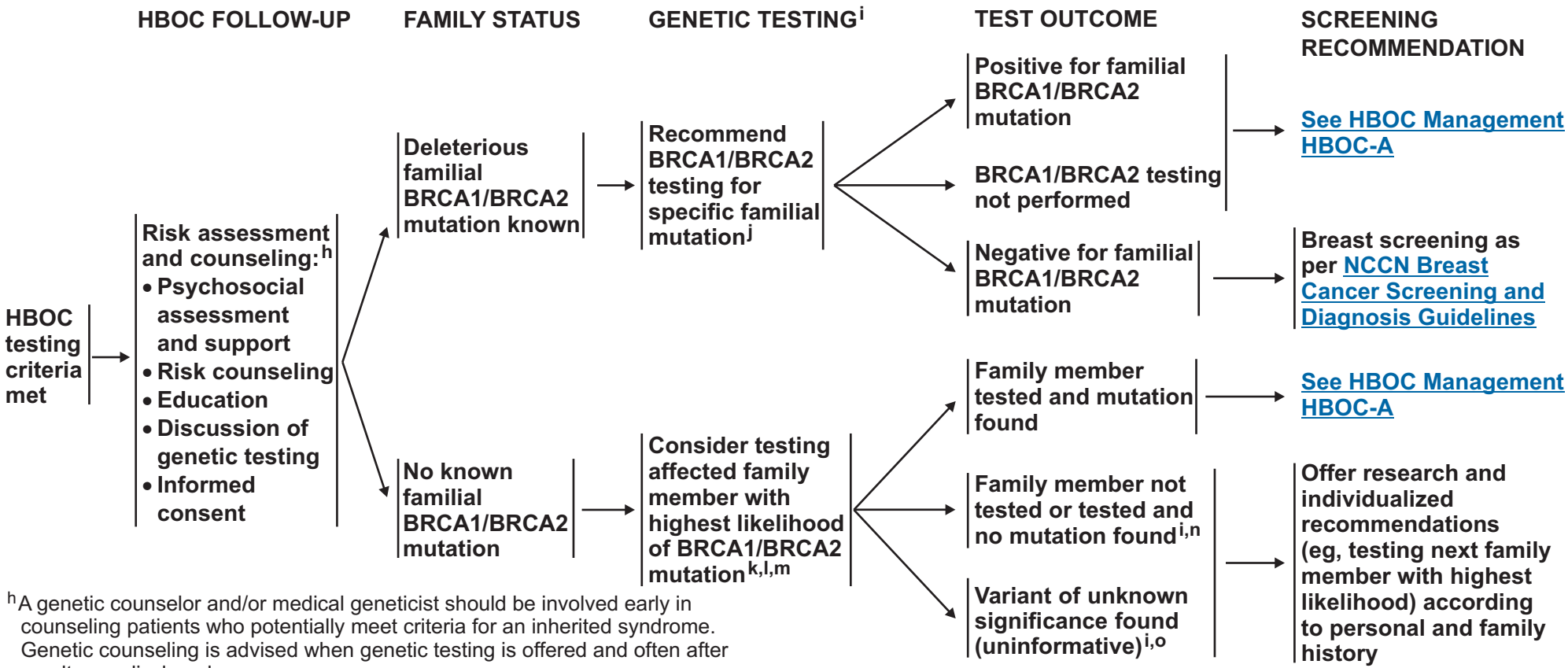
Back to Assessment (see BR/OV-1)



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

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

[j] If of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.

[k] If more than one affected, first 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 first- or second- degree family members affected with cancers thought to be related to BRCA1/BRCA2 eg, prostate, pancreas, or melanoma.

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

[m] 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 if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. If all affected family members are deceased, consider testing of paraffin-derived DNA from deceased relatives, if DNA is obtainable. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial mutation, full sequence testing is the approach, if testing is done.

[n] If individual affected with breast cancer is < 30 y especially if there is a family history of sarcoma, brain tumor, or adrenocortical carcinoma, consider p53 gene testing.

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

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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,[1] starting at age 25 y.**
- **Annual mammogram and breast MRI[2] screening starting at age 25 y, or individualized based on earliest age of onset in family.[3]**
- **Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks.**
- **Recommend risk-reducing salpingo-oophorectomy,[4] ideally between 35 and 40 y, and 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, possible short term hormone replacement therapy (HRT), and related medical issues.**
- **For those patients who have not elected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound + CA-125,[5] every 6 mo starting at age 35 y or 5-10 y before 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[6] (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

[1] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending semiannual clinical breast exam is the concern for interval breast cancers.

[2] High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably day 1-15 of menstrual cycle for premenopausal women.

[3] The appropriateness of imaging scheduling is still under study.

[4] Given the high rate of occult disease, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (Powell C, Kenley E, Chen L, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: Role of serial sectioning in the detection of occult malignancy. J Clin Oncol; 2005;127-132.) See the College of American Pathologists, Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary.

[5] 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.

[6] Data suggest that oral contraceptives (OC) reduce ovarian cancer risk in BRCA mutation carriers. The risk/benefit ratio is uncertain because of contradictory evidence about OC increasing breast cancer risk; however, OC use for contraception is acceptable. (Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev. 2006;15:1863-1870.)

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HBOC SYNDROME MANAGEMENT (2 of 2)

MEN

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

MEN and WOMEN

- Education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene mutations.[7]
- Refer to appropriate NCCN guidelines for other cancer screening[8] (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

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

[7] Some families also have an increased incidence of prostate cancer, pancreatic cancer, and melanoma.
[8] Consider full body skin exam for melanoma and investigational protocols for pancreatic cancer.
[9] Offit K, Sagi M, Hurley K. Preimplantation genetic diagnosis for cancer syndromes: a new challenge for preventive medicine. JAMA 2006;296:2727-2730.
[10] Offit K, Levran O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548-1551.

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Li-Fraumeni Syndrome

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LI-FRAUMENI SYNDROME TESTING CRITERIA[a]

- **Individual from a family with a known TP53 mutation**
- **Classic Li-Fraumeni syndrome criteria:**
  - **Combination of an individual diagnosed < age 45 y with a sarcoma[b]**
    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,[b] brain tumor, or adrenocortical carcinoma diagnosed < age 45 y**
    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[c] especially if there is a family history of sarcoma,[b] brain tumor, or adrenocortical carcinoma**

FOLLOW-UP

Classic LFS or LFS-like testing criteria met → **See Follow-up (LIFR-2)**

Classic LFS or LFS-like tesing criteria not met → **Individualized recommendations according to personal and family history**

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**

[a] 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.

[b] Ewing sarcoma is less likely to be related to Li-Fraumeni syndrome than other types of sarcomas.

[c] Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: Clinical characteristics of families with p53 germline mutations. J Clin Oncol 2009;27:1250-1256

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Li-Fraumeni Syndrome

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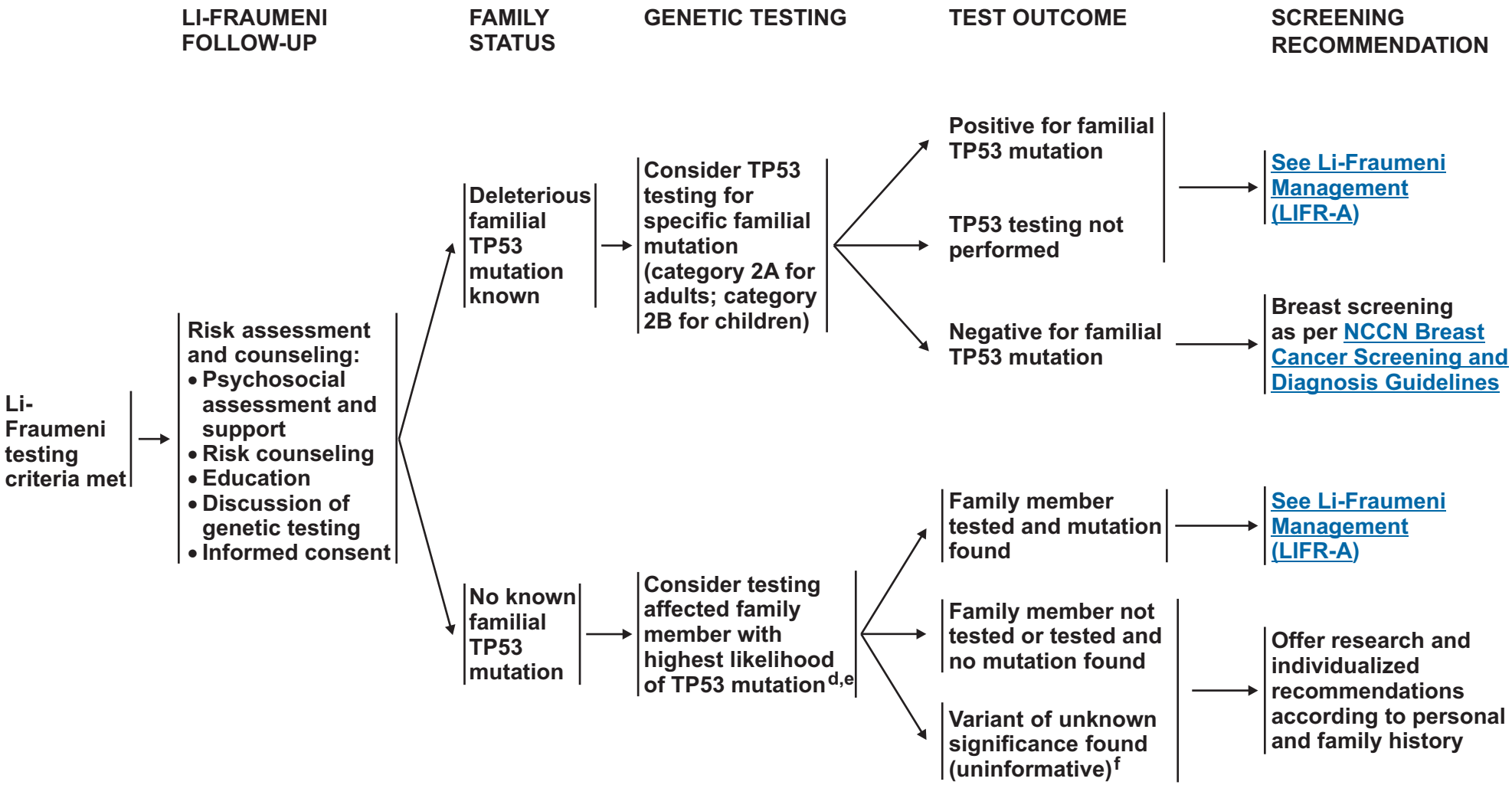

[d] Youngest age at diagnosis, bilateral disease, multiple primaries, sarcoma at age < 45 y.

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

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

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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/or breast MRI screening starting at age 20-25 y, or individualized based on earliest age of onset in family.[1,2]
- 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).
- 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.
- Pediatricians should be apprised of the risk of childhood cancers in affected families.
- Discuss option to participate in novel screening approaches using technologies such as PET scan, abdominal ultrasound, and brain MRI within clinical trials when possible.[3]
- Target surveillance based on individual family histories.
- Education regarding signs and symptoms of cancer.

RISK TO RELATIVES

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

[1] The appropriateness of imaging scheduling is still under study.
[2] High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability.
[3] Some centers are evaluating novel imaging techniques as investigational tools.

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Cowden Syndrome

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COWDEN SYNDROME TESTING CRITERIA[a,b]

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

FOLLOW-UP

Cowden syndrome testing criteria met → See Follow-up (COWD-2)

Cowden syndrome testing criteria not met → Individualized recommendations according to personal and family history

Major criteria:

- Breast cancer
- Mucocutaneous lesions[e]
  - One biopsy proven trichilemmoma
  - Multiple palmoplantar keratoses
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)
  - Macular pigmentation of glans penis
- Macrocephaly (megalocephaly) (ie, ≥ 97th percentile, 58 cm in adult women, 60 cm in adult men)[f]
- Endometrial cancer
- Non-medullary thyroid cancer
- Multiple GI hamartomas or ganglioneuromas

Minor criteria:

- Other thyroid lesions (eg, adenoma, nodule(s), goiter)
- Mental retardation (ie, IQ ≤ 75)
- Autism spectrum disorder
- Single GI hamartoma or ganglioneuroma
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Renal cell carcinoma
- Uterine fibroids

[a] These are testing criteria; not clinical diagnostic criteria.

[b] If two criteria involve the same structure/organ/tissue, both may be included as criteria. For example, breast cancer (as a major criteria) and fibrocystic breast disease (as a minor criteria).

[c] If an individual has two or more major criteria, such as breast cancer and non-medullary thyroid cancer, but does not have macrocephaly, one of the major criteria may be included as one of the three minor criteria to meet testing criteria.

[d] At-risk individual can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing.

[e] The literature available on mucocutaneous lesions is not adequate to specify accurately the number or extent of mucocutaneous lesions required to be a major criterion for Cowden syndrome. Clinical judgement should be used.

[f] Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: Birth to 18 years. Pediatrics 1987;79:706-712.

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

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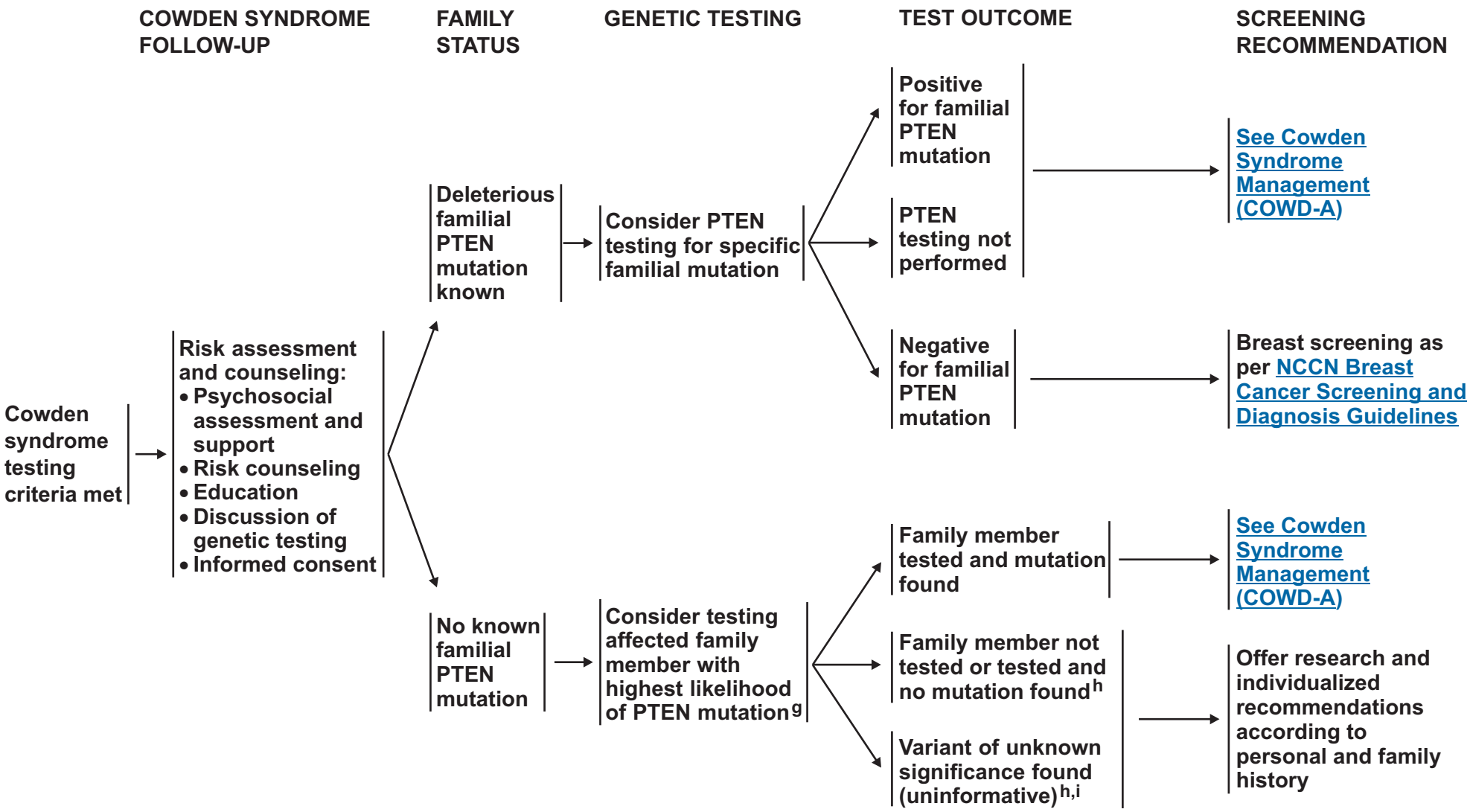

[g] Testing of unaffected family members when no affected member is available may be considered. Significant limitations of interpreting test results should be discussed.
[h] Certain mutations (ie, large rearrangements) are not detectable by the primary sequencing assay and supplementary testing may be necessary.
[i] Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.

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 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 comes first).[1, 2]
- For endometrial cancer screening,[3] encourage patient education and prompt response to symptoms and participation in a clinical trial to determine the effectiveness and necessity of screening modalities.
- Discuss option of risk-reducing mastectomy and hysterectomy on case-by-case basis and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.

MEN AND WOMEN

- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to breast and thyroid exam.
- Baseline thyroid ultrasound at age 18 y, and consider annually thereafter.
- Consider annual dermatologic exam.
- Education regarding the signs and symptoms of cancer.

RISK TO RELATIVES

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

[1] The appropriateness of imaging scheduling is still under study.

[2] High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance experienced radiologists in breast MRI, and regional availability.

[3] There are limited data regarding the lifetime risk of endometrial cancer in Cowden syndrome. 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

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

All cancers develop as a result of mutations in certain genes, such as those involved in the regulation of cell growth and/or DNA repair,[1,2] although not all of these mutations are inherited from a parent. For example, sporadic mutations can occur in somatic/tumor cells only, and de novo mutations can occur for the first time in a germ cell (ie, egg or sperm) or in the fertilized egg itself during early embryogenesis. However, family studies have long documented an increased risk 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. These individuals may have an increased susceptibility to cancer as the result of one or more gene mutations present in parental germline cells; cancers developing in these individuals may be classified as hereditary or familial cancers.

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

Assessment of an individual's risk of familial or hereditary cancer is based on a thorough evaluation of the family history. With respect to hereditary cancers, advances in molecular genetics have identified a number of genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, *BRCA1, BRCA2, PTEN, TP53, CDH1*) and provided a means of characterizing the specific gene mutation or mutations present in certain individuals and families exhibiting an increased risk of cancer. The field of cancer genetics has implications for all aspects of cancer management of individuals with hereditary or familial cancers, including prevention, screening, and treatment.

The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian 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. Furthermore, these guidelines were not developed as a substitute for professional genetic counseling. Rather, they are intended to help health care providers identify individuals who may benefit from cancer risk assessment and genetic counseling, to provide genetic counselors with an updated tool for the assessment of individual breast cancer and ovarian cancer risk and to guide decisions related to genetic testing, and to facilitate a multidisciplinary approach in the management of individuals at increased risk of hereditary breast and/or ovarian cancer. Although cancers other than breast and ovarian cancers are associated with these hereditary syndromes, the main focus of these Guidelines is on the management of breast and ovarian cancer risk in these individuals.

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

Hereditary Breast or Breast/Ovarian Cancer Syndromes

Breast cancer is the most prevalent type of cancer in women in the United States and the second leading cause of cancer death in U.S. women. Up to 10% of breast cancers are due to specific mutations in single genes that are passed down in a family.[6,8] Specific patterns of hereditary breast/ovarian cancers are linked to mutations in the *BRCA1* or *BRCA2* genes.[9,10] In addition, two very rare hereditary cancer syndromes exhibiting an increased risk of breast cancer are Li-Fraumeni syndrome and Cowden syndrome which are related to germline mutations in the *TP53* and *PTEN* genes, respectively.[11,12] Similar to the *BRCA 1/2* genes, the *TP53* and *PTEN* genes encode for proteins involved in processes related to tumor suppression, such as DNA repair and cell cycle regulation. Hereditary diffuse gastric cancer (HDGC) is another rare hereditary syndrome that is also associated with development of lobular breast cancer. This syndrome arises from mutation(s) in the *CDH1* (cadherin 1, type 1, E-cadherin [epithelial]) gene which encodes for a tumor suppressor gene product.[13] In an analysis of 4 predominantly gastric cancer pedigrees from Newfoundland with a specific *CDH1* mutation, the cumulative risk of female lobular breast cancer by the age of 75 was estimated to be as high as 52%.[14,15] Furthermore, germline *CDH1* mutations may be associated with lobular breast cancer in the absence of diffuse gastric cancer.[16]

These hereditary syndromes share several features beyond elevation of breast cancer risk. They are due to germline mutations that are not in sex-linked chromosomes; hence, they can be inherited from either the mother or the father. They are associated with breast cancer onset at an early age and development of other types of cancer, and they exhibit an autosomal dominant inheritance pattern (see Table 1). Offspring of an individual with one of these hereditary syndromes have a 50% chance of inheriting the mutation. In addition, individuals with these hereditary syndromes share increased risks of multiple cases of early onset disease as well as bilateral disease. The gene mutations associated with these hereditary syndromes are considered to be highly penetrant although a subsequent alteration in the second copy of the gene without the hereditary mutation is believed to be necessary for the initiation of cancer development (ie, 2-hit hypothesis).[17,18] In addition, the manifestations (ie, expression) of these hereditary syndromes are often variable in individuals within a single family (ie, age of onset, tumor site, and number of primary tumors). The risk of developing cancer in individuals with one of these hereditary syndromes depends upon numerous variables including the gender and age of the individual.

Hereditary Breast/Ovarian Cancer Syndrome

The overall prevalence of disease-related mutations in *BRCA1* and *BRCA2* genes has been estimated as 1 in 300 and 1 in 800, respectively.[19,20] Currently, hundreds of unique mutations have been identified in both *BRCA1* and *BRCA2* genes. However, a number of founder effects (see Table 1) have been observed in certain

populations, wherein the same mutation has been found in multiple, unrelated families and can be traced back to a common ancestor. Among the Ashkenazi Jewish population, for example, the frequency of 187delAG and 5385insC mutations in *BRCA1* and of the 6174delT mutation in *BRCA2* approximates 1 in 40.[6,21] Certain founder mutations have also been identified in populations from the Netherlands, Sweden, Hungary, Iceland, and French Canada[19,22-27] (see HBOC-1). It has been estimated that over 90% of early onset cancers in families with both breast and ovarian cancers are caused by mutation(s) in the *BRCA 1* or *BRCA2* genes.[28] Hence, the degree of clinical suspicion for a *BRCA* mutation in a single individual with both breast and ovarian cancer or someone with a family history of both breast and ovarian cancer should be very high.

Both the *BRCA1* and *BRCA2* genes encode for proteins involved in tumor suppression. The *BRCA1* gene is located on chromosome 17. It is believed to be involved in both the repair of DNA lesions and in the regulation of cell-cycle checkpoints in response to DNA damage. However, the molecular mechanism through which *BRCA1* functions to preserve genomic stability remains unclear.[29] The *BRCA2* gene, located on chromosome 13, is involved in repair of replication-mediated double-strand breaks.[30,31]

Mutations in the *BRCA1* or *BRCA2* genes can be highly penetrant (see Table 1) although the probability of cancer development in carriers of *BRCA1* or *BRCA2* mutations is variable, even within families with the same mutation.[32-34] Estimates of penetrance range from a 45% to 84% lifetime risk for breast cancer, as well as an increased risk of contralateral breast cancer.[35-37] In addition, female carriers of these genes have an estimated 11% to 62% lifetime risk for ovarian cancer, depending upon the population studied.[35-39] 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* genes have an excessive risk for both breast and ovarian cancer that warrants consideration of more intensive preventive and screening strategies.

Some histopathologic features have been reported to occur more frequently in breast cancers characterized by a *BRCA1/2* mutation. For example, several studies have shown that *BRCA1* breast cancer is more likely to be characterized as ER-,PR-negative, and HER2-negative (ie, “triple negative”).[40-43] In a recent study, 11% of 54 young (≤ 40 years) women with high-grade, triple-negative breast cancer were found to be carriers of a BRCA1 gene mutation.[43]

An increased frequency of other malignancies has been reported in families with a mutation or mutations in the *BRCA 1* or *BRCA2* gene.[44] Germline *BRCA1* and *BRCA2* mutations have been associated with an increased risk of prostate cancer[34,45-47] and *BRCA2* mutations carriers have been reported to also have a higher risk of pancreatic cancer, and melanoma.[45-49] Some data related to the risk of cancers in this population at some sites other than the breast/ovary are contradictory.[50] For example, it has been suggested that the increased risk of endometrial cancer observed in some *BRCA1* or *BRCA2* mutation carriers is mainly due to the use of tamoxifen therapy by these women as opposed to the presence of a gene mutation.[51]

Germline mutations in *BRCA1* and *BRCA2* are responsible for 5%-10% of epithelial ovarian cancers (ie, ovarian cancer developing on the surface of the ovary).[52] Increased risks of cancers of the fallopian tube and primary peritoneal cancer are also observed in this population.

The histology of ovarian cancers in carriers of a *BRCA1* or *BRCA2* mutation is more likely to be characterized as serous adenocarcinoma and high grade compared with ovarian cancers in non-mutation carriers, although endometrioid and clear cell ovarian cancers have

also been reported in the former population.[52-56] In the setting of a diagnosis of invasive ovarian cancer as many as 15% of unselected individuals will have a germline *BRCA1* or *BRCA2* mutation.[57,58] However, it has been reported that about half of families showing a genetic predisposition to ovarian cancer do not have identifiable mutations in *BRCA1/2* genes.[59] Hence, other gene mutations predisposing to ovarian cancer are likely to exist.[60] Of note, ovarian cancer is a component tumor of Lynch syndrome which is associated with germline mutations in mismatch repair genes.[61] Interestingly, results from a prospective study suggest that women from families at increased risk of hereditary breast cancer without site-specific *BRCA* mutations are not at increased risk for ovarian cancer, although these results may have been confounded by the ethnic characteristics and size of the study population.[62]

Male carriers of a BRCA gene mutation also have a greater risk for cancer susceptibility.[46] In one study of 26 high-risk families with at least one case of male breast cancer, 77% demonstrated a *BRCA2* mutation.[28] However, among males with breast cancer who were not selected on the basis of family history, only 4%-14% tested positive for a germline *BRCA2* mutation.[63,64] For males with a *BRCA2* mutation, the risk of breast cancer by age 80 years has been estimated at 6.9%.[65] In contrast, for men without such a mutation, the lifetime risk of breast cancer has been estimated at about 1/10th of 1% (1 in 1,000).[66]

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline *TP53* gene mutations.[12] It has been estimated to be involved in only approximately 1% of hereditary breast cancer,[67] although results from a recent study suggest that germline *TP53* gene mutations may be more common than previously believed.[68] The tumor suppressor gene, *TP53*, is located on chromosome 17,[69,70] and the protein product of the *TP53* gene (ie, p53) is located in the cell nucleus and binds directly to DNA. It has been called the “guardian of the genome” and plays important roles in controlling cell cycling and apoptosis.[69-71] Germline mutations in the *TP53* gene have been observed in over 50% (and in over 70% in some studies) of families meeting the classic definition of LFS (see LIFR-1).[12,68,72] Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.[73]

LFS, a highly penetrant cancer syndrome associated with a high life-time risk of cancer, is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft-tissue sarcomas, osteosarcomas (although Ewing’s sarcoma is less likely to be associated with LFS), premenopausal breast cancer, acute leukemia, and cancer of the colon, adrenal cortex, and brain tumors.[12,68,71,74-79] Sarcoma, breast cancer, adrenocortical tumors and certain brain tumors have been referred to as the “core” cancers of LFS since they account for the majority of cancers observed in individuals with germline mutations in the *TP53* gene, and in one study, at least one of these cancers was found in one or more members of all families with a germline *TP53* gene mutation.[68] Individuals with LFS often present with certain cancers (eg, soft-tissue sarcomas, brain tumors, and adrenocortical carcinomas) in early childhood,[76] and have an increased risk of developing multiple primary cancers during their lifetimes.[80] Results of a segregation analysis of data collected on the family histories of 159 patients with childhood soft tissue sarcoma showed carriers of germline *TP53* mutations to have estimated cancer risks of approximately 60% and 95% by age 45 and 70 years, respectively.[81] Although similar cancer risks are observed in men and women with LFS when gender-specific cancers are not considered, female breast cancer is commonly associated with the syndrome.[68] It is important to mention that estimations of cancer risks associated with LFS are limited to at least some degree by selection bias since dramatically affected

kindreds are more likely to be identified and become the subject of further study.

A number of different sets of criteria have been used to help identify individuals with LFS. For the purposes of the Guidelines, 2 sets of these criteria are used to facilitate the identification of individuals who are candidates for *TP53* gene mutation testing. Chompret and colleagues have described 3 characteristics of an ideal set of testing criteria.[82] Such criteria would enable one to look for a mutation in situations where it is likely to exist (ie, the criteria should have a high positive predictive value), miss as few mutations as possible (ie, the criteria should have a high sensitivity), and not select subjects who are not carriers of the mutations (ie, the criteria should have a high specificity).

Classic LFS criteria, based on a study by Li and Fraumeni involving 24 LFS kindreds, include the following: member of a kindred with a known *TP53* mutation; combination of an individual diagnosed at age 45 years or younger with a sarcoma, and a first-degree relative diagnosed with cancer at age 45 years or younger, and an additional first- or second-degree relative in the same lineage with cancer diagnosed at age < 45 years or a sarcoma at any age (see LIFR-1). Classic LFS criteria have been estimated to have a high positive predictive value as well as a high specificity, although the sensitivity is relatively low (eg, estimated at 40% in one study).[68] Thus it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.[79,83] Classic LFS criteria make up one set of criteria included in the Guidelines to guide selection of individuals for *TP53* gene mutation testing (see LIFR-1).

Other groups have broadened the classic LFS criteria to facilitate identification of individuals with LFS,[74,82,84,85] One set of these less strict criteria proposed by Birch and colleagues shares many of the features of classic LFS criteria, although a larger range of cancers are included.[74] These criteria include the following: combination of an individual diagnosed with a childhood tumor or sarcoma, brain tumor or adrenocortical carcinoma diagnosed at age younger than 45 years, and a first- or second-degree relative with a typical LFS tumor at any age, and another first- or second-degree relative with cancer diagnosed before age 60 years. The sensitivity of these LFL criteria has been estimated to be high, although the estimated specificity is relatively low.[68] These LFL criteria are also included in the Guidelines to help identify candidates for *TP53* gene mutation testing (see LIFR-1). Uncommonly, individuals with de novo germline *TP53* mutations (no mutation in either biological parent) have been identified.[68,75] These cases would not be identified as *TP53* testing candidates by either classic LFS or the LFL criteria listed above since both require the presence of a family history.

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

Finally, a member of a family with a known *TP53* mutation is considered to be at sufficient risk to warrant gene mutation testing, even in the absence of any other risk factors.

Cowden Syndrome

Cowden syndrome, a rare hereditary cancer syndrome, was first described in 1963 and named after the Cowden family, the first family documented with signs of the disease.[88] The incidence of Cowden syndrome has been reported to be 1 in 200,000, although it is likely to be underestimated due to difficulties associated with making a clinical diagnosis of the disease.[89,90] It is considered to be part of the PTEN hamartoma tumor syndrome (PHTS) which also includes Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, and Proteus-like syndrome[91] (although there is controversy as to whether true Proteus cases have been shown to have a *PTEN* mutation[92]). Hamartomas, a common manifestation of these syndromes, are benign tumors resulting from an overgrowth of normal tissue. The *PTEN* ("phosphatase and TENsin homologue deleted on chromosome TEN"[93]) gene located on chromosome 10 encodes for a tumor-suppressor protein involved in cell cycle control and cell survival.[11]

Cowden syndrome is the only PHTS disorder associated with a documented predisposition to malignancies, hence it is the one addressed in these Guidelines. However, it has been suggested that patients with other PTHS diagnoses associated with *PTEN* mutations should be assumed to have Cowden-associated cancer risks. Cowden syndrome is associated with multiple hamartomatous and/or cancerous lesions in various organs and tissues, including the skin, mucous membranes, breast, thyroid, endometrium and brain.[11,94]

Women diagnosed with Cowden syndrome have a high risk of benign fibrocystic breast disease and their lifetime risk of breast cancer has been estimated at 25%-50% with an average age of 38 to 46 years at diagnosis.[94,95] There have been only 2 cases of breast cancer reported in men with Cowden syndrome.[11] Thyroid disease, including benign multinodular goiter, adenomatous nodules, and follicular adenomas have been reported to occur in up to approximately 70% of individuals with Cowden syndrome[96] and the lifetime risk of thyroid cancer (follicular or papillary) has been estimated at 3-10%.[11,97] As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.[98] Although not well defined, women with Cowden syndrome may have a 5%-10% risk of endometrial cancer,[11,99] and an increased risk of uterine fibroids. In addition, skin cancers, renal cell carcinomas, brain tumors, and vascular malformations affecting any organ are occasionally seen in individuals with Cowden syndrome, although the risks for developing these conditions are not well defined. It is important to note, however, that most of the data on the frequencies of the clinical features of Cowden syndrome are from compilations of case reports of relatively young individuals who may have subsequently developed additional signs of the disease (ie, new cancerous lesions), and these data are also likely to be confounded by selection bias.[11] Furthermore, a considerable number of these studies were published prior to the establishment in 1996 of the International Cowden Consortium operational diagnostic criteria for the syndrome which were based on published data and the expert opinion of individuals representing a group of centers mainly in North America and Europe.[11,100]

Classic features of the disease include mucocutaneous papillomatous papules, palmoplantar keratoses, and trichilemmomas (ie, benign tumors derived from the outer root sheath epithielium of a hair follicle).[11,101] Most individuals with Cowden syndrome exhibit characteristic mucocutaneous lesions by their twenties, and such lesions have been reported to occur in 99% of individuals with Cowden syndrome, a syndrome showing nearly complete penetrance.[52,91] The presence of 2 or more trichilemmomas has been reported to be

pathognomonic for Cowden syndrome.[102,103] However, since most of this evidence is from the older literature, it is possible that the association between these 2 entities is somewhat overestimated.[11] There are reports of individuals with a solitary trichilemmoma who do not have Cowden syndrome.[102,103] Nevertheless, due to the strong association between these lesions and Cowden syndrome and the difficulty in clinically distinguishing between a trichilemmoma and another mucocutaneous lesion, it is important that a diagnosis of trichilemmoma is histologically confirmed.

It has historically been reported that about 40% individuals with Cowden syndrome have gastrointestinal polyps (often colonic), although more recent data suggest that this risk may be 80% or higher. Most of the polyps are hamartomatous, although ganglioneuromas (ie, rare, benign peripheral nervous system tumors) have also been reported to occur.[11,104]

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

The BRRS variant of PTEN hamartoma tumor syndrome (PHTS) has been characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay, and in males, pigmented macules on the glans penis,[113] although formal diagnostic criteria have not been established for this syndrome. *PTEN* gene mutations testing in individuals characterized with BRRS have been reported in approximately 60% of these patients.[114] Further, in another study, 10% of patients with BRRS for whom a *PTEN* gene mutation test was negative were shown to be carriers of large *PTEN* gene deletions.[105]

The *PTEN* mutation frequency in individuals meeting International Cowden Consortium criteria for Cowden syndrome has been estimated at about 80%.[11] The International Cowden Consortium criteria have been updated several times since 1996[11,91,115,116] and they have served as the basis for the list of criteria included in the NCCN Guidelines. On the basis of literature reports and expert consensus, the NCCN Panel has recently revised both the list of criteria associated with this genetic syndrome as well as the combinations of criteria that establish which individuals are candidates for *PTEN* gene mutation testing (COWD-1 and section on Cowden syndrome). Similar to earlier versions, criteria are grouped into 3 general categories. A patient is considered for *PTEN* gene mutation testing based on whether he/she meets certain criteria or combinations of criteria from these 3 categories. The first criteria category include a personal history of BRRS, Adult LDD, autism spectrum disorder with macrocephaly, or 2 or more biopsy proven trichilemmomas (see COWD-1). Any individual presenting with one or more of these diagnoses warrants *PTEN* testing. Previously, some of the criteria from this group have sometimes been referred to as “pathognomonic” although, as discussed earlier, it is unlikely that any of these conditions can stand alone as a definitive diagnostic criterion of Cowden syndrome. Another criterion which can be considered to be sufficient to warrant *PTEN* gene mutation testing is a family history which includes the presence of a known deleterious *PTEN* mutation.

The next category of criterion represent “major” features associated with Cowden syndrome. The major criteria include the presence of breast cancer, macrocephaly (ie, megalocephaly),[112] endometrial cancer, non-medullary thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (eg, one biopsy proven trichilemmoma, multiple palmoplantar keratoses, etc. – see COWD-1 for complete list). An individual exhibiting 2 or more major criteria where one of these is macrocephaly meets the testing threshold. In addition, 3 or more major criteria are considered sufficient to warrant testing. With respect to decisions related to the presence of mucocutaneous lesions, the NCCN Panel did not consider the available literature to be adequate to accurately specify the number or extent of these lesions required for the condition to be defined as a major criterion for Cowden syndrome, and clinical judgment is needed when evaluating such lesions.

The final category of criteria represents features with a “minor” association with Cowden syndrome. These include thyroid lesions other than non-medullary thyroid cancer, mental retardation, autism spectrum disorder, a single gastrointestinal hamartoma or ganglioneuroma, fibrocystic disease of the breast, lipomas, fibromas, renal cell carcinoma, and uterine fibroids. An individual would need to exhibit 4 minor criteria or 3 minor and one major criterion to meet testing criteria. Furthermore, if an individual meets 2 or more major criteria but does not have macrocephaly, one of the major criteria can be substituted for a minor criterion (see COWD-1 and the section on Risk Assessment, Counseling, and Management: Cowden Syndrome).

Initial Risk Assessment

For a patient concerned about or suspected of having a hereditary propensity to breast and/or ovarian cancer, an initial risk evaluation should be performed in order to determine if a formal risk assessment should be undertaken. The first step in this primary assessment is a broad and flexible evaluation of the personal and family history of the individual with respect to breast and/or ovarian cancer.[117,118] The magnitude of the risk increases with the number of affected relatives in the family, the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.[119,120] The younger the age at diagnosis, the more likely it is that a genetic component is present. When assessing a family history for a hereditary pattern, the equal likelihood of paternal or maternal transmission of a gene that predisposes to breast cancer must also be kept in mind.

If an individual or a close family member of that individual meets any one of the following criteria presented in BR/OV-1 that individual may be at increased risk for breast and/or ovarian cancer, and a referral for genetic assessment is recommended. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer (see BR/OV-2).

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

Formal Risk Assessment and Genetic Counseling

Risk Assessment

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

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

Statistical models based on personal and family history characteristics have been developed to estimate a person's interval and lifetime risks of developing breast cancer. For example, the Claus tables may be useful in providing breast cancer risk estimates for white women without a known cancer-associated gene mutation who have one or two first- or second-degree female relatives with breast cancer.[121] In addition, decision models developed to estimate the likelihood that a *BRCA1/2* mutation is present include BRCAPRO[122,123] and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)[122]; A lifetime risk of breast cancer of 20% -25% or greater as assessed by models based largely on family history has been used in some guidelines to identify a woman as being at high risk of breast cancer. For example, this risk threshold was used in a recent update to the American Cancer Society (ACS) guidelines on breast screening which incorporates magnetic resonance imaging (MRI).[124]

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

Evaluation of Patient's Needs and Concerns

The first step in evaluating a individual's risk for hereditary breast cancer is to assess her/his concerns and reasons for seeking counseling and to guarantee that her/his personal needs and priorities will be addressed in the counseling process. Several studies have documented a highly exaggerated perception of risk among women with a family history of breast cancer who seek cancer risk counseling.[125] This is a situation that can interfere with the adoption of appropriate health behaviors. In addition, the patient's knowledge about the benefits, risks, and limitations of genetic testing should be assessed as well as the patient's goals. A positive, supportive interaction with the counseling team is an important determinant of ultimate satisfaction with the counseling process and of adherence to recommended health behaviors.

Detailed Family History

A detailed family history is the cornerstone of effective genetic counseling. An examination of family history involves development of an expanded pedigree collected beginning with the health of the proband (index case) and proceeding outward to include first-, second-, and third-degree relatives on both the maternal and paternal sides (see BR/OV-2). Standardized pedigree nomenclature should be used.[126,127] Unaffected family members, both living and deceased, are also included, as their histories also provide information about the magnitude of genetic risk.

Information collected includes cancer diagnoses by primary site, age at diagnosis, bilaterality (when appropriate), and current age or age at death. Whenever possible, cancer diagnoses in the family are verified by obtaining medical records, pathology reports, or death certificates.

This is particularly important in the case of a report of an "abdominal" cancer in a female relative - a situation in which cancers of the cervix, uterus, ovary, and/or colon are often confused. It is also important to know the ancestry/ethnicity of the individual.

Other medical conditions that may be associated with or predispose an individual to breast and/or ovarian cancer should also be noted. Family history data are then graphically represented on a pedigree that follows standard nomenclature to illustrate family relationships and disease information. Factors that limit the informativeness of the pedigree are small family size, a small number of individuals of the susceptible gender for sex-limited cancers, reduced penetrance, early deaths in family members (which precludes the possibility that they will develop adult diseases), prophylactic surgeries that remove an organ from subsequent risk of cancer (eg, hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members.[5,128]

A recent prospective registry study of 306 women diagnosed with breast cancer at < 50 years of age, who had no first- or second-degree relatives with breast or ovarian cancer, showed that those individuals with a limited family history, defined as fewer than 2 first- or second-degree female relatives or fewer than 2 female relatives surviving beyond age 45 years in either lineage, may have an underestimated probability of a *BRCA1/2* gene mutation based on models dependent on family history.[129]

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.[130,131] Pathologic verification of these diagnoses is encouraged. Carcinogen exposure history (eg, 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.[132-135]

Focused Physical Examination

A physical examination may be part of the risk assessment. Particular attention should be paid to organs/areas of the body known to be affected in individuals with specific hereditary breast and/or ovarian syndromes. For example, certain patterns of mucocutaneous manifestations are associated with Cowden syndrome.

Genetic Counseling

Genetic counseling is a critical component of the cancer risk assessment process. Counseling for hereditary breast and/or ovarian cancer uses a broad approach to place genetic risk in the context of other related risk factors, thereby customizing counseling to the experiences of the individual. The purpose of cancer genetic counseling is to educate individuals about the genetic, biological, and environmental factors related to the individual's cancer diagnosis and/or risk of disease; and to help them derive personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. Individuals need to understand the relevant genetic,

medical, and psychosocial information and be able to integrate this information before they can make an informed decision. The presentation of information is most effective when tailored to the age and education of the person undergoing counseling, and that individual's personal exposure to the disease, level of risk, and social environment.[7]

Pretest counseling is an essential element of the genetic counseling process in the event that genetic testing for a gene mutation associated with a hereditary cancer syndrome is under consideration.[7] The foundation of pretest genetic counseling is based on the principle of informed consent. Pre-test counseling should include a discussion of why the test is being offered and how test results may impact medical management, cancer risks associated with the gene mutation in question, the significance of possible test results (see section on Genetic Testing, below), the likelihood of a positive result, technical aspects and accuracy of the test, economic considerations, risks of genetic discrimination, psychosocial aspects, confidentiality issues, as well as other topics.[7] A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act (GINA) enacted in 2008 which prohibits health insurers and employers from discrimination on the basis of genetic test results.[136]

Post-test counseling must also be performed and includes disclosure of results, a discussion of the significance of the results, an assessment of the impact of the results on the emotional state of the individual, a discussion of the impact of the results on the medical management of the individual, and how and where the patient will be followed. In addition, identification of a gene mutation associated with a hereditary predisposition to breast and/or ovarian cancer in an individual necessitates a discussion of possible inherited cancer risk to relatives and the importance of informing family members about test results.[7] It may also be appropriate to offer gene testing to both parents of an individual who tests positive for one of these gene mutations (ie, *BRCA1/2*, *PTEN*, *TP53*) when the lineage is in question.

Genetic Testing

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

In the statement on Genetic Testing for Cancer Susceptibility from the American Society of Clinical Oncology (ASCO) updated in 2003, genetic testing is recommended when there is: (i) a personal or family history suggesting genetic cancer susceptibility (ii) the test can be adequately interpreted and (iii) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.[137] These recommendations were reiterated in the 2010 ASCO update on genetic and genomic testing for cancer susceptibility with respect to testing individuals for gene mutations known to cause hereditary breast and/or ovarian cancer(s).[138]

As part of pre-test counseling, the counselor reviews the distinctions between true-positive, true-negative, indeterminate (or uninformative),

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

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

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

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

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

In the case of hereditary breast/ovarian cancer (ie, BRCA mutation), if no family member with breast or ovarian cancer is living, consideration can be given to testing first- or second-degree family members affected with cancers thought to be related to the deleterious mutation in question (eg, prostate or pancreatic cancer).

Another counseling dilemma is posed by the finding of a variant or mutation of unknown significance (see Table 2) - a mutation that may actually represent a benign polymorphism unrelated to an increased breast cancer risk or may indicate an increased breast cancer risk. The individual must be counseled in such a situation, because additional information about that specific mutation will be needed before its significance can be understood. These patients should be considered for referral to research studies that aim to define the functional impact of the gene variant.

Finally, it is important to mention that certain large genomic rearrangements are not detectable by a primary sequencing assay, thereby necessitating supplementary testing, in some cases.[139-142] For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the *BRCA1* and *BRCA2* genes that not detected by sequencing the *BRCA1/2* genes.

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

Detailed on HBOC-1 are specific risk assessment criteria which form part of the decision-making process in evaluating whether an individual suspected of being carriers of a *BRCA1/2* mutation should be considered for genetic testing. For example, a personal history of female breast cancer diagnosed at age 45 years or younger, a personal

history of male breast cancer, or a personal history of epithelial ovarian/fallopian tube/primary peritoneal cancer, is considered to be sufficient to meet the testing threshold. Following risk assessment and counseling, genetic testing should be considered in individuals for whom hereditary breast/ovarian cancer syndrome testing criteria are met. The NCCN Panel recommends such testing if the patient is a member of a family with a known deleterious *BRCA1* or *BRCA2* mutation. Initial testing for the 3 known founder mutations is recommended if the individual meeting testing criteria is of Ashkenazi Jewish descent. Full sequence testing is recommended for those from other ethnic groups who meet testing criteria.

Counseling issues specific for both female and male carriers of a *BRCA1/2* mutation include the increased incidence of pancreatic cancer and melanoma. In addition, the risks to family members of individuals with a known *BRCA*1/2 gene mutation (see sections on Risk Assessment and Genetic Testing) should also be discussed as well as the importance of genetic counseling for these individuals (see HBOC-A 2 of 2). Counseling issues pertaining specifically to male breast cancer have also been described, and include an increased risk of prostate cancer in male carriers of a *BRCA1/2* mutation.[143] In addition, counseling related to the risks and benefits of reproductive options for couples expressing the desire that their offspring not carry a familial *BRCA1/2* gene mutation may also be an option.[144,145]

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 *BRCA1/2* carriers (HBOC-A). An individual with a known deleterious BRCA1/2 mutation in a close family member who does not undergo gene testing should be followed according to the same guidelines as a carrier of a *BRCA1/2* mutation. Individuals not meeting testing criteria, including those with an increased risk of familial breast cancer, should be followed according to the recommendations in the NCCN Breast Cancer Screening and Diagnosis Guidelines.

Screening Recommendations

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.[146] For a woman who is a carrier of a *BRCA1/2* mutation, training in breast self-examination with regular monthly practice should begin at age 18 years, and semiannual clinical breast examinations should begin by age 25 years. The woman should begin having annual mammograms and breast MRI screening at age 25 years or on an individualized timetable based on the earliest age of cancer onset in family members. [124,146-149]

The overall sensitivity of screening mammography was reported to be only 33% in a study of women with suspected or known *BRCA1/2* mutations who were more likely to be younger and to have dense breasts.[150] Other reasons for the low sensitivity of mammography in women with *BRCA1/2* mutations include an increased likelihood of developing tumors with more benign mammographic characteristics (eg, less likely to appear as a spiculated mass).[151] Annual MRI as an adjunct to screening mammogram and clinical breast examination for women aged 25 years or older with a genetic predisposition for breast cancer is supported by recent guidelines from the ACS.[124]

For individuals who have not elected ovarian cancer risk-reducing surgery, concurrent transvaginal ultrasound and CA-125 determination should be considered every 6 months, starting at age 35 years or 5-10 years earlier that the earliest age of first diagnosis of ovarian cancer in the family, for the early detection of ovarian cancer (HBOC-A). Although there are retrospective data indicating that annual ovarian screening using transvaginal ultrasound and measurement of serum CA-125 levels is neither an effective strategy for the early detection of

ovarian tumors nor a reasonable substitute for a bilateral risk-reduction salpingo-oophorectomy,[152,153] the data are limited regarding the effectiveness of these screening interventions when used every 6 months. Investigational imaging and screening studies may be considered for this population. A full body skin examination for melanoma screening and investigational protocols for pancreatic cancer screening should be considered.

Men testing positive for a *BRCA1/2* mutation should have a 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. A full body skin exam for melanoma screening and investigational protocols for pancreatic cancer screening should be considered.

Risk Reduction Surgery

Bilateral Total Mastectomy

Retrospective analyses with median follow-up periods of 13-14 years have indicated that bilateral risk reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known *BRCA1/2* mutation carriers.[154,155] Results from smaller prospective studies with shorter follow-up periods have provided support for concluding that RRM provides a high degree of protection against breast cancer in women with a *BRCA1/2* mutation.[156,157]

The NCCN Panel supports discussion of the option of RRM for women on a case-by-case basis. Counseling regarding the degree of protection offered by such surgery and the degree of cancer risk should be provided.

It is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well studied.[158] Multidisciplinary consultations are recommended prior to surgery and should include the discussions of the risks and benefits of surgery, and surgical breast reconstruction options. Immediate breast reconstruction is an option for many women following RRM, and early consultation with a reconstructive surgeon is recommended for those considering either immediate or delayed breast reconstruction.[159]

Bilateral Salpingo-oophorectomy

Women with a *BRCA1/2* mutation are at increased risk for both breast and ovarian cancers (including fallopian tube cancer and primary peritoneal cancer).[160,161] Although the risk of ovarian cancer is generally considered to be lower than the risk of breast cancer in a *BRCA1/2* mutation carrier,[35,162,163] the absence of reliable methods of early detection and the poor prognosis associated with advanced ovarian cancer have lent support for the performance of bilateral risk reduction salpingo-oophorectomy (RRSO) after completion of childbearing in these women. In the studies of Rebbeck et al., the mean age at diagnosis of ovarian cancer was 50.8 years for *BRCA1/2* carriers.[164]

The effectiveness of RRSO in reducing the risk of ovarian cancer in carriers of a *BRCA1/2* mutation has been demonstrated in a number of studies. For example, results of a meta-analysis involving 10 studies of *BRCA1/2* mutation carriers showed an approximately 80% reduction in the risk of ovarian or fallopian cancer following RRSO.[165] However, a 1-4.3% residual risk of a primary peritoneal carcinoma has been reported in some studies.[164-169]

RRSO is also reported to reduce the risk of breast cancer in carriers of a *BRCA1/2* mutation by approximately 50%.[164,165,169,170] In the case-control international study of Eisen et al., a 56% (odds ratio=0.44; 95% CI, 0.29-0.66) and a 46% (odds ratio=0.57; 95% CI, 0.28-1.15) breast cancer risk reduction was reported following RRSO in carriers of a

BRCA1 and a *BRCA2* mutation, respectively.[170] Hazard ratios of 0.47 (95% CI, 0.29-0.77)[164] and 0.30 (95% CI, 0.11-0.84)[168] were reported in two other studies comparing breast cancer risk in women with a *BRCA1/2* mutation who had undergone RRSO with carriers of these mutations who opted for surveillance only. These studies are further supported by a recent meta-analysis which found similar reductions in breast cancer risk of approximately 50% for *BRCA1* and *BRCA2* mutation carriers following RRSO,[165] although results of a recent prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA1* mutation carriers compared with *BRCA2* mutation carriers.[171]

Reductions in breast cancer risk for carriers of a *BRCA1/2* mutation undergoing RRSO may be associated with decreased hormonal exposure following surgical removal of the ovaries. Greater reductions in breast cancer risk were observed in women with a *BRCA1* mutation who had a RRSO at age 40 years or younger (odds ratio=0.36, 95% CI, 0.20-0.64) relative to *BRCA1* carriers aged 41-50 years who had this procedure (odds ratio=0.50, 95% CI, 0.27-0.92).[170] A nonsignificant reduction in breast cancer risk was found for women aged 51 or older although only a small number of women were included in this group.[170] However, results from Rebbeck et al (1999) also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.[169] Due to the limited data, an optimal age for RRSO is difficult to specify.

The NCCN Panel recommends RRSO for women with a known *BRCA1/2* mutation, ideally between ages 35-40 years and upon completion of child bearing or at an individualized age based on earliest age of ovarian cancer diagnosed in the family. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.[172] (For details on pathologic evaluation of surgical specimens, see www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/Ovary_09protocol.pdf).

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

It has been reported that short-term hormone replacement therapy (HRT) in women undergoing RRSO does not negate the reduction in breast cancer risk associated with the surgery.[173] In addition, results of a recent case-control study of *BRCA1* mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.[174] However, caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.[175,176]

Chemoprevention

An evaluation of the subset of healthy individuals with a *BRCA1/2* mutation in the BCPT study revealed that breast cancer risk was reduced by 62% in those with a *BRCA2* mutation receiving tamoxifen relative to placebo (risk ratio, 0.38; 95% CI, 0.06-1.56). However, tamoxifen use was not associated with a reduction in breast cancer risk in those with a *BRCA1* mutation.[177] These findings may be related to the greater likelihood for development of estrogen receptor-positive tumors in *BRCA2* mutation carriers relative to *BRCA1* mutation carriers. However, this analysis was limited by the very small number of individuals with a *BRCA1/2* mutation.

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

substantially lower risk in women with 3 or more years of exposure.[178,179] However, results of other studies suggest that oral contraceptive use may increase the risk of breast cancer in this population, especially if used for 5 or more years.[180,181]

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

The approach to families with other hereditary breast cancer syndromes, such as LFS, reflects that of hereditary breast/ovarian cancer in many ways. However, there are some syndrome-specific differences with regard to assessment and management. In the case of LFS, there are multiple associated cancers, both pediatric and adult, that should be reflected in the expanded pedigree (LIFR-1). Cancers associated with LFS 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.[68,80] Verification of these sometimes very rare cancers is particularly important.

Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met (see LIFR-1; LIFR-2).This recommendation is category 2A for adults and 2B for children. The NCCN Panel also suggests consideration of *TP53* mutation testing in those with early onset breast cancer (< 30 years of age) for whom *BRCA1/2* testing result is negative, especially if there is a family history of LFS related cancers. In the absence of additional family history, early breast cancer alone is associated with a low likelihood of mutation identification. Individuals who have tested positive for a *TP53* mutation may have greater distress than anticipated, so provisions for supportive interventions should be provided. An individual with a known deleterious *TP53* mutation in a close family member who does not undergo gene testing should be followed according to the same guidelines as a carrier of a *TP53* mutation (see LIFR-A).

Individuals not meeting criteria for either classic LFS or LFL syndrome should be followed according to their personal and family history.

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

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 when there is a high index of suspicion for second malignancies (LIFR-A). Clinicians should address screening limitations for other cancers associated with LFS. The option to participate in clinical trials evaluating novel screening approaches using technologies such as positron emission tomography (PET) scan, abdominal ultrasound and brain MRI should also be discussed if such trials are available. Colonoscopy should be considered every 2-5 years, starting at no later than 25 years. Education regarding signs and symptoms of cancer is important. Patients should be advised about the risk to relatives, and genetic counseling for relatives is recommended.

Annual 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.

Risk Assessment, Counseling, and Management: Cowden Syndrome

The assessment of individuals suspected of having Cowden syndrome incorporates both a history of the benign and malignant conditions associated with the syndrome and a targeted physical examination, including the skin and oral mucosa, breast, and thyroid gland (COWD-1). The NCCN Panel has recently revised both the list of criteria associated with this genetic syndrome as well as the combinations of criteria that establish which individuals are candidates for *PTEN* gene mutation testing (COWD-1 and section on Cowden Syndrome). These criteria are for the direction of testing strategies and are not meant to serve as clinical diagnostic criteria. Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met (COWD-2). Unlike the "pathognomonic" criteria, none of the individual major or minor criteria are considered by the NCCN Panel to be sufficient to warrant genetic testing in the absence of other clinical evidence of Cowden syndrome. However, the Panel recommends genetic testing in an individual exhibiting 2 or more major criteria where one is macrocephaly, 3 or more major criteria when one is not macrocephaly, one major criterion along with 3 or more minor criteria, or in someone meeting specifications for 4 minor criteria. Furthermore, any of the major criteria can be classified as a minor criterion for the purpose of meeting the threshold required for genetic testing if 2 or more major criteria are present in a single individual but the individual does not have macrocephaly. The testing threshold is lower for an individual considered to be "at risk" (eg, a first-degree relative of an individual and/or proband with a clinical diagnosis of Cowden syndrome or BRRS for whom genetic testing has not been performed). In this case, any one major criterion or 2 minor criteria are considered to be sufficient for genetic testing to be recommended. Recommendations for individuals not meeting these testing criteria should be individualized according to personal and family history.

An individual with a known deleterious *PTEN* mutation in a close family member who does not undergo gene testing should be followed according to the same guideline as a carrier of a *PTEN* mutation (see COWD-A). Current medical management recommendations for individuals with Cowden syndrome focus on primary and secondary prevention options for breast cancer and on annual physical examinations, starting at age 18 years or 5 years before the youngest age of diagnosis of a component cancer in the family, to detect skin changes and to monitor the thyroid gland for abnormalities A baseline thyroid ultrasound should be performed at age 18 years and considered annually thereafter for both men and women with Cowden syndrome. 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 counseling is recommended for at-risk relatives.

Women should begin regular monthly breast self examinations at age 18 years and have a semiannual clinical breast examination, beginning at age 25 years or 5-10 years earlier than the earliest known breast cancer in the family. Women should also have an annual mammogram and breast MRI screening starting at ages 30-35 years, or 5 to 10 years earlier than the earliest known breast cancer in the family. Although there are no data regarding risk reduction surgery in women with Cowden syndrome, the option of risk-reduction mastectomy and hysterectomy should be discussed on a case-by-case basis (see section on Bilateral Total Mastectomy for HBOC). The Panel recommends patient education regarding the symptoms of endometrial

cancer including the necessity of a prompt response to such symptoms. Women diagnosed with Cowden syndrome should consider participation in a clinical trial to determine the effectiveness and necessity of endometrial cancer screening.

Table 1: Glossary of relevant genetic terms (from the National Cancer Institute [NCI])

Autosomal dominant
Autosomal dominant inheritance refers to genetic conditions that occur when a mutation is present in one copy of a given gene (i.e., the person is heterozygous).

Autosomal recessive
Autosomal recessive inheritance refers to genetic conditions that occur only when mutations are present in both copies of a given gene (i.e., the person is homozygous for a mutation, or carries two different mutations of the same gene, a state referred to as compound heterozygosity).

de novo mutation
An alteration in a gene that is present for the first time in one family member as a result of a mutation in a germ cell (egg or sperm) of one of the parents, or a mutation that arises in the fertilized egg itself during early embryogenesis. Also called new mutation.

Familial: A phenotype or trait that occurs with greater frequency in a given family than in the general population; familial traits may have a genetic and/or nongenetic etiology.

Family history
The genetic relationships within a family combined with the medical history of individual family members. When represented in diagram form using standardized symbols and terminology, it is usually referred to as a pedigree or family tree.

Founder effect
A gene mutation observed with high frequency in a population founded by a small ancestral group that was once geographically or culturally isolated, in which one or more of the founders was a carrier of the mutant gene.

Germline
The cells from which eggs or sperm (i.e., gametes) are derived.

Kindred
An extended family.

Pedigree
A graphic illustration of family history.

Penetrance
A characteristic of a genotype; it refers to the likelihood that a clinical condition will occur when a particular genotype is present.

Proband
The individual through whom a family with a genetic disorder is ascertained. In males this is called a propositus, and in females it is called a proposita.

Sporadic cancer
This term has two meanings. It is sometimes used to differentiate cancers occurring in people who do not have a germline mutation that confers increased susceptibility to cancer from cancers occurring in people who are known to carry a mutation. Cancer developing in people who do not carry a high-risk mutation is referred to as sporadic cancer. The distinction is not absolute, because genetic background may influence the likelihood of cancer even in the absence of a specific predisposing mutation. Alternatively, sporadic is also sometimes used to describe cancer occurring in individuals without a family history of cancer

Table 2

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

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

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