

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 3.2013

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Genetic/Familial High-Risk Assessment: Breast and Ovarian

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[NCCN Genetic/Familial High-Risk Assessment Panel Members](#) [Summary of the Guidelines Updates](#)

[Breast and/or Ovarian Genetic Assessment \(BR/OV-1\)](#)

[Hereditary Breast and/or Ovarian Cancer \(HBOC-1\)](#) [HBOC Syndrome Management \(HBOC-A\)](#)

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[Additional Genetic Mutations Associated with Breast/Ovarian Cancer Risk \(GENE-1\)](#)

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

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

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

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

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Updates in Version 3.2013 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 2.2013 include:

Hereditary Breast and Ovarian Cancer:

HBOC-1

- A personal history of breast cancer + one or more of the following
 - Sub-bullet, “Diagnosed any age with ≥ 1 close blood relative with breast cancer ≤ 50 y and/or ≥ 1 close blood relative with epithelial ovarian cancer at any age” was replaced with
 - ◊ A revised 3rd sub-bullet by adding: “Diagnosed age ≤ 50 y with ≥ 1 close blood relative with breast cancer at any age or with a limited family history.”
 - ◊ A new 7th sub-bullet: “Diagnosed at any age with ≥ 1 close blood relative with epithelial ovarian cancer.”
 - 5th sub-bullet was added: “Diagnosed at any age with ≥ 1 close blood relative with breast cancer diagnosed ≤ 50 y.”

Updates in Version 2.2013 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2013 include:

Cowden Syndrome:

COWD-1

- Cowden Syndrome Testing Criteria
 - A new criterion was added: “Individual meeting clinical diagnostic criteria for CS” with a corresponding reference, “Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;37:828-830.”
- Footnote “b” was revised: “If two criteria involve the same structure/organ/tissue, both may be included as criteria. ~~For example, breast cancer (as a major criterion) and fibrocystic breast disease (as a minor criterion).~~”

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Updates in Version 1.2013 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2012 include:

Genetic/Familial High-Risk Assessment:

BR/OV-1

- An affected individual
 - 1st bullet was added: “A known mutation in a breast cancer susceptibility gene within the family.”
 - 6th bullet was reorganized and modified: “**≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations and/or macrocephaly; hamartomatous polyps of GI tract on the same side of family; diffuse gastric cancer**” (Also for an unaffected individual)
- An unaffected individual
 - “A known mutation in a breast cancer susceptibility gene within the family” was moved as the first bullet.
 - “**≥2 breast primaries, either in 1 individual or 2 different individuals from the same side of family (maternal or paternal)**” was separated into 2nd and 3rd bullets.
- Footnotes
 - Footnote “e” was modified by adding: “Ovarian/fallopian tube/primary peritoneal cancers are component tumors of hereditary non-polyposis colorectal cancer/Lynch syndrome...”
 - Footnote “f” was modified: “...requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian *or pancreatic* cancer at any age).”
 - Footnote “h” was added: “For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa...”

BR/OV-2

- Focused physical exam clarified by adding: “conducted by physician or nurse” and noting the findings related to Cowden syndrome
 - **Cowden syndrome specific:**
 - ✦ Dermatologic, including oral mucosa
 - ✦ Head circumference
 - ✦ Thyroid (*enlarged or nodular on palpation*)

Hereditary Breast and Ovarian Cancer:

HBOC-1

- A personal history of breast cancer + one or more of the following
 - 2nd sub-bullet was modified: “Diagnosed *any age* ≤50-y with ≥1 close blood relative with breast cancer...”
 - 6th sub-bullet was modified: “Diagnosed at any age with ≥2 close blood relatives with breast cancer ~~and/or epithelial ovarian cancer~~ at any age.”
 - 7th sub-bullet was modified: “Diagnosed at any age with ≥2 close blood relatives with pancreatic cancer *or aggressive prostate cancer (Gleason score ≥7)* at any age.”
- 5th bullet was modified: “Personal history of pancreatic cancer *or aggressive prostate cancer (Gleason score ≥7)* at any age with ≥2 close blood relatives with breast and/or ovarian and/or pancreatic *or aggressive prostate cancer (Gleason score ≥7)* at any age.”
- Family history only
 - 1st bullet was added: “Clinical judgement should be used to determine if the patient has reasonable likelihood of a mutation...”
 - 2nd bullet was modified: “Testing of unaffected ~~family members~~ *individuals* should only be considered when *an appropriate affected family member is unavailable for testing. no affected family member is available and then the unaffected family member with the highest probability of mutation should be tested.*”
 - 3rd bullet was modified: “Significant limitations of interpreting test results *for an unaffected individual* should be discussed.”
- HBOC testing criteria not met, “Cancer screening as per NCCN Screening Guidelines” replaced “See NCCN Breast Cancer Screening and Diagnosis Guidelines.”
- Footnotes
 - Footnote “a” was modified: “...further personalized risk assessment, genetic counseling, *and often genetic testing* and management” and “~~Other malignancies~~ *Melanoma has been reported in some HBOC families include prostate and melanoma.*”
 - Footnote “e” was modified: “Close blood relatives include first-, second-, and third-degree relatives *on same side of family.*”

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Updates in Version 1.2013 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2012 include:

Hereditary Breast and Ovarian Cancer (continued):

HBOC-2

- No known familial *BRCA1/BRCA2* mutation
 - Genetic testing recommendation was modified: “Consider comprehensive testing of patient or, if unaffected, test of an affected family member...”
 - Test outcomes were modified:
 - ◊ “~~Family member tested and Mutation found~~”
 - ◊ “~~Family member Not tested or tested and no mutation found~~”
- If negative for familial *BRCA1/BRCA2* mutation, the screening recommendation was changed from “Breast Cancer as per NCCN Breast Cancer Screening and Diagnosis Guidelines” to “Cancer screening as per NCCN Screening Guidelines.”
- Footnotes
 - Footnote “p” was modified by adding: “For additional information on other genetic mutations associated with breast/ovary cancer risk for which genetic testing is clinically available, see GENE-1.”
 - Footnote “q” was modified: “Testing *family members* for a variant of unknown significance...”

HBOC-A 1 of 2

- HBOC management for women
 - 1st bullet was modified: “~~Breast self-exam training and education awareness~~ starting at age 18 y” with a corresponding footnote, “Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.”
 - 4th bullet was modified: “~~Discuss option of risk-reducing mastectomy on case-by-case basis and~~
 - ◊ Counseling *may include a discussion* regarding degree of protection, reconstruction options, and risks.”
 - 6th bullet was added: “Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.”

• Footnotes

- Footnote “4” was modified: “*The best screening strategy for woman age 25-30 is uncertain with some data suggesting that mammogram be added to MRI only after age 30. The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118:2021-2030.*”
- Footnote “5” was modified: “Given the high rate of occult *neoplasms disease*...”
- Footnote “7” was modified by adding: “Other chemoprevention options for breast cancer include tamoxifen and raloxifene; however, only very limited data with these agents are available in patients with *BRCA* mutations.”

HBOC-A 2 of 2

- HBOC management for men
 - 4th bullet, “Consider prostate cancer screening starting at age 40 y” replaced “Adhere to screening guidelines for prostate cancer (See NCCN Prostate Cancer Early Detection Guidelines).”
- HBOC management for men and women
 - 2nd bullet, “No specific guidelines exist for pancreatic cancer and melanoma, but screening may be individualized based on cancers observed in the family” replaced “Refer to appropriate NCCN guidelines for other cancer screening.”
- Reproductive options
 - 1st bullet, “For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis” replaced “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.”

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Updates in Version 1.2013 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2012 include:

Li-Fraumeni Syndrome:

LIFR-1

- Li-Fraumeni syndrome testing criteria
 - Early-onset breast cancer criteria was revised: “Individual with breast cancer ≤ 35 y ~~≤ 30 y~~ with a negative *BRCA1/BRCA2* test.”
- Footnote
 - Footnote “b” was revised from “Ewing sarcoma is less likely to be related to Li-Fraumeni syndrome than other types of sarcomas” to “To date, there have been no reports of Ewing sarcoma, GIST, desmoid tumor or angiosarcoma in *TP53* mutation carriers.”

LIFR-2

- No known familial *TP53* mutation
 - Genetic testing recommendation was modified: “Consider comprehensive testing of patient or if unaffected, test of an ~~affected~~ family member...”
 - Test outcomes were modified:
 - ◊ “~~Family member tested and Mutation found~~”
 - ◊ “~~Family member Not tested or tested and no mutation found~~”
- If negative for familial *TP53* mutation, the screening recommendation was changed from “Average-risk cancer screening as per NCCN Screening Guidelines” to “Cancer screening as per NCCN Screening Guidelines.
- Footnotes
 - Footnote “j” was modified by adding: “For additional information on other genetic mutations associated with breast/ovary cancer risk for which genetic testing is clinically available, see GENE-1.”
 - Footnote “k” was modified: “Testing *family members* for a variant of unknown significance...”

LIFR-A

- Breast cancer risk for women
 - 1st bullet was modified: “~~Breast self-exam training and education~~ awareness starting at age 18 y” with a corresponding footnote, “Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.”
 - 4th bullet was modified: “Discuss ~~option of~~ risk-reducing mastectomy ~~on case-by-case basis...~~”
 - 5th bullet was added: “Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy.”
- Other cancer risks
 - 11th bullet was modified: “~~Target~~ Additional surveillance based on individual family histories.”
- Reproductive options
 - Bullet, “For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis” replaced “For couples expressing the desire that their offspring not carry a familial *TP53* mutation, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis.”
- Footnotes
 - Footnote “2” was modified by adding: “*Given theoretical concerns with harmful effects of radiation exposure in LFS*, for patients age 20-30 y, annual MRI-only screening may be sufficient based on physician’s discretion.”
 - Footnote “4” was added: “A surveillance study has been published that utilizes these screening approaches (Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: a prospective observational study. *Lancet Oncol* 2011;12:559-567).”

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Updates in Version 1.2013 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 1.2012 include:

Cowden Syndrome:

COWD-1

- Major criteria
 - 3rd bullet was modified: “~~Non-medullary~~ Follicular thyroid cancer”
- Minor criteria
 - The following were added: colon cancer, esophageal glycogenic acanthosis (≥ 3), papillary or follicular variant of papillary thyroid cancer, testicular lipomatosis, and vascular anomalies (including multiple intracranial developmental venous anomalies).
- Footnote “i” was added: “Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.”

COWD-2

- For no known familial *PTEN* mutation
 - Genetic testing recommendation was modified: “Consider comprehensive testing of patient or if unaffected, test of an affected family member...”
 - Test outcomes were modified:
 - ◊ “~~Family member tested and Mutation found~~”
 - ◊ “~~Family member Not tested or tested and no mutation found~~”
- If negative for familial *PTEN* mutation, the screening recommendation was changed from “Breast Cancer as per NCCN Breast Cancer Screening and Diagnosis Guidelines” to “Cancer screening as per NCCN Screening Guidelines.”
- Footnotes
 - Footnote “l” was modified by adding: “For additional information on other genetic mutations associated with breast/ovary cancer risk for which genetic testing is clinically available, see GENE-1.”
 - Footnote “m” was modified: “Testing family members for a variant of unknown significance...”
- Footnote was removed: “Certain mutations (ie, large rearrangements) are not detectable by the primary sequencing assay and supplementary testing may be necessary.”

COWD-A

- Cowden syndrome management for women
 - 1st bullet was modified: “~~Breast self-exam training and education~~ awareness starting at age 18 y” with a corresponding footnote, “Women should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent BSE may facilitate breast self awareness. Premenopausal women may find BSE most informative when performed at the end of menses.”
 - 3rd bullet was modified: “Annual mammography and breast MRI screening starting at age 30-35 y *or individualized based on earliest age of onset in family 5-10 y before the earliest known breast cancer in the family (whichever comes first).*”
 - 5th bullet was modified: “Discuss ~~option of~~ risk-reducing mastectomy and hysterectomy ~~on case-by-case basis and...~~”
 - 6th bullet was added: “Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.”
- Reproductive options
 - Bullet “For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis” replaced “For couples expressing the desire that their offspring not carry a familial *PTEN* mutation, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis.”
- Footnote
 - Footnote “5” was added: “Oophorectomy is not indicted for CS alone but may be indicated for other reasons.”

GENE-1

- “Additional Genetic Mutations Associated with Breast/Ovarian Cancer Risk” is a new page.

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CRITERIA FOR FURTHER GENETIC RISK EVALUATION^a

An affected individual with one or more of the following:

- A known mutation in a breast cancer susceptibility gene within the family
- Early-age-onset breast cancer^b
- Triple negative (ER-, PR-, HER2-) breast cancer
- Two breast cancer primaries^c in a single individual
- Breast cancer at any age, and
 - ≥1 close blood relative^d with breast cancer ≤50 y, or
 - ≥1 close blood relative^d with epithelial ovarian^e cancer at any age, or
 - ≥2 close blood relatives^d with breast cancer and/or pancreatic cancer at any age
 - From a population at increased risk^f
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations^g and/or macrocephaly, hamartomatous polyps of GI tract;^h diffuse gastric cancerⁱ
- Ovarian^e cancer
- Male breast cancer

^aThe criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

^bClinically use age ≤50 y because studies define early onset as either ≤40 or ≤50 y.

^cTwo breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

^dClose blood relatives include first-, second-, and third-degree relatives. (See BR/OV-3)

^eFor the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome/hereditary non-polyposis colorectal cancer; be attentive for clinical evidence of this syndrome. See [NCCN Guidelines for Colorectal Cancer Screening](#).

An unaffected individual with a family history of one or more of the following:^f

- A known mutation in a breast cancer susceptibility gene within the family
- ≥2 breast primaries in single individual
- ≥2 individuals with breast primaries on the same side of family (maternal or paternal)
- ≥1 ovarian^e cancer primary from the same side of family (maternal or paternal)
- First- or second-degree relative with breast cancer ≤45 y
- ≥1 family member on same side of family with a combination of breast cancer and ≥1 of the following (especially if early onset): pancreatic cancer, aggressive prostate cancer (Gleason score ≥7); sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, leukemia/lymphoma; thyroid cancer, dermatologic manifestations^g and/or macrocephaly, hamartomatous polyps of GI tract;^h diffuse gastric cancerⁱ
- Male breast cancer

Referral to cancer genetics professional recommended^j

See [Assessment \(BR/OV-2\)](#)

^fFor populations at increased risk, requirements for inclusion may be modified (eg, women of Ashkenazi Jewish descent with breast or ovarian or pancreatic cancer at any age).

^gFor dermatologic manifestations, see COWD-1.

^hFor hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, STK11 testing should be considered. See [NCCN Guidelines for Colorectal Cancer Screening](#): Peutz-Jeghers syndrome.

ⁱFor lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.

^jGenetic counseling is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

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ASSESSMENT

Patient needs and concerns:

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

Detailed family history:

- Expanded pedigree to include first-, second-, and third-degree relatives (parents, siblings, children, grandparents, aunts, uncles, nieces, nephews, grandchildren, half-siblings, great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins) ([See BR/OV-3](#))
- Types of cancer
- Bilaterality
- Age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation as needed, particularly pathology reports of primary cancers

Detailed medical and surgical history:

- Any personal cancer history
- Carcinogen exposure (eg, history of radiation therapy)
- Reproductive history
- Hormone use
- Previous breast biopsies
- History of salpingo-oophorectomy

Focused physical exam (conducted by physician or nurse):

- Breast/ovarian
- Cowden syndrome specific:
 - Dermatologic,^k including oral mucosa
 - Head circumference
 - Thyroid (enlarged or nodular on palpation)

^kFor dermatologic manifestations, [see COWD-1](#).

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

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

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



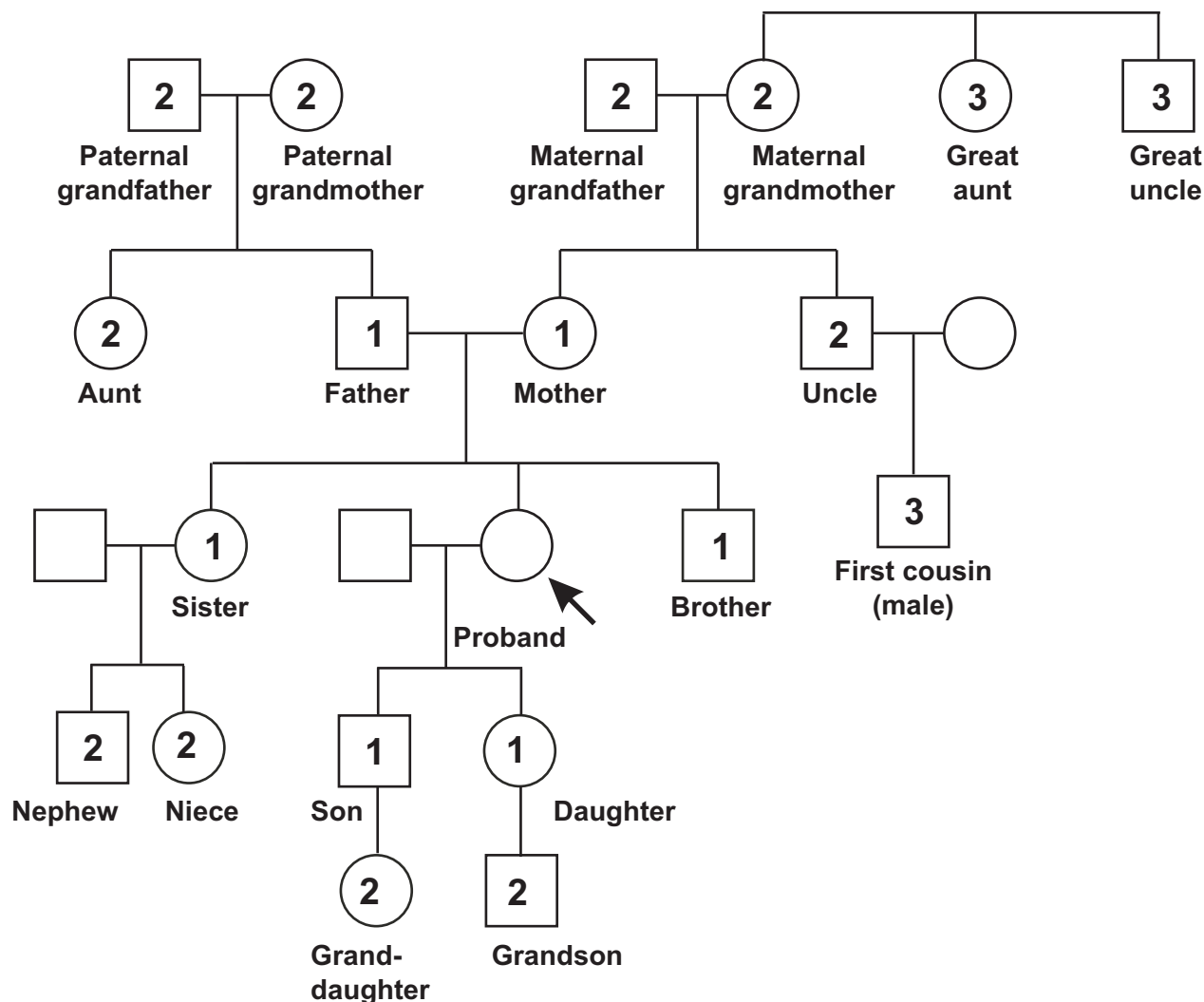
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Breast and/or Ovarian Cancer Genetic Assessment

PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND¹



¹First-degree relatives: parents, siblings, and children;
second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings;
third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.

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HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA^{a,b,c}

- Individual from a family with a known deleterious *BRCA1/BRCA2* mutation
- Personal history of breast cancer^d + one or more of the following:
 - Diagnosed age ≤45 y
 - Two breast primaries^g when first breast cancer diagnosis occurred ≤ age 50 y
 - Diagnosed age ≤50 y with ≥1 close blood relative^e with breast cancer at any age or with a limited family history^c
 - Diagnosed age ≤60 y with a triple negative breast cancer
 - Diagnosed at any age with ≥1 close blood relative^e with breast cancer diagnosed ≤50 y
 - Diagnosed at any age with ≥2 close blood relatives^e with breast cancer at any age
 - Diagnosed at any age with ≥1 close blood relative^e with epithelial ovarian cancer
 - Diagnosed at any age with ≥2 close blood relatives^e with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
 - Close male blood relative^e with breast cancer
 - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required^h
- Personal history of epithelial ovarian^f cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives^e with breast and/or ovarian^f and/or pancreatic or aggressive prostate cancer (Gleason score ≥7) at any age
- Family history only
 - Clinical judgement should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.
 - Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.
 - Significant limitations of interpreting test results for an unaffected individual should be discussed.
 - First- or second-degree blood relative meeting any of the above criteria
 - Third-degree blood relative with breast cancer^d and/or ovarian^f cancer with ≥2 close blood relatives^e with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian^f cancer

HBOC testing criteria met

See Follow-up (HBOC-2)

HBOC testing criteria not met

Cancer screening as per NCCN Screening Guidelines

^aOne or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. The maternal and paternal sides should be considered independently. Melanoma has been reported in some HBOC families.

^bPatients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

^cIndividuals 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.

^dFor the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

^eClose blood relatives include first-, second-, and third-degree relatives on same side of family. (See BR/OV-3)

^fFor the purposes of these guidelines, fallopian tube and primary peritoneal cancers are included. Ovarian/fallopian tube/primary peritoneal cancers are component tumors of Lynch syndrome/hereditary non-polyposis colorectal cancer; be attentive for clinical evidence of this syndrome. See NCCN Guidelines for Colorectal Cancer Screening.

^gTwo breast primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

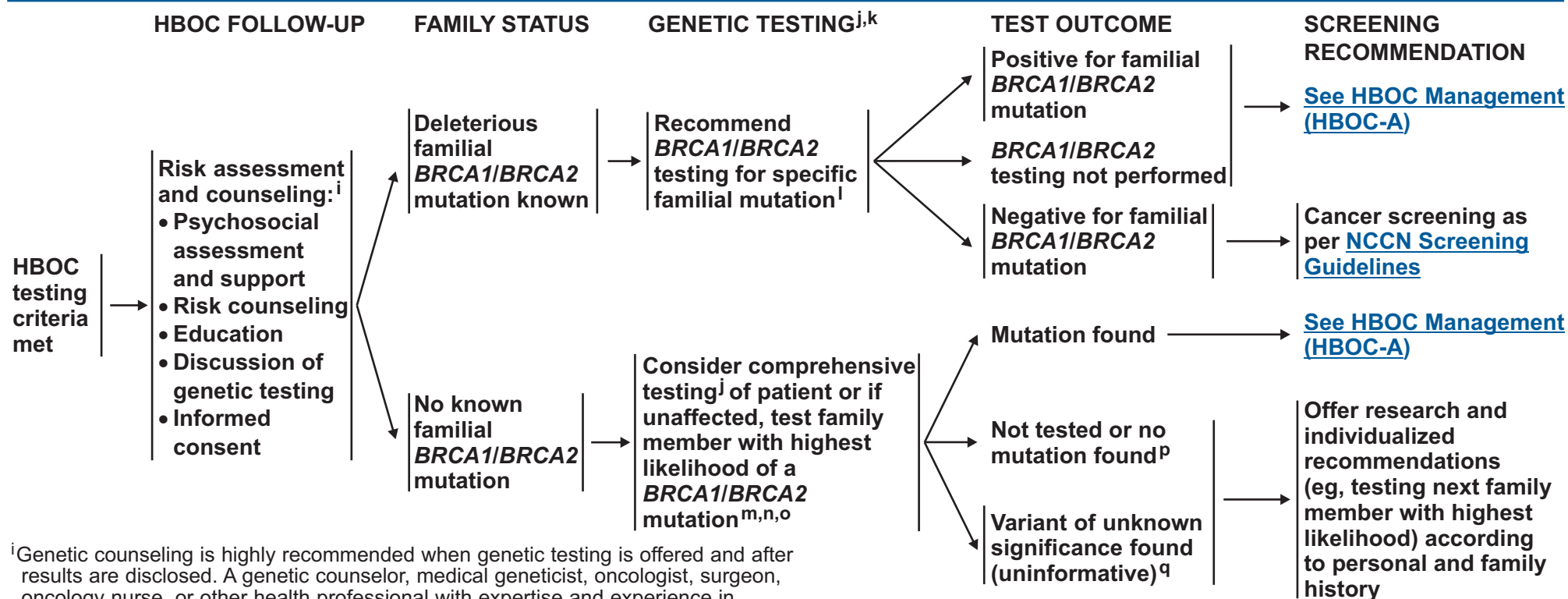
^hTesting for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Full sequencing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. Founder mutations exist in other populations.

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Hereditary Breast and/or Ovarian Cancer Syndrome



ⁱGenetic counseling is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

^jComprehensive genetic testing includes full sequencing of *BRCA1/BRCA2* and testing for large genomic rearrangements.

^kGenetic testing for familial *BRCA1/2* in children <18 y is generally not recommended.

^lIf of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.

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

ⁿIf more than one family member affected, first consider: youngest age at diagnosis, bilateral disease, multiple primaries, ovarian cancer, and most closely related to the proband/patient. 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, melanoma).

^oFor both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations and ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met, consider comprehensive genetic testing. 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, comprehensive genetic testing is the approach, if done.

^pIf no mutation is found, consider other hereditary breast/ovary cancer syndromes such as Li-Fraumeni ([LIFR-1](#)) and/or Cowden syndrome ([COWD-1](#)). For additional information on other genetic mutations associated with breast/ovary cancer risk for which genetic testing is clinically available, see [GENE-1](#).

^qTesting family members for a 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.

HBOC SYNDROME MANAGEMENT (1 of 2)

WOMEN

- **Breast awareness¹ starting at age 18 y.**
- **Clinical breast exam, every 6-12 mo,² starting at age 25 y.**
- **Annual mammogram and breast MRI³ screening starting at age 25 y, or individualized based on earliest age of onset in family.⁴**
- **Discuss risk-reducing mastectomy**
 - **Counseling may include a discussion regarding degree of protection, reconstruction options, and risks.**
- **Recommend risk-reducing salpingo-oophorectomy,⁵ 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 to a recommended maximum age of natural menopause, and related medical issues.**
- **Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.**
- **For those patients who have not elected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound (preferably day 1-10 of menstrual cycle in premenopausal women) + CA-125 (preferably after day 5 of menstrual cycle in premenopausal women)⁶ every 6 mo starting at age 30 y or 5-10 y before the earliest age of first diagnosis of ovarian cancer in the family.**
- **Consider chemoprevention options for breast and ovarian cancer, including discussing risks and benefits⁷**
([See NCCN Guidelines for Breast Cancer Risk Reduction](#)).
- **Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.**

[Continued on next page](#)

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

²Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6-12 mo is the concern for interval breast cancers.

³High-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 7-15 of menstrual cycle for premenopausal women.

⁴The best screening strategy for woman age 25-30 is uncertain with some data suggesting that mammogram be added to MRI only after age 30. The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. Cancer 2012;118:2021-2030.

⁵Given the high rate of occult neoplasms, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (See Discussion for details.) See the College of American Pathologists, [Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary](#).

⁶There are data that show 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.

⁷Data suggest that oral contraceptives (OCs) reduce ovarian cancer risk in BRCA mutation carriers. The risk/benefit ratio is uncertain because of contradictory evidence about OCs increasing breast cancer risk; however, OC use for contraception is acceptable. Other chemoprevention options for breast cancer include tamoxifen and raloxifene; however, only very limited data with these agents are available in patients with BRCA mutations. (See Discussion for details.)

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.

HBOC SYNDROME MANAGEMENT (2 of 2)

MEN

- Breast self-exam training and education starting at age 35 y
- Clinical breast exam, every 6-12 mo, starting at age 35 y
- Consider baseline mammogram at age 40 y; annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study.
- Consider prostate cancer screening starting at age 40 y.

MEN AND WOMEN

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

RISK TO RELATIVES

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

REPRODUCTIVE OPTIONS

- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. See Discussion for details.
- For *BRCA2* mutations carriers, risk of a rare (recessive) Fanconi anemia/brain tumor phenotype in offspring should be discussed if both partners carry a *BRCA2* mutation.⁹

⁸Consider full-body skin exam for melanoma and investigational protocols for pancreatic cancer.

⁹Offit K, Levrn O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548-1551.

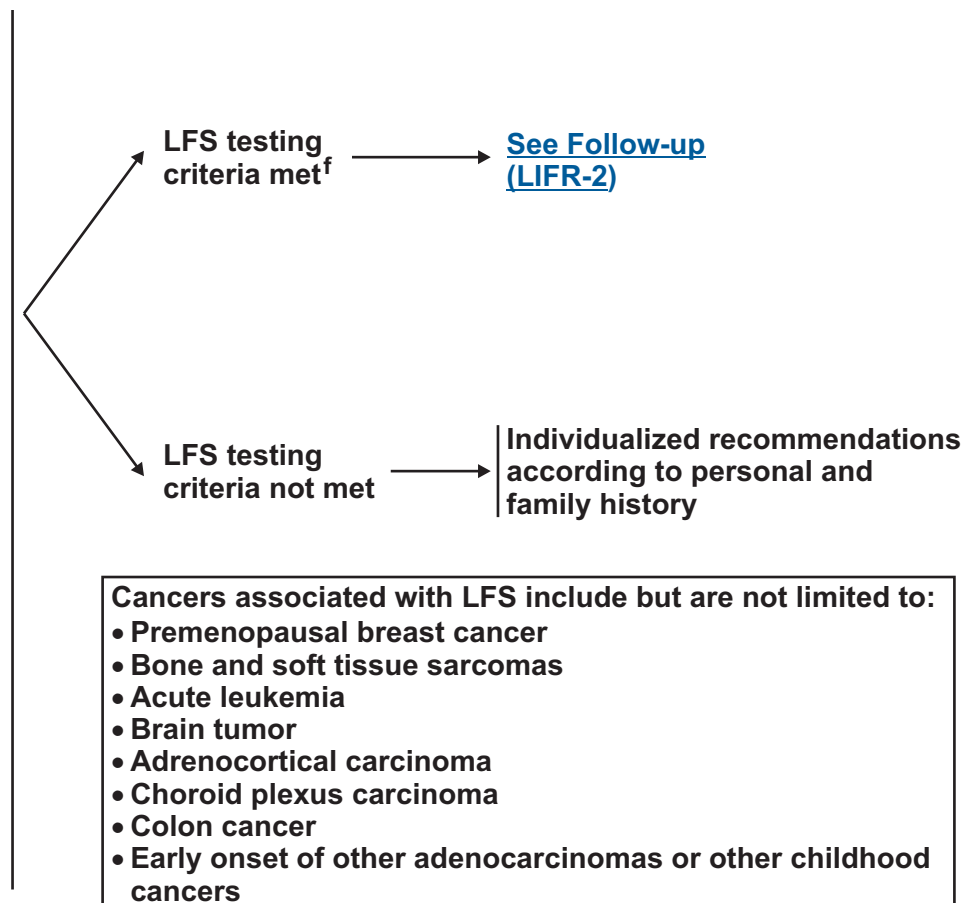
Note: All recommendations are category 2A unless otherwise indicated.

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

LI-FRAUMENI SYNDROME TESTING CRITERIA

- Individual from a family with a known *TP53* mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:^a
 - 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
- Chompret criteria:^{c,d}
 - Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocortical carcinoma, leukemia, lung bronchoalveolar cancer) before 46 years of age, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age OR
 - Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years OR
 - Individual with adrenocortical carcinoma or choroid plexus carcinoma^{d,e} at any age of onset, regardless of the family history
- Early-onset breast cancer:
 - Individual with breast cancer ≤35 y with a negative BRCA1/BRCA2 test

FOLLOW-UP



^aLi FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 1988;48:5358-5362.

^bTo date, there have been no reports of Ewing sarcoma, GIST, desmoid tumor or angiosarcoma in *TP53* mutation carriers.

^cChompret A, Abel A, Stoppa-Lyonnet D, et al. Sensitivity and predictive value of criteria for p53 germline mutation screening. *J Med Genet* 2001;38:43-47.

^dTinat J, Bougeard G, Baert-Desurmont S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. *J Clin Oncol* 2009;27:e108-9.

^eGonzalez 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.

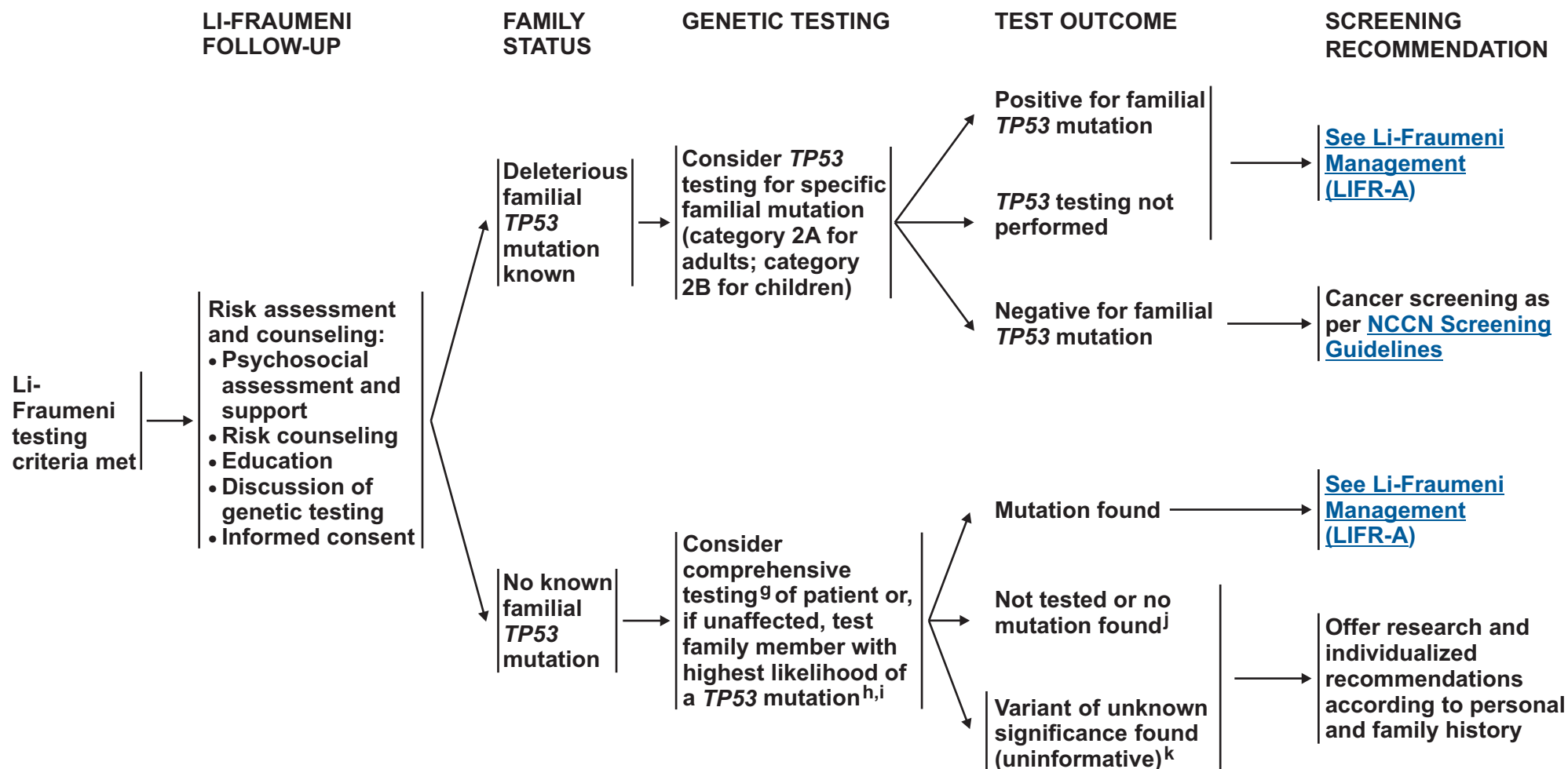
^fPatients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

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

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Li-Fraumeni Syndrome



^gComprehensive genetic testing includes full sequencing of *TP53* and deletion/duplication analysis.

^hYoungest age at diagnosis, bilateral disease, multiple primaries, sarcoma at age <45 y.

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

^jIf no mutation is found, consider other hereditary breast cancer syndromes such as HBOC ([HBOC-1](#)) and/or Cowden syndrome ([COWD-1](#)). For additional information on other genetic mutations associated with breast/ovary cancer risk for which genetic testing is clinically available, see [GENE-1](#).

^kTesting family members for a 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, WOMEN

- Breast awareness¹ starting at age 18 y.
- Clinical breast exam, every 6-12 mo, starting at age 20-25 y or 5-10 y before the earliest known breast cancer in the family (whichever comes first).
- Annual mammogram and breast MRI screening starting at age 20-25 y,² or individualized based on earliest age of onset in family.^{3,4}
- Discuss risk-reducing mastectomy and counsel regarding degree of protection, degree of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy.

OTHER CANCER RISKS

- Address limitations of screening for many cancers associated with LFS. Because of the remarkable risk of additional primary neoplasms, screening may be considered for cancer survivors with LFS and a good prognosis from their prior tumor(s).
- Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors: include careful skin and neurologic examinations.
- Therapeutic RT for cancer should be used with caution.
- 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 within clinical trials when possible, such as whole-body MRI, abdominal ultrasound, and brain MRI.⁵
- Additional 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.

REPRODUCTIVE OPTIONS

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

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

²Given theoretical concerns with harmful effects of radiation exposure in LFS, for patients age 20-30 y, annual MRI-only screening may be sufficient based on physician's discretion.

³The appropriateness of imaging modalities and scheduling is still under study.

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

⁵A surveillance study has been published that utilizes these screening approaches (Villani A, Tabori U, Schiffman J, et al. Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol 2011;12:559-567).

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

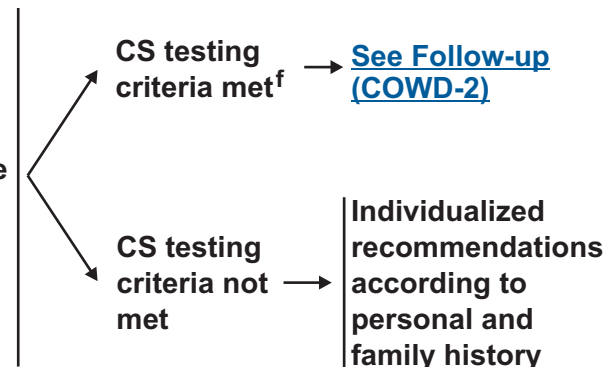
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

COWDEN SYNDROME TESTING CRITERIA^{a,b}

- Individual from a family with a known *PTEN* mutation
- Individual meeting clinical diagnostic criteria^c for CS
- Individual with a personal history of:
 - Bannayan-Riley-Ruvalcaba syndrome (BRRS) or
 - Adult Lhermitte-Duclos disease (cerebellar tumors) or
 - Autism spectrum disorder and macrocephaly or
 - Two or more biopsy-proven trichilemmomas or
 - Two or more major criteria (one must be macrocephaly) or
 - Three major criteria, without macrocephaly or
 - One major and \geq three minor criteria^d or
 - \geq Four minor criteria

- At-risk individual^e with a relative with a clinical diagnosis of CS or BRRS for whom testing has not been performed
 - The at-risk individual must have the following:
 - ◊ Any one major criterion or
 - ◊ Two minor criteria

FOLLOW-UP



Major criteria:

- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas
- Macrocephaly (megalcephaly) (ie, $\geq 97\%$, 58 cm in adult women, 60 cm in adult men)^g
- Macular pigmentation of glans penis
- Mucocutaneous lesions^h
 - One biopsy proven trichilemmoma
 - Multiple palmpoplantar keratoses
 - Multifocal or extensive oral mucosal papillomatosis
 - Multiple cutaneous facial papules (often verrucous)

Minor criteria:ⁱ

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthosis (≥ 3)
- Lipomas
- Mental retardation (ie, IQ ≤ 75)
- Papillary or follicular variant of papillary thyroid cancer
- Thyroid structural lesions (eg, adenoma, nodule(s), goiter)
- Renal cell carcinoma
- Single GI hamartoma or ganglioneuroma
- Testicular lipomatosis
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

^aThese are testing criteria, not clinical diagnostic criteria.

^bIf two criteria involve the same structure/organ/tissue, both may be included as criteria.

^cEng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;37:828-830.

^dIf 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.

^eAn 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.

^fPatients who have received an allogeneic bone marrow transplant should not have molecular genetic testing via blood or buccal samples due to unreliable test results from contamination by donor DNA. If available, DNA should be extracted from a fibroblast culture. If this source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

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

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

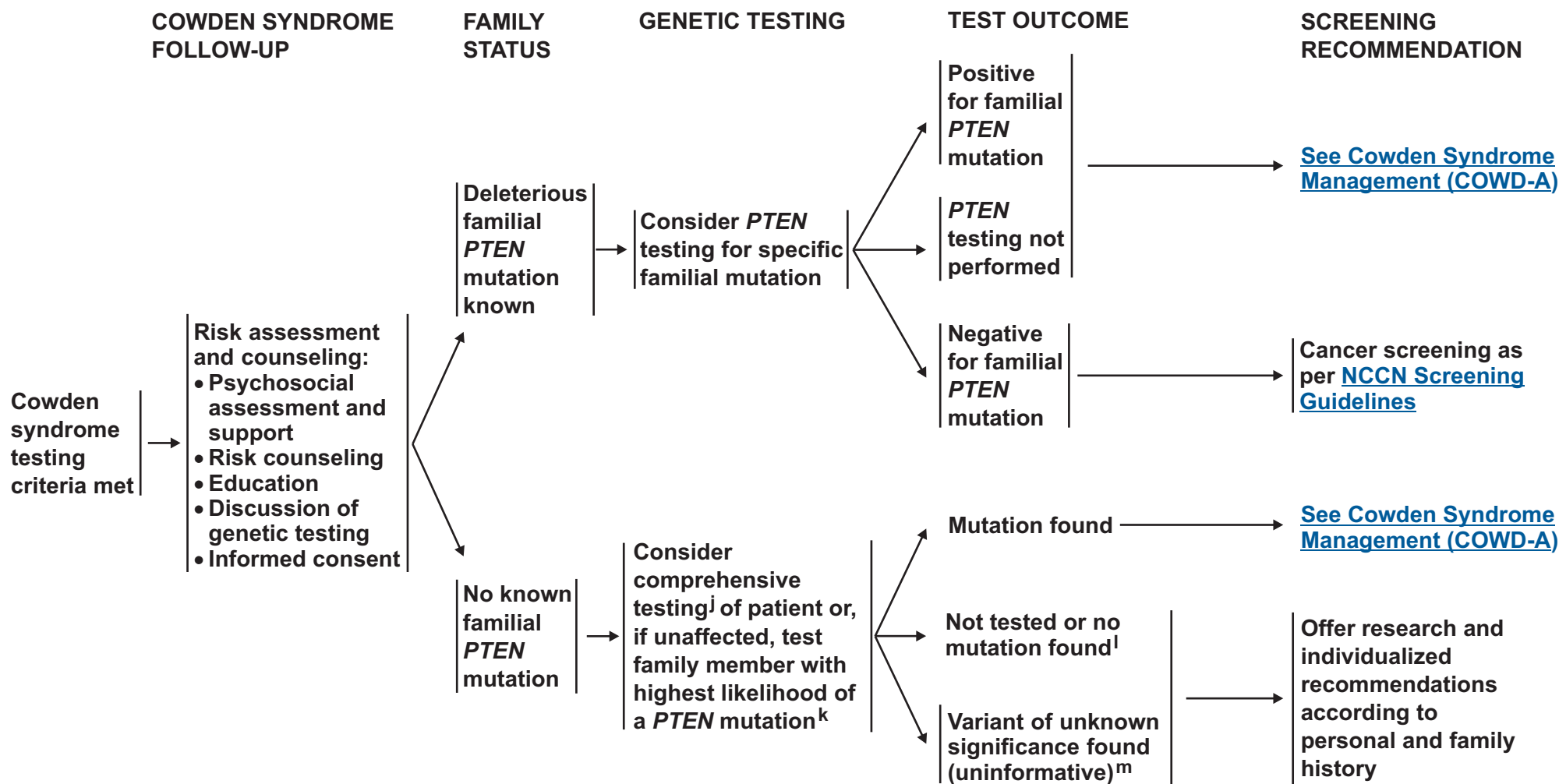
ⁱInsufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

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Cowden Syndrome



^jComprehensive genetic testing should include full sequence analysis, deletion/duplication analyses, and promoter analysis.

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

^lIf no mutation is found, consider other hereditary breast cancer syndromes such as HBOC ([HBOC-1](#)) and/or Li Fraumeni syndrome ([LIFR-1](#)). For additional information on other genetic mutations associated with breast/ovary cancer risk for which genetic testing is clinically available, see [GENE-1](#).

^mTesting family members for a 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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COWDEN SYNDROME MANAGEMENT

WOMEN

- Breast awareness¹ starting at age 18 y.
- Clinical breast exam, every 6-12 mo, starting at age 25 y or 5-10 y before the earliest known breast cancer in the family.
- Annual mammography and breast MRI screening starting at age 30-35 y or individualized based on earliest age of onset in family.^{2,3}
- For endometrial cancer screening,⁴ encourage patient education and prompt response to symptoms and participation in a clinical trial to determine the effectiveness and necessity of screening modalities.
- Discuss risk-reducing mastectomy and hysterectomy⁵ and counsel regarding degree of protection, extent of cancer risk, and reconstruction options.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or hysterectomy.

MEN AND WOMEN

- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to breast and thyroid exam.
- Baseline thyroid ultrasound at age 18 y, and consider annually thereafter.
- Consider colonoscopy, starting at age 35 y, then every 5-10 y or more frequently if patient is symptomatic or polyps found.
- 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.

REPRODUCTIVE OPTIONS

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

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

²The appropriateness of imaging modalities and scheduling is still under study.

³High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance by experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably days 7-15 of menstrual cycle for premenopausal women.

⁴There are limited data regarding the lifetime risk of endometrial cancer in Cowden syndrome. Surveillance screening and surgical intervention should be on an individual basis.

⁵Oophorectomy is not indicated for CS alone but may be indicated for other reasons.

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

ADDITIONAL GENETIC MUTATIONS ASSOCIATED WITH BREAST/OVARIAN CANCER RISK

Syndromes

- Hereditary Diffuse Gastric Cancer Syndrome
 - *CDH1* gene
 - Diffuse gastric cancer – 67%-83% risk
 - Lobular cancer of the breast – 39%-52% risk
- Peutz-Jeghers Syndrome ([See NCCN Guidelines for Colorectal Cancer Screening](#) for more information)
 - *STK11/LKB1* gene
 - Breast cancer – 44%-50% risk
 - Ovarian cancer – 18%-21% risk (ovarian sex cord tumors are the most common)
- Lynch Syndrome ([See NCCN Guidelines for Colorectal Cancer Screening](#) for more information)
 - Mismatch Repair (MMR) genes – *MLH1*, *MSH2*, *MSH6*, *PMS2*
 - *EPCAM* gene deletion
 - Ovarian cancer – 9% risk
 - Breast cancer – conflicting data regarding increased risks

Gene Panels

- New genetic testing panels using next-generation sequencing for hereditary breast, ovarian, and other cancers have recently been introduced.
- These panels are intended for individuals who have tested negative for high penetrance genes (eg, *BRCA1/2*) and for those whose family history is suggestive of more than one syndrome.
- The genetic testing laboratories include somewhat different, but often overlapping, genes. Examples of currently available genes within these panels include:

<i>ATM</i>	<i>MRE11A</i>
<i>BARD1</i>	<i>NBN</i>
<i>BRIP</i>	<i>PALB2</i>
<i>CDH1</i>	<i>PMS2</i>
<i>CHEK1</i>	<i>PTEN</i>
<i>CHEK2</i>	<i>RAD50</i>
<i>MLH1</i>	<i>RAD51B</i>
<i>MSH2</i>	<i>RAD51C</i>
<i>MSH6</i>	<i>RAD51D</i>
<i>MUTYH</i>	<i>STK11</i>
	<i>TP53</i>

- Limitations of these panels include an unknown percentage of variants of unknown significance, uncertainty of level of risk associated with most of these genes, and lack of clear guidelines on risk management of carriers of some of these mutations.
- Because of the complexity and limited data regarding their clinical utility, hereditary multigene cancer panels should only be ordered in consultation with a cancer genetics professional.

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

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



Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/02/2012.

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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Overview

All cancers develop as a result of mutations in certain genes, such as those involved in the regulation of cell growth and/or DNA repair,^{1,2} although not all of these mutations are inherited from a parent. For example, sporadic mutations can occur in somatic/tumor cells only, and de novo mutations can occur for the first time in a germ cell (i.e., 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 (i.e., parents, siblings, and children) and second-degree relatives (i.e., grandparents, aunts or uncles, grandchildren, and nieces or nephews) of affected individuals. These individuals may have an increased susceptibility to cancer as the result of 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 (i.e., 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 (i.e., 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 (e.g., *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 Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast and Ovarian were developed with an acute awareness of the preliminary nature of much of our knowledge regarding the clinical application of the rapidly emerging field of molecular genetics, and with an appreciation for the need for flexibility when applying these guidelines to individual families. Furthermore, it should be emphasized that these guidelines were not developed as a substitute for professional genetic counseling. Rather, they are intended to serve as a resource for healthcare providers to 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 this NCCN 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.⁹ In the U.S., the numbers of new cases and deaths in 2012 due to breast cancer are estimated as 229,060 and 39,920, respectively (estimated figures include both genders).⁹ 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.^{10, 11} 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.^{12, 13} 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.¹⁴ 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%.^{15, 16} Furthermore, germline *CDH1* mutations may be associated with lobular breast cancer in the absence of diffuse gastric cancer.¹⁷

These hereditary syndromes share several features beyond elevation of breast cancer risk. These syndromes arise from germline gene mutations that are not within sex-linked genes; hence, the mutations can be inherited from either parent. The syndromes are associated with breast cancer onset at an early age and development of other types of

cancer, and exhibit an autosomal dominant inheritance pattern (see Table 1). Offspring of an individual with one of these hereditary syndromes have a 50% chance of inheriting the mutation. In addition, individuals with these hereditary syndromes share increased risks 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 (i.e., 2-hit hypothesis).^{18, 19} In addition, the manifestations (i.e., expression) of these hereditary syndromes are often variable in individuals within a single family (e.g., age of onset, tumor site, 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.^{20, 21} 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 the 6174delT mutation in *BRCA2* approximates 1 in 40.^{6, 22} Certain founder mutations have also been identified in other populations.^{20, 23-28} 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 *BRCA1* or *BRCA2* genes.²⁹ 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.³⁰ The *BRCA2* gene, located on chromosome 13, is involved in repair of replication-mediated double-strand breaks.^{31, 32}

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.³³⁻³⁵ Estimates of penetrance range from a 45% to 84% lifetime risk for breast cancer, as well as an increased risk of contralateral breast cancer.³⁶⁻³⁸ In addition, female carriers of these genes have an estimated 11% to 62% lifetime risk for ovarian cancer, depending upon the population studied.³⁶⁻⁴⁰ 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 screening and preventive strategies.

Some histopathologic features have been reported to occur more frequently in breast cancers characterized by a *BRCA1/2* mutation. For example, several studies have shown that *BRCA1* breast cancer is more likely to be characterized as ER-,PR-negative, and HER2-

negative (i.e., “triple negative”).⁴¹⁻⁴⁶ Studies have reported *BRCA1* mutations in 11% to 28% of patients with triple-negative breast cancer.⁴⁶⁻⁵⁰ In addition, it appears that among patients with triple-negative disease, *BRCA* mutation carriers were diagnosed at a younger age compared with non-carriers.^{48, 51} A recent study (N=284) reported a mean age of diagnosis of 40 years (range, 28-57 years) in carriers of *BRCA1* mutations with triple-negative disease.⁴⁷ Moreover, the incidence of *BRCA1* mutations among patients with early-onset (age at diagnosis ≤40 years) triple-negative breast cancer ranged from 11% to 47% in recent studies.^{46, 47}

An increased frequency of other malignancies has been reported in families with mutations in the *BRCA1* or *BRCA2* gene.^{37, 52, 53} Germline *BRCA1* and *BRCA2* mutations have been associated with an increased risk of prostate cancer in numerous reports.^{37, 52-58} In particular, *BRCA2* mutations have been associated with 2- to 5-fold increase in risk of prostate cancer,^{54-56, 58} while increased risks were not observed for *BRCA1* mutation carriers in some studies.⁵⁴⁻⁵⁶ Prostate cancer in patients with *BRCA2* mutations has been associated with a higher histologic grade.^{54, 55} Analyses of data obtained from cancer registries and treatment center databases showed that *BRCA2* mutation carriers with prostate cancer had more aggressive or rapidly progressive disease, and significantly decreased survival compared with patients who were *BRCA1* mutation carriers or non-carriers.⁵⁹⁻⁶¹ In a study of patients with prostate cancer from a population-based cancer registry in Iceland (N=596), patients with *BRCA2* mutations had significantly decreased median survival compared with non-carriers (having wild type *BRCA2*) patients (2 years vs. 12 years; $P<0.001$).⁶¹ Moreover, in a study of patients with prostate cancer using data obtained from cancer center databases (N=301), patients with *BRCA2* mutations had significantly decreased median survival compared with patients with

BRCA1 mutations (4 years vs. 8 years; $P<0.01$).⁵⁹ *BRCA2* mutation carriers have also been reported to have a higher risk of pancreatic cancer and melanoma.^{52, 53, 58, 62, 63} Both *BRCA1* and *BRCA2* mutations have been associated with increased propensity for developing pancreatic cancer.^{58, 63-66} In an analysis of samples taken from patients with familial pancreatic cancer (kindreds in which ≥ 3 family members had pancreatic cancer, at least 2 of which were first-degree relatives), *BRCA2* mutations were detected in 17% of patient samples.⁶⁶ Among the Ashkenazi Jewish population, *BRCA2* mutations have been identified in about 4% of patients with pancreatic cancer.^{62, 67}

Some data related to the risk of cancers in this population at some sites other than the breast/ovary are contradictory.⁶⁸ 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.⁶⁹

Germline mutations in *BRCA1* and *BRCA2* are responsible for 5%-10% of epithelial ovarian cancers (i.e., ovarian cancer developing on the surface of the ovary).⁷⁰ Increased risks of cancers of the fallopian tube and primary peritoneal cancer are also observed in this population. In the setting of an invasive ovarian cancer diagnosis, as many as 15% of unselected individuals will have a germline *BRCA1* or *BRCA2* mutation.^{71, 72} 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.⁷³ Hence, other gene mutations predisposing to ovarian cancer are likely to exist.⁷⁴ Of note, ovarian cancer is a component tumor of Lynch syndrome which is associated with germline mutations in mismatch repair genes.⁷⁵ 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.⁷⁶

It is interesting to note that several recent studies have reported more favorable survival outcomes among *BRCA1/2* mutation carrier patients with ovarian cancer compared with non-carrier patients.⁷⁷⁻⁸¹ In a case-control study of patients with epithelial ovarian cancer ($N=66$), patients with *BRCA1/2* mutations had improved outcomes compared with patients with non-hereditary ovarian cancer, including significantly longer median survival from time of diagnosis (101 months vs. 35 months; $P<0.002$).⁸⁰ In a large case-control study of Jewish patients with epithelial invasive ovarian cancer ($N=779$), patients with *BRCA1/2* mutations had significantly longer median survival compared with non-carrier patients (54 months vs. 38 months; $P=0.002$).⁷⁹ Results from a recent pooled analysis from 26 observational studies that included invasive epithelial ovarian cancer cases from *BRCA1/2* mutation carriers ($n=1213$) and non-carriers ($n=2666$) showed favorable survival outcomes for patients with *BRCA1/2* mutations.⁷⁷ The 5-year survival rate for non-carriers, *BRCA1* carriers and *BRCA2* carriers was 36%, 44%, and 52%, respectively. The survival advantage compared with non-carriers was significant for both the *BRCA1* carriers (hazard ratio=0.78; 95% CI, 0.68-0.89; $P<0.001$) and *BRCA2* mutation carriers (hazard ratio=0.61; 95% CI, 0.50-0.76; $P<0.001$).⁷⁷ Outcomes appeared to be most favorable for *BRCA2* mutation carriers. In an observational study of patients with high-grade serous ovarian cancer ($N=316$), patients with *BRCA2* mutations had significantly favorable survival outcomes (hazard ratio=0.33; 95% CI, 0.16-0.69; $P=0.003$; 5-year rate: 61% vs. 25%) and progression-free survival (hazard ratio=0.40; 95% CI, 0.22-0.74; $P=0.004$; 3-year rate: 44% vs. 16%) compared with non-carrier patients (having wild type *BRCA*).⁸¹

Additionally, *BRCA2* mutations were associated with significantly higher response rates (compared with non-carriers or with *BRCA1* mutation carriers) to primary chemotherapy. In contrast, *BRCA1* mutations were not associated with prognosis or improved chemotherapy response.⁸¹

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.^{70, 82-85} In studies of women with *BRCA1/2* mutations who underwent risk reduction salpingo-oophorectomy (RRSO), occult gynecological carcinomas were identified in 4.5%-9% of cases based on rigorous pathological examinations of the ovaries and fallopian tubes.⁸⁶⁻⁸⁸ Tubal intraepithelial carcinoma (TIC) is thought to represent an early precursor lesion for serous ovarian cancers, and TIC (with or without other lesions) was detected in 5%-8% of cases from patients with *BRCA1/2* mutations who underwent RRSO.^{86, 89, 90} The fimbriae or distal tube was reported to be the predominant site of origin for these early malignancies found in patients with *BRCA1/2* mutations.^{86, 90, 91} Although TIC appeared to present more frequently among *BRCA1/2* mutation carriers compared with non-carriers undergoing RRSO,^{90, 91} TIC has also been documented among patients with serous carcinomas unselected for family history or *BRCA* mutation status.⁹² Because TIC was identified in individuals who underwent surgery for risk reduction (for *BRCA1/2* mutation carriers) or other gynecological indications, the incidence and significance of these early lesions within the general population is unclear. Hence, at the present time, there is no justifiable role for *BRCA* testing for cases based solely on the finding of TIC during pathology evaluation for gynecological indications.

Male carriers of a *BRCA* gene mutation also have a greater risk for cancer susceptibility.⁵³ In one study of 26 high-risk families with at least one case of male breast cancer, 77% demonstrated a *BRCA2* mutation.²⁹ 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.^{93, 94} For males with a *BRCA2* mutation, the risk of breast cancer by age 80 years has been estimated at 6.9%.⁹⁵ 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).⁹⁶

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare hereditary cancer syndrome associated with germline *TP53* gene mutations.¹³ It has been estimated to be involved in only about 1% of hereditary breast cancer cases,⁹⁷ although results from a recent study suggest that germline *TP53* gene mutations may be more common than previously believed.⁹⁸ The tumor suppressor gene, *TP53*, is located on chromosome 17,^{99, 100} and the protein product of the *TP53* gene (i.e., p53) is located in the cell nucleus and binds directly to DNA. It has been called the “guardian of the genome” and plays important roles in controlling the cell cycle and apoptosis.⁹⁹⁻¹⁰¹ 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 Guidelines section on Li-Fraumeni Syndrome Testing Criteria).^{13, 98, 102} Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.¹⁰³

LFS, a highly penetrant cancer syndrome associated with a high lifetime 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.^{13, 98, 101, 104-109} 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.⁹⁸ Interestingly, recent retrospective studies have reported a very high frequency of HER2-positive breast tumors (67%-83% of evaluated breast tumors) among patients with germline *TP53* mutations, which suggest that amplification of HER2 may arise in conjunction with *TP53* mutations.^{110, 111} This association between HER2-positive breast cancer and germline *TP53* mutations warrants further investigation, as such patients may potentially benefit from chemoprevention therapies that incorporate HER2-targeted agents.

Individuals with LFS often present with certain cancers (e.g., soft-tissue sarcomas, brain tumors, and adrenocortical carcinomas) in early childhood,¹⁰⁶ and have an increased risk of developing multiple primary cancers during their lifetimes.¹¹² 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.¹¹³ 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.⁹⁸ It is important to mention that estimations of cancer risks associated with LFS are limited to at least some degree by selection bias since dramatically affected kindreds are more likely to be identified and become the subject of further study.

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

Classic LFS criteria, based on a study by Li and Fraumeni involving 24 LFS kindreds, include the following: 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 Guidelines section on Li-Fraumeni Syndrome Testing Criteria). Classic LFS criteria have been estimated to have a high positive predictive value (estimated at 56%) as well as a high specificity, although the sensitivity is relatively low (estimated at 40%).⁹⁸ Thus, it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.^{109, 114}

Classic LFS criteria make up one set of criteria included in the Guidelines to guide selection of individuals for *TP53* gene mutation testing (see Guidelines section on Li-Fraumeni Syndrome Testing Criteria).

Other groups have broadened the classic LFS criteria to facilitate identification of individuals with LFS,^{104, 115-117} 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.^{98, 104} Uncommonly, individuals with de novo germline *TP53* mutations (no mutation in either biological parent) have been identified.^{98, 105, 118} These cases would not be identified as *TP53* testing candidates based upon classic LFS criteria due to requirement of a family history. This issue is circumvented, in part, by the criteria for *TP53* testing proposed by Chompret and colleagues, which

recommends testing for patients with multiple primary tumors of at least 2 “core” tumor types (i.e., sarcoma, breast cancer, adrenocortical carcinoma, brain tumors) diagnosed at age <36 years or patients with adrenocortical carcinoma diagnosed at any age, regardless of family history (see Guidelines section on Li-Fraumeni Syndrome Testing Criteria).¹¹⁶ The Chompret criteria have an estimated positive predictive value of 20%-35%,^{98, 116} and when incorporated as part of *TP53* testing criteria in conjunction with classic LFS criteria, have been shown to improve the sensitivity to 95% (i.e., the Chompret criteria added to classic LFS criteria detected 95% of patients with *TP53* mutations).⁹⁸ The Chompret criteria are the second set of criteria included in the NCCN Guidelines. Although not part of the original published criteria set forth by Chompret et al., the panel recommends adding lung bronchoalveolar cancer and leukemia as one of the core tumor types (for inclusion in criterion 1 and 2 of the Chompret criteria) and also recommends testing individuals with choroid plexus carcinoma diagnosed at any age and regardless of family history (for inclusion in criterion 3), based upon reports of high incidence of *TP53* mutations found in patients with this rare form of brain tumor.^{98, 105, 119, 120} The above inclusion of lung bronchoalveolar cancer and leukemia as one of the core tumors and recommendation for testing for individuals with choroid plexus carcinoma (i.e., updated Chompret criteria) was recently proposed by Tinat et al,¹²⁰ and is supported by the NCCN Guidelines panel. The panel also supports the broader age cut-offs proposed by Tinat et al, based upon a study in a large number of families, which detected germline *TP53* mutations in affected individuals with later tumor onsets.^{119, 120}

Women with early-onset breast cancer (age of diagnosis < 30 years), with or without family history of core tumor types, are another group for whom *TP53* gene mutation testing may be considered. Several recent

studies have investigated the likelihood of a germline *TP53* mutation in this population.^{98, 119, 121-123} In a study of *TP53* mutations evaluated at a single reference laboratory, Gonzalez et al. found that all women < 30 years of age with breast cancer who had a first- or second-degree relative with at least one of the core cancer types (n=5), had germline *TP53* mutations.⁹⁸ Among women <30 years of age with breast cancer and without a family history, the incidence of *TP53* mutations was 3%-7%.^{98, 122, 123} 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.¹¹⁹ Furthermore, Ginsburg and colleagues found no germline *TP53* mutations in 95 unselected women with early-onset breast cancer who previously tested negative for *BRCA* mutations.¹²¹

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.¹²⁴ 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.^{125, 126} 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 syndrome¹²⁷ (although there is controversy as to whether true Proteus cases have been shown to have a *PTEN* mutation¹²⁸). 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”¹²⁹) gene located on chromosome 10 encodes for a tumor-suppressor protein involved in cell cycle control and cell survival.¹²

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.^{12, 130}

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.^{130, 131} There have been only 2 cases of breast cancer reported in men with Cowden syndrome.¹² 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 syndrome¹³² and the lifetime risk of thyroid cancer (follicular or papillary) has been estimated at 3%-10%.^{12, 133} As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.¹³⁴ Although not well defined, women with Cowden syndrome may have a 5%-10% risk of endometrial cancer,^{12, 135} and an increased risk of uterine fibroids. In addition, skin cancers, renal cell carcinomas, colorectal cancer, 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 (i.e., new cancerous lesions), and these data are also likely to be confounded by selection bias.¹² 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.^{12, 136}

Classic features of the disease include mucocutaneous papillomatous papules, palmoplantar keratoses, and trichilemmomas (i.e., benign tumors derived from the outer root sheath epithelium of a hair follicle).^{12, 137} 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.^{70, 127} The presence of 2 or more trichilemmomas has been reported to be pathognomonic for Cowden syndrome.^{138, 139} However, since most of this evidence is from the older literature, it is possible that the association between these 2 entities is somewhat overestimated.¹² There are reports of individuals with a solitary trichilemmoma who do not have Cowden syndrome.^{138, 139} 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. Indeed, a recent analysis of *PTEN* mutation carriers reported gastrointestinal

polyps in 93% of patients.¹⁴⁰ Most of the polyps are hamartomatous, although ganglioneuromas (i.e., rare, benign peripheral nervous system tumors) have also been reported to occur.^{12, 141} However, early-onset (age <50 years) colorectal cancer has been reported in 13% of patients with *PTEN* mutation-associated Cowden syndrome, suggesting that routine colonoscopy may be warranted in this population.¹⁴⁰

Adult Lhermitte-Duclos disease (LDD) and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome.^{127, 134, 142} A rare, slow growing, benign hamartomatous lesion of the brain, LDD is a dysplastic gangliocytoma of the cerebellum.¹² The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a *PTEN* gene mutation,¹³⁴ although exceptions have been reported.¹⁴³ 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.¹⁴⁴⁻¹⁴⁸ Macrocephaly (defined as head circumference greater than the 97th percentile)¹⁴⁹ 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.¹²

The BRRS variant of PHTS has been characterized by the presence of multiple lipomas, gastrointestinal hamartomatous polyps, macrocephaly, hemangiomas, developmental delay, and in males, pigmented macules on the glans penis,¹⁵⁰ 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.¹⁵¹ 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.¹⁴²

The *PTEN* mutation frequency in individuals meeting International Cowden Consortium criteria for Cowden syndrome has been estimated at about 80%.¹² The International Cowden Consortium criteria have been updated several times since 1996^{12, 127, 152, 153} 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 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 (see Guidelines section on Cowden Syndrome Testing Criteria). 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. 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 represents “major” features associated with Cowden syndrome. The major criteria include the presence of breast cancer, macrocephaly (i.e., megalcephaly),¹⁴⁹ endometrial cancer, non-medullary thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (e.g., one biopsy proven trichilemmoma, multiple palmoplantar keratoses, etc.).

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 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 Guidelines section on Cowden Syndrome Testing Criteria and the Discussion section below 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 (see Guidelines section on Criteria for Further Genetic Risk Evaluation). The first step in this preliminary assessment is a broad and flexible evaluation of the personal and family history of the individual with respect to breast and/or ovarian cancer.^{154, 155} 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.^{156, 157} The younger the age at diagnosis, the more likely it is that a genetic component is present. When assessing a family history for a hereditary pattern, the equal likelihood of paternal or maternal transmission of a gene that predisposes to breast cancer must also be kept in mind.

If an individual or a close family member of that individual meets any one of the criteria presented in the NCCN Guidelines (see Guidelines section on Criteria for Further Genetic Risk Evaluation), that individual may be at increased risk for breast and/or ovarian cancer, and a referral for genetic assessment is recommended. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

For individuals potentially meeting established criteria for one or more of the hereditary cancer syndromes, genetic testing should be considered along with appropriate pre-test counseling. A genetic counselor 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 (e.g., a change in the frequency of, or modalities used for, breast cancer screening).⁵ The panel recommends that these individuals follow recommendations in the NCCN Guidelines for Breast Cancer Screening and Diagnosis.

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.¹⁵⁸ In addition, decision models developed to estimate the likelihood that a *BRCA1/2* mutation is present include BRCAPRO^{159, 160} and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)¹⁵⁹; 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 recent updates to the American Cancer Society (ACS) guidelines on breast screening which incorporates magnetic resonance imaging (MRI).^{161, 162}

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.¹⁶³ 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. Standardized pedigree nomenclature should be used.^{164, 165} 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 is 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 (e.g., hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members.^{5, 166}

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.¹⁶⁷

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.^{168, 169} Pathologic verification of these diagnoses is encouraged. History of salpingo-oophorectomy and potential exposure to carcinogens (e.g., radiation therapy) should also be included in the

patient's assessment. When taking the medical history, the clinician should also be alert to the physical manifestations of Cowden syndrome, especially skin conditions.

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.¹⁷⁰⁻¹⁷³

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 to help them derive personal meaning from cancer genetic information, to 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

Pre-test counseling is an essential element of the genetic counseling process in the event that genetic testing for a gene mutation associated with a hereditary cancer syndrome is under consideration.⁷ The foundation of pre-test 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.¹⁷⁴

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 genetic testing to both parents of an individual who tests positive for one of these gene mutations (i.e., *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 based on the individual's 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.¹⁷⁵ These recommendations were reiterated in the latest 2010 ASCO update on Genetic and Genomic Testing for Cancer Susceptibility with respect to testing individuals for gene mutations known to cause hereditary breast and/or ovarian cancer(s).¹⁷⁶

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

and inconclusive (or variants of unknown significance) test results (see Table 2), as well as the technical limitations of the testing process. A clear distinction is made between the probability of being a mutation carrier and the probability of developing cancer. The probabilistic nature of genetic test results and the potential implications for other family members must also be discussed. Individuals who have received allogeneic hematopoietic stem cell transplantation (HSCT) should not have molecular genetic testing performed on blood samples, as these blood cells would represent donor-derived DNA. In such cases, DNA of the individual being tested should be extracted from a fibroblast culture, if available. If this is not possible, buccal cells may be considered as an alternative source for DNA; however, a study has reported that over time, buccal epithelial cells are replaced by donor-derived cells in allogeneic HSCT recipients.^{177, 178} Therefore, genetic testing using buccal swab samples may be limited given this known risk of donor DNA contamination.

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

For the majority of families in whom mutation status is unknown, it is best to consider testing an affected family member first, especially a family member with early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood for a

positive test result. Unless the affected individual is a member of an ethnic group for which particular founder gene mutations are known, comprehensive genetic testing (i.e., full sequencing of the genes and detection of large gene rearrangements) should be performed.

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

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

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

Another counseling dilemma is posed by the finding of a variant or mutation of unknown significance (see Table 2), a mutation that may actually represent a benign polymorphism unrelated to an increased breast cancer risk or may indicate an increased breast cancer risk. The

individual must be counseled in 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.¹⁷⁹⁻¹⁸² For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the *BRCA1* and *BRCA2* genes that are otherwise not detected by direct sequencing of the *BRCA1/2* genes. Therefore, the NCCN Guidelines panel emphasizes the need for comprehensive testing, which encompasses full *BRCA1/2* sequencing and detection of large gene rearrangements.

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

Detailed in the NCCN Guidelines is a set of 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 (see Guidelines section on Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria). For example, a personal history of female breast cancer diagnosed at age ≤ 45 years, a personal history of triple-negative breast cancer diagnosed at age ≤ 60 years, 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 for individuals for whom hereditary breast/ovarian cancer syndrome testing criteria are met. The NCCN Guidelines panel recommends such testing if the patient is a member of a family with a

known deleterious *BRCA1* or *BRCA2* mutation. Testing is generally not recommended in children under the age of 18 years. Initial testing for the three known founder mutations, in addition to the specific familial mutation, is recommended if the individual meeting testing criteria is of Ashkenazi Jewish descent. Comprehensive genetic testing (i.e., full sequence of *BRCA1/2* and testing for large gene rearrangements) is recommended for those from other ethnic groups who meet testing criteria. 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 Guidelines for Breast Cancer Screening and Diagnosis.

Counseling issues specific for both female and male carriers of a *BRCA1/2* mutation include the increased incidence of pancreatic cancer and melanoma. In addition, the risks to family members of individuals with a known *BRCA1/2* gene mutation (see Discussion sections on Risk Assessment and Genetic Testing) should also be discussed as well as the importance of genetic counseling for these individuals. Counseling issues pertaining specifically to male breast cancer have also been described, and include an increased risk of prostate cancer in male carriers of a *BRCA1/2* mutation.¹⁸³⁻¹⁸⁵

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. An individual with a known deleterious *BRCA1/2* mutation in a close family member who does not undergo gene testing should be followed according to the same screening/management guidelines as a carrier of a *BRCA1/2* mutation. An individual from a family with a known deleterious *BRCA1/2* mutation who tests negative for the familial mutation should be followed according to the recommendations in the NCCN Guidelines for Breast

Cancer Screening and Diagnosis. In situations where an individual (or family member) from a family with no known familial *BRCA1/2* mutations undergoes genetic testing, and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met (see sections on Li-Fraumeni Syndrome Testing Criteria and Cowden Syndrome Testing Criteria).

Screening Recommendations

The emphasis on initiating screening considerably earlier than standard recommendations is a reflection of the early age of onset seen in hereditary breast/ovarian cancer.¹⁸⁶ 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 at age 25 years. The woman should begin having annual mammograms and breast MRI screening (to be performed on day 7-15 of menstrual cycle for premenopausal women) at age 25 years or on an individualized timetable based on the earliest age of cancer onset in family members.^{161, 186-189}

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.¹⁹⁰ Other reasons for the low sensitivity of mammography in women with *BRCA1/2* mutations include an increased likelihood of developing tumors with more benign mammographic characteristics (e.g., less likely to appear as a spiculated mass).¹⁹¹ 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.¹⁶¹

For women 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 30 years or 5-10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family, for the early detection of ovarian cancer (see Guidelines section on HBOC Syndrome Management). 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,^{192, 193} 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.

Men testing positive for a *BRCA1/2* mutation should have a semiannual clinical breast examination, and undergo training in breast self-examination with regular monthly practice starting at age 35 years. Baseline mammography should be considered at age 40 years, 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. For both men and women testing positive for a *BRCA1/2* mutation, 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.^{194, 195} 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.^{196, 197}

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

It is important that the potential psychosocial effects of RRM are addressed, although these effects have not been well studied.¹⁹⁸ 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.¹⁹⁹

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).^{200, 201} Although the risk of ovarian cancer is generally considered to be lower than the risk of breast cancer in a *BRCA1/2* mutation carrier,^{36, 202, 203} 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.²⁰⁴

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.²⁰⁵ In a large prospective study of women who carried deleterious *BRCA1* or *BRCA2* mutations (N=1079), RRSO significantly reduced the risk of *BRCA1*-associated gynecological tumors (including ovarian, fallopian tube or primary peritoneal cancers) by 85% compared with observation, during a 3-year follow-up period (hazard ratio=0.15; 95% CI, 0.04-0.56; *P*=0.005).²⁰⁶ However, a 1%-4.3% residual risk of a primary peritoneal carcinoma has been reported in some studies.^{87, 204, 205, 207-209}

RRSO is also reported to reduce the risk of breast cancer in carriers of a *BRCA1/2* mutation by approximately 50%.^{204, 205, 209, 210} In the case-control international study by Eisen et al., a 56% (odds ratio=0.44; 95% CI, 0.29-0.66; *P*<0.001) and a 43% (odds ratio=0.57; 95% CI, 0.28-1.15; *P*=0.11) breast cancer risk reduction (adjusted for oral contraceptive use and parity) was reported following RRSO in carriers of a *BRCA1* and a *BRCA2* mutation, respectively.²¹⁰ Hazard ratios of 0.47 (95% CI, 0.29-0.77)²⁰⁴ and 0.30 (95% CI, 0.11-0.84; *P*=0.022)²⁰⁸ 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,²⁰⁵ although results of a prospective cohort study suggest that RRSO may be associated with a greater reduction in breast cancer risk for *BRCA2* mutation carriers compared with *BRCA1* mutation carriers.²⁰⁶

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).²¹⁰ 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.²¹⁰ However, results from Rebbeck et al also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.²⁰⁹ Due to the limited data, an optimal age for RRSO is difficult to specify.

The NCCN Guidelines 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.^{88, 89} The protocol published by the College of American Pathologists (2009) can be consulted for details on specimen evaluation.²¹¹

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.²¹² 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.²¹³ However, caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.^{214, 215}

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.²¹⁶ 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 have demonstrated that oral contraceptives reduced the risk of ovarian cancer by 45%-50% in *BRCA1* mutation carriers and by 60% in *BRCA2* mutation carriers^{217, 218}; moreover, risks appeared to decrease with longer duration of oral contraceptive use.²¹⁸ In a recent meta-analysis conducted in a large number of *BRCA1/2* mutation carriers with (n=1503) and without (n=6315) ovarian cancer, use of oral contraceptives significantly reduced the risk of ovarian cancer by approximately 50% for both the *BRCA1* mutation carriers (summary relative risk [SRR]=0.51; 95% CI, 0.40-0.65) and *BRCA2* mutation carriers (SRR=0.52; 95% CI, 0.31-0.87).²¹⁹

Studies on the effect of oral contraceptive use on breast cancer risk among *BRCA1/2* mutation carriers have reported conflicting data. In

one case-control study, use of oral contraceptives was associated with a modest but statistically significant increase in breast cancer risk among *BRCA1* mutation carriers (odds ratio=1.20; 95% CI, 1.02-1.40), but not among *BRCA2* mutation carriers.²²⁰ Among *BRCA1* mutation carriers, breast cancer risks with oral contraceptives were significantly associated with ≥5 years of oral contraceptive use (odds ratio=1.33; 95% CI, 1.11-1.60), breast cancer diagnosed before age 40 (odds ratio=1.38; 95% CI, 1.11-1.72), and use of oral contraceptives before 1975 (odds ratio=1.42; 95% CI, 1.17-1.75).²²⁰ In another case-control study, oral contraceptive used for at least 1 year was not significantly associated with breast cancer risks in either *BRCA1* or *BRCA2* mutation carriers.²²¹ However, among *BRCA2* mutation carriers, use of oral contraceptives for at least 5 years was associated with a significantly increased risk for breast cancer (odds ratio=2.06; 95% CI, 1.08-3.94); results were similar when only the cases with oral contraceptives use on or after 1975 were considered.²²¹ Other case-control studies have reported no significant associations with oral contraceptives use (especially with the use of low-dose formulations after 1975) and risks for breast cancer in *BRCA1/2* mutation carriers.^{222, 223} In fact, in one study, the use of low-dose oral contraceptives for at least 1 year was associated with significantly decreased risks for breast cancer among *BRCA1* mutation carriers (odds ratio=0.22; 95% CI, 0.10-0.49; $P<0.001$), though not for *BRCA2* mutation carriers.²²³ Differences in the study design employed by these case-control studies make it difficult to compare outcomes between studies, and likely accounts for the conflicting results. The study design might have differed with regards to factors such as the criteria for defining the ‘control’ population for the study (e.g., non-*BRCA1/2* mutation carriers vs mutation carriers without a cancer diagnosis), consideration of family history of breast or ovarian cancer, baseline demographics of the population studied (e.g., nationality, ethnicity, geographic region, age groups), age of onset of

breast cancer, and formulations or duration of oral contraceptives used. In a meta-analysis conducted in a large number of *BRCA1/2* mutation carriers with (n=2855) and without (n=2954) breast cancer, use of oral contraceptives was not found to be significantly associated with breast cancer risks in either the *BRCA1* mutation carriers (SRR=1.09; 95% CI, 0.77-1.54) or the *BRCA2* mutation carriers (SRR=1.15; 95% CI, 0.61-2.18).²¹⁹

Reproductive Options

The outcomes of genetic testing can have profound impact on family planning decisions for individuals of reproductive age who are found to be carriers of *BRCA1/2* mutations. For example, in cases where both partners carry a *BRCA2* mutation, there may be a high risk for the offspring to develop a rare Fanconi anemia/brain tumor phenotype (recessive disorder).¹⁸⁴ Counseling for reproductive options such as prenatal diagnosis, preimplantation genetic diagnosis (PGD) and assisted reproduction may therefore be warranted for couples expressing concern over the *BRCA* mutation carrier status of their future offspring. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options.

Prenatal diagnosis involves postimplantation genetic analysis of an early embryo, utilizing chorionic villi or amniotic fluid cell samples; genetic testing is typically conducted between week 12 and week 16 of gestation, and testing results may potentially lead to a couple’s decision to terminate pregnancy.^{185, 224} During the past 2 decades, PGD has emerged as an alternative method of genetic testing in early embryos. PGD involves the testing of 1 or 2 cells from embryos in very early stages of development (i.e., 6 to 8 cells) after in vitro fertilization (IVF). This procedure allows for the selection of unaffected embryos to be transferred to the uterus,^{185, 224} and may, therefore, offer the advantage

of avoiding potential termination of pregnancy. However, procedures such as PGD are not without limitations as it may still require a confirmatory prenatal diagnosis depending upon a couple's medical needs or requests. Moreover, the PGD process requires the use of IVF regardless of the fertility status of the couple (i.e., also applies to couples without infertility issues), and IVF may not always lead to a successful pregnancy. Lastly, the technology or expertise may not be readily available in a couple's geographical location. Various factors, both medical and personal, must be weighed in the decision to utilize prenatal diagnosis or PGD. Medical considerations may include factors such as the age of onset of the hereditary cancer, penetrance, severity or associated morbidity and mortality of the cancer, and availability of effective cancer risk reduction methods or effective treatments.^{185, 224} Although the use of prenatal diagnosis or PGD is relatively well established for severe hereditary disorders with very high penetrance, their use in conditions associated with lower penetrance (e.g., hereditary breast or ovarian cancer syndrome) remains somewhat controversial from both an ethical and regulatory standpoint. Personal considerations for the decision to utilize prenatal diagnosis or PGD may include individual ethical beliefs, value systems, cultural and religious beliefs, as well as social and economic factors. Based on results from surveys administered to women at high risk for hereditary breast or ovarian cancer, 50%-75% of respondents felt that PGD was an acceptable option for high-risk individuals,^{225, 226} yet only about 14%-33% would consider undergoing PGD themselves.^{225, 227} Importantly, the surveys suggested that the majority of high-risk women have little or no knowledge of PGD,^{226, 228} highlighting the need for better awareness and education regarding potential reproductive options. Successful births have been reported with the use of PGD and IVF in *BRCA1/2* mutation carriers,^{229, 230} but data in the published literature are still very limited. In addition, data pertaining to long-term safety or outcomes of

PDG and assisted reproduction in *BRCA* mutation carriers are not yet available.

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

The approach to families with other hereditary breast cancer syndromes, such as LFS, reflects that of hereditary breast/ovarian cancer in many ways. However, there are some syndrome-specific differences with regard to assessment and management. In the case of LFS, there are multiple associated cancers, both pediatric and adult, that should be reflected in the expanded pedigree (see Guidelines section on Li-Fraumeni Syndrome Testing Criteria). 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.^{98, 112} 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. This recommendation is category 2A for adults and 2B for children. The NCCN Guidelines 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. The NCCN Guidelines panel recommends comprehensive testing, which should include full sequencing and analysis of gene deletion/duplication. In the absence of additional family history, early breast cancer alone is associated with a low likelihood of mutation identification. 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 Guidelines section on Li-Fraumeni Syndrome Management). Individuals not meeting criteria for either classic LFS or LFL syndrome should be followed according to their personal and family history. In situations where an individual (or family member) from a family with no known familial *TP53* mutation undergoes genetic testing, and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met (see sections on Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria and Cowden Syndrome Testing Criteria).

Management of LFS should address the limitations of screening for the many cancers associated with this syndrome. For those at risk for breast cancer, training and education in breast self-examination should start at age 18 years, with the patient performing regular self-examination on a monthly basis. For members of families with LFS, it is recommended that breast cancer surveillance by clinical breast examination, every 6 to 12 months, begin between the ages of 20 and 25 years (or 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 breast MRI screening should begin at ages 20 to 25 years or be individualized, based on earliest age of onset in the family. For relatively young patients (age 20 to 30 years), only an annual breast MRI screening may be warranted based on the physician's discretion. 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 Discussion 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 (Guidelines section on Li-Fraumeni Syndrome Management). 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 whole-body MRI, abdominal ultrasound and brain MRI should also be discussed if such trials are available. Colonoscopy should be considered every 2 to 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. For couples expressing the desire that their offspring not carry a familial *TP53* mutation, options for prenatal diagnosis should be discussed (for discussion on known risks, limitations, and benefits of such technologies, see section above on Reproductive Options under Risk Assessment, Counseling, and Management: Hereditary Breast and/or Ovarian Cancer Syndrome).

A recent prospective observational study incorporated a clinical surveillance protocol for asymptomatic *TP53* mutation carriers from eight families affected by LFS.²³¹ In this study, 18 of the 33 asymptomatic mutation carriers agreed to undergo surveillance while the remainder of the carriers did not. The surveillance protocol included both biochemical methods and imaging techniques, such as annual brain MRI for brain tumor surveillance (both children and adults); annual rapid total-body MRI (both children and adults) and ultrasound of

abdomen and pelvis every 6 months (for adults only) for soft tissue/bone sarcoma surveillance; colonoscopy every 2 years beginning at age 40 years (or 10 years before earliest known colon cancer in the family); ultrasound of abdomen and pelvis every 3-4 months, complete urinalysis every 3-4 months, blood test every 4 months for adrenocortical carcinoma surveillance (children only); and complete blood counts and blood tests every 4 months for leukemia/lymphoma surveillance (both children and adults); for surveillance of breast cancers, the protocol was similar to the NCCN Guidelines for LFS management.²³¹ Using this surveillance protocol, asymptomatic tumors were detected in 7 of the patients; after a median follow-up time of 24 months, all 7 of these carriers were alive. Ten individuals in the non-surveillance group developed high-grade, advanced stage tumors; only 2 of these individuals were alive at the end of follow up. The 3-year overall survival rate was significantly higher for the surveillance group compared with the non-surveillance group (100% vs. 21%; $P=0.016$).²³¹ Although this was a small study in a limited number of patients, the clinical surveillance protocol employed was feasible and detected asymptomatic tumors in about 40% of individuals with *TP53* mutations. The protocol may represent an emerging option for surveillance/management of at-risk individuals from families with LFS; further evaluation of this protocol is warranted.

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 (see Guidelines section on Cowden Syndrome Testing Criteria). The NCCN Guidelines 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 (see Guidelines section on Cowden Syndrome Testing Criteria and Discussion section on Cowden Syndrome). These criteria are recommended to assess the need for further risk assessment and genetic testing, but are not intended to serve as clinical diagnostic criteria. Following risk assessment and counseling, genetic testing should be considered in individuals for whom testing criteria are met. The NCCN Guidelines panel recommends comprehensive testing, which should include full sequencing, gene deletion/duplication analysis, and promoter analysis. Unlike the “pathognomonic” criteria, none of the individual major or minor criteria are considered by the NCCN Guidelines 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” (e.g., 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 Guidelines section on Cowden Syndrome Management). In situations where an individual (or family member) from a family with no known familial *PTEN* mutation undergoes genetic testing, and no mutation is found, testing for other hereditary breast syndromes should be considered if testing criteria are met (see sections on Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria and Li-Fraumeni Syndrome Testing Criteria).

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. In addition, colonoscopy should be considered starting at age 35 years, performed every 5 to 10 years or more frequently in cases where the patient is symptomatic or polyps are found. 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 Discussion section on Bilateral Total Mastectomy). 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. For couples expressing the desire that their offspring not carry a familial *PTEN* mutation, options for prenatal diagnosis should be discussed (for discussion on known risks, limitations, and benefits of such technologies, see section above on Reproductive Options under Risk Assessment, Counseling, and Management: Hereditary Breast and/or Ovarian Cancer Syndrome).

Table 1. Glossary of relevant genetic terms (from the National Cancer Institute)

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.



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Table 2. Genetic test results to determine the presence of a cancer-predisposing gene

Result	Description
<i>True-positive</i>	The person is a carrier of an alteration in a known cancer-predisposing gene.
<i>True-negative</i>	The person is not a carrier of a known cancer-predisposing gene that has been positively identified in another family member.
<i>Indeterminate (Uninformative)</i>	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.
<i>Inconclusive (Variants of unknown significance)</i>	The person is a carrier of an alteration in a gene that currently has no known significance.

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**Discussion
update in
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