

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

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

Version 1.2017 — September 19, 2016

**NCCN.org**

**Continue**



# NCCN Guidelines Version 1.2017 Panel Members

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

\* Mary B. Daly, MD, PhD/Chair †  
Fox Chase Cancer Center

\* Robert Pilarski, MS, CGC/Vice-chair Δ  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

Michael Berry, MD ¶  
St. Jude Children's Research Hospital/  
The University of Tennessee  
Health Science Center

Sandra S. Buys, MD ‡ †  
Huntsman Cancer Institute  
at the University of Utah

Meagan Farmer, MS, CGC Δ  
University of Alabama at Birmingham  
Comprehensive Cancer Center

Susan Friedman, DVM ¥  
FORCE: Facing Our Risk of Cancer Empowered

Judy E. Garber, MD, MPH †  
Dana-Farber/Brigham and  
Women's Cancer Center

Noah D. Kauff, MD Δ Ω  
Duke Cancer Institute

Seema Khan, MD ¶  
Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University

Catherine Klein, MD † †  
University of Colorado Cancer Center

Wendy Kohlmann, MS, CGC Δ  
Huntsman Cancer Institute  
at the University of Utah

Allison Kurian, MD, MSc † † Δ  
Stanford Cancer Institute

Jennifer K. Litton, MD †  
The University of Texas  
MD Anderson Cancer Center

Lisa Madlensky, PhD, CGC Δ  
UC San Diego Moores Cancer Center

Sofia D. Merajver, MD, PhD ‡ †  
University of Michigan  
Comprehensive Cancer Center

Kenneth Offit, MD † † Δ  
Memorial Sloan Kettering Cancer Center

Tuya Pal, MD Δ  
Moffitt Cancer Center

Gwen Reiser, MS, CGC Δ  
Fred & Pamela Buffett Cancer Center

Kristen Mahoney Shannon, MS, CGC Δ  
Massachusetts General Hospital Cancer Center

Elizabeth Swisher, MD Ω  
University of Washington Medical Center/  
Seattle Cancer Care Alliance

Shaveta Vinayak, MD † †  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer Center and  
Cleveland Clinic Taussig Cancer Institute

Nicoleta C. Voian, MD, MPH Δ &  
Roswell Park Cancer Institute

Jeffrey N. Weitzel, MD † ‡ Δ  
City of Hope Comprehensive Cancer Center

Myra J. Wick, MD, PhD Ω Δ  
Mayo Clinic Cancer Center

Georgia L. Wiesner, MD, MS † Δ  
Vanderbilt-Ingram Cancer Center

**NCCN**  
Susan Darlow, PhD  
Mary Dwyer, MS

**Continue**

† Medical oncology  
Δ Cancer/Medical genetics  
† Internal medicine  
‡ Hematology/Hematology oncology  
Ω Gynecologic oncology/Gynecology  
¶ Breast surgical oncology  
& Public health and preventive medicine  
¥ Patient advocacy  
\*Discussion Writing Committee Member



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

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

### [BRCA-Related Breast and/or Ovarian Cancer Syndrome \(BRCA-1\) BRCA Mutation-Positive Management \(BRCA-A\)](#)

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

### [Cowden Syndrome/PTEN Hamartoma Tumor Syndrome \(COWD-1\) Cowden Syndrome/PHTS Management \(COWD-A\)](#)

### [Multi-Gene Testing \(GENE-1\)](#)

**Clinical Trials:** NCCN believes that the best management for any patient with cancer 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](http://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](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2016.

Updates in Version 1.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 2.2016 include:

### General

- “With contrast” was added to imaging as appropriate throughout the Guidelines.
- Page was removed, “Example of Additional Genetic Mutations Associated with Breast/Ovarian Cancer Risk.”

### Breast and Ovarian Cancer Genetic Assessment

#### BR/OV-1

- Criteria for further genetic risk evaluation
  - ▶ First column, 2nd bullet, “An individual with a breast cancer diagnosis meeting any of the following”
    - ◊ 4th sub-bullet for breast cancer at any age, an additional criterion was added, “Pancreatic cancer at any age.”
- After the criteria, the statement for referral to a genetics professional was revised, “Consider referral to cancer genetics professional **recommended**.”

#### BR/OV-2

- Detailed family history
  - ▶ 4th bullet was modified, “Medical record documentation as needed, particularly *prior genetic testing results for patient and their family members* and pathology reports of primary cancers.”
- Focused physical exam
  - ▶ “Breast/ovarian” was removed.

#### BR/OV-A 1 of 2

- Post-test counseling includes discussions of:
  - ▶ 2nd sub-bullet was added, “Interpretation of results in context of personal and family history of cancer.”
- Genetic testing considerations
  - ▶ 3rd bullet was modified, “Patients 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 *until other technologies are available*.”
  - ▶ 5th bullet was revised from “Genetic testing for adult onset diseases (eg, BRCA1/2) in children <18 y is generally not recommended” to “In children <18 y, genetic testing is generally not recommended when results would not impact medical management.”

#### BR/OV-A 2 of 2

- Genetic testing approach
  - ▶ 4th bullet, 2nd sentence was added, “Consider a referral to research studies that aim to define the functional impact of variants such as variant reclassification programs through clinical labs or registries.”
- Reproductive options
  - ▶ 2nd bullet was revised, “BRCA2 gene mutations may be associated with the rare autosomal recessive condition, Fanconi anemia” to “Biallelic mutations in some genes, such as BRCA2 and certain other genes included on gene panels, may be associated with rare autosomal recessive conditions.” (Also for BRCA-A 2 of 2)
- References
  - ▶ Reference 1 was updated, “Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol 2015;33:3660-3667.”
  - ▶ Reference 7 was added, “Offit K, Levran O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548-1551.”

### BRCA-Related Breast and/or Ovarian Cancer Syndrome

#### BRCA-1

- BRCA1/2 Testing Criteria
  - ▶ 2nd bullet, 4th sub-bullet, Diagnosed at any age with:
    - ◊ The following bullet was added, “≥2 close blood relatives with breast cancer, pancreatic cancer or prostate cancer (Gleason score ≥7) at any age”
    - ◊ The following bullets were removed, “≥2 close blood relatives with breast cancer at any age” and “≥2 close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age”
  - ▶ 8th bullet was added, “BRCA1/2 mutation detected by tumor profiling in the absence of germline mutation analysis”

[Continued](#)

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

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

Updates in Version 1.2017 of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian from Version 2.2016 include:

### BRCA-Related Breast and/or Ovarian Cancer Syndrome (continued)

#### BRCA-A 1 of 2

- BRCA Mutation-Positive Management for Women
  - ▶ 4th bullet, 1st sub-bullet was revised, “Counseling ~~may~~ *should* include a discussion regarding degree of protection, reconstruction options, and risks.”
  - ▶ 5th bullet,
    - ◊ 1st sub-bullet was revised, “...management of menopausal symptoms, possible short-term hormone replacement therapy ~~to a recommended maximum age of natural menopause~~, and related medical issues.”
    - ◊ 2nd sub-bullet was revised, “...In addition, in premenopausal women, oophorectomy *likely* reduces the risk of developing breast cancer ~~by up to 50% depending upon age of procedure but the magnitude is uncertain and may be gene-specific.~~”
  - ▶ 7th bullet was revised, “For those patients who have not elected RRSO, ~~while there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening~~; transvaginal ultrasound for ovarian cancer...”
- Footnotes
  - ▶ Footnote 4 was added, “Lehman CD, et al. Screening MRI in women with a personal history of breast cancer. J Natl Cancer Inst 2016;108.”
  - ▶ Footnote 5 was revised, “...the ability to perform biopsy under MRI guidance, *radiologists experienced in breast MRI*, and...”

#### BRCA-A 2 of 2

- BRCA Mutation-Positive Management for Men
  - ▶ 3rd bullet regarding prostate cancer was revised, “Starting at age ~~40~~ 45 y: (See *Guidelines for Prostate Early Detection*)”
- Footnote “8” was revised by adding, “See International Cancer of the Pancreas Screening Consortium recommendations.”

### Li-Fraumeni Syndrome

#### LIFR-1

- “LFS testing criteria not met” was clarified as, “If LFS testing criteria not met, consider testing for other hereditary syndromes, if appropriate.”
- Footnote “f” was added, “Leukemia remains a controversial component of LFS, particularly hypodiploid leukemia.”

### Li-Fraumeni Syndrome (continued)

#### LIFR-2

- Footnote i was revised by adding, “and/or constitutional mismatch repair deficiency (CMMRD).”

#### LIFR-A 1 of 2

- Other cancer risks
  - ▶ 7th bullet was revised, “Perform annual whole body MRI (*or equivalent*) (*category 2B*), *preferably in context of a longitudinal study (rapid non-contrast exams per ACRIN model).*”

### Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

#### COWD-1

- Testing criteria was reorganized:
  - ▶ 2nd bullet, “Individual with a personal history Bannayan-Riley-Ruvalcaba syndrome (BRRS)” was moved from under the 4th bullet to be its own criteria.
  - ▶ 4th bullet was clarified by adding, “Individual *not meeting clinical diagnostic criteria* for CS/PH with a personal history of:”
- “CS/PHTS testing criteria not met” was clarified as, “If CS/PHTS testing criteria not met, consider testing for other hereditary syndromes, if appropriate.”

### Multi-Gene Testing

#### GENE-1

- 3rd bullet was revised, “There ~~is also~~ *may be* a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains ~~strongly~~ suggestive of an inherited susceptibility.”
- 8th bullet was revised, “Mutations in many breast cancer susceptibility genes involved in DNA repair may be associated with ~~the~~ rare autosomal recessive conditions, *Fanconi anemia*.”

#### GENE-2, GENE-3 and GENE-4

- The table for “Breast and Ovarian Management Based on Genetic Test Results” has been extensively revised.

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

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

# NCCN Guidelines Version 1.2017

## Breast and/or Ovarian Cancer Genetic Assessment

### CRITERIA FOR FURTHER GENETIC RISK EVALUATION<sup>a</sup>

- An individual with an ovarian<sup>e</sup> cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer<sup>b</sup>
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries<sup>c</sup> in a single individual
  - Breast cancer at any age, and
    - ◊ ≥1 close blood relative<sup>d</sup> with breast cancer ≤50 y, or
    - ◊ ≥1 close blood relative<sup>d</sup> with invasive ovarian<sup>e</sup> cancer at any age, or
    - ◊ ≥2 close blood relatives<sup>d</sup> with breast cancer and/or pancreatic cancer at any age, or
    - ◊ Pancreatic cancer at any age, or
    - ◊ From a population at increased risk<sup>f</sup>
  - Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
- An individual with a personal and/or family history of three or more of the following (especially if early onset<sup>b</sup> and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer<sup>l</sup>, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations<sup>g,h</sup> and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract<sup>h</sup>
- An individual with no personal history of cancer but with
  - A close relative with any of the following:<sup>d,f</sup>
    - ◊ A known mutation in a cancer susceptibility gene within the family
    - ◊ ≥2 breast cancer primaries in a single individual
    - ◊ ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - ◊ Ovarian<sup>e</sup> cancer
    - ◊ Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset<sup>b</sup> and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer<sup>l</sup>, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations<sup>g,h</sup> and/or macrocephaly, hamartomatous polyps of GI tract<sup>h</sup>

Consider referral to cancer genetics professional<sup>j</sup>

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

<sup>a</sup>The 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.

<sup>b</sup>Clinically use age ≤50 y because studies define early onset as either ≤40 or ≤50 y.

<sup>c</sup>Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either diagnosed synchronously or asynchronously.

<sup>d</sup>Close blood relatives include first-, second-, and third-degree relatives. ([See BR/OV-B](#))

<sup>e</sup>Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome ([See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#)). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

<sup>f</sup>For populations at increased risk due to founder mutations, requirements for inclusion may be modified.

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

<sup>h</sup>For 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 Genetic/Familial High-Risk Assessment: Colorectal](#)—Peutz-Jeghers syndrome. Melanoma has been reported in some *BRCA*-related families.

<sup>i</sup>For lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.

<sup>j</sup>For further details regarding the nuances of genetic counseling and testing, [see BR/OV-A](#).

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

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



### 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, particularly around individuals with a diagnosis of cancer, to include a three-generational pedigree ([See BR/OV-B](#))
- Types of cancer, bilaterality, age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation as needed, particularly prior genetic testing results for patient and their family members and pathology reports of primary cancers

#### Detailed medical and surgical history:

- Any personal cancer history (eg, age, histology, laterality)
- Carcinogen exposure (eg, history of radiation therapy)
- Reproductive history
- Hormone or oral contraceptive use
- Previous breast biopsies and pathology results
- History of salpingo-oophorectomy

#### Focused physical exam (conducted by qualified clinician):

- Cowden syndrome/PTEN Hamartoma Tumor Syndrome (PHTS) specific:
  - Dermatologic,<sup>k</sup> including oral mucosa
  - Head circumference
  - Thyroid (enlarged or nodular on palpation)

### GENE TESTING<sup>l</sup>

See Targeted Testing Criteria for  
[BRCA-Related Breast/Ovarian Cancer Syndrome \(BRCA-1\)](#)  
[Li-Fraumeni Syndrome \(LIFR-1\)](#)  
[Cowden Syndrome/PHTS \(COWD-1\)](#)

[See Multi-Gene Testing \(GENE-1\)](#)

<sup>k</sup>For Cowden syndrome dermatologic manifestations, [see COWD-1](#) and for PJS dermatologic manifestations, [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

<sup>l</sup>In some cases, multi-gene testing may be a preferable way to begin testing over the single-gene testing process.

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

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

### PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Cancer risk assessment and genetic counseling is highly recommended when genetic testing is offered (ie, pre-test counseling) and after results are disclosed (ie, post-test counseling).<sup>1-5</sup> 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 the counseling of patients.

<ul style="list-style-type: none"> <li>• Pre-test counseling includes: <ul style="list-style-type: none"> <li>▶ Collection of a comprehensive family history <ul style="list-style-type: none"> <li>◊ Note that when assessing family history, close blood relatives include first-, second-, and third-degree relatives on each side of the family (<a href="#">See BR/OV-B</a>)</li> </ul> </li> <li>▶ Evaluation of a patient's cancer risk</li> <li>▶ Generating a differential diagnosis and educating the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity</li> <li>▶ Preparing the patient for possible outcomes of testing including positive, negative, and uncertain findings and obtaining informed consent</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Post-test counseling includes discussions of: <ul style="list-style-type: none"> <li>▶ Results along with their significance and impact and recommended medical management options</li> <li>▶ Interpretation of results in context of personal and family history of cancer</li> <li>▶ Informing and testing at-risk family members</li> <li>▶ Available resources such as disease-specific support groups and research studies</li> </ul> </li> </ul>
---	---

### Genetic Testing Considerations

- Testing should be considered in appropriate high-risk individuals where it will impact the medical management of the tested individual and/or their at-risk family members. It should be performed in a setting in which it can be adequately interpreted.<sup>1</sup>
- The probability of mutation detection associated with these criteria will vary based on family structure. Individuals with unknown or limited family history/structure, such as fewer than 2 female first- or second-degree relatives having lived beyond age 45 in either lineage, may have an underestimated probability of familial mutation detection. The estimated likelihood of mutation detection may be very low in families with a large number of unaffected female relatives.
- Patients 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 until other technologies are available. 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.
- Comprehensive genetic testing includes full sequencing and testing for large genomic rearrangements.
- In children <18 y, genetic testing is generally not recommended when results would not impact medical management.<sup>6</sup>

[Continued on next page](#)

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

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





### PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

#### Genetic Testing Approach

- If more than one family member is affected with cancers highly associated with a particular inherited cancer susceptibility syndrome, consider testing first a family member with youngest age at diagnosis, bilateral disease, multiple primary cancers, or other cancers associated with the syndrome, or most closely related to the proband/patient. If there are no living family members with cancer that is a cardinal feature of the syndrome in question, consider testing first- or second-degree family members affected with other cancers thought to be related to the gene in question (eg, prostate, pancreas, melanoma with *BRCA1/2*).
- Testing for unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.
- If no mutation is found, consider other hereditary cancer syndromes. For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see [GENE-1](#).
- Testing family members for a variant of unknown significance should not be used for clinical purposes. Consider a referral to research studies that aim to define the functional impact of variants such as variant reclassification programs through clinical labs or registries.

#### 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.
- Biallelic mutations in some genes, such as *BRCA2* and certain other genes included on gene panels, may be associated with rare autosomal recessive conditions. Thus, for these types of genes, consideration would be given to carrier testing the partner for mutations in the same gene if it would inform reproductive decision-making and/or risk assessment and management.<sup>7</sup>

<sup>1</sup>Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*. 2015;33:3660-3667.

<sup>2</sup>Berliner JL, Fay AM, Cummings SA, Burnett B, Tillmanns T. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast and ovarian cancer. *J Genet Couns* 2013;22:155-163.

<sup>3</sup>American College of Obstetricians and Gynecologists; ACOG Committee on Practice Bulletins--Gynecology; ACOG Committee on Genetics; Society of Gynecologic Oncologists. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009;113:957-966.

<sup>4</sup>Lancaster JM, Powell CB, Chen LM, Richardson DL; SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2015;136:3-7.

<sup>5</sup>Weitzel JN, Blazer KR, Macdonald DJ, Culver JO, Offit K. Genetics, genomics, and cancer risk assessment: State of the art and future directions in the era of personalized medicine. *CA Cancer J Clin* 2011;61:327-359.

<sup>6</sup>Committee on Bioethics; Committee on Genetics, and American College of Medical Genetics and; Genomic Social; Ethical; Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 2013;131:620-622.

<sup>7</sup>Offit K, Levran O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. *J Natl Cancer Inst* 2003;95:1548-1551.

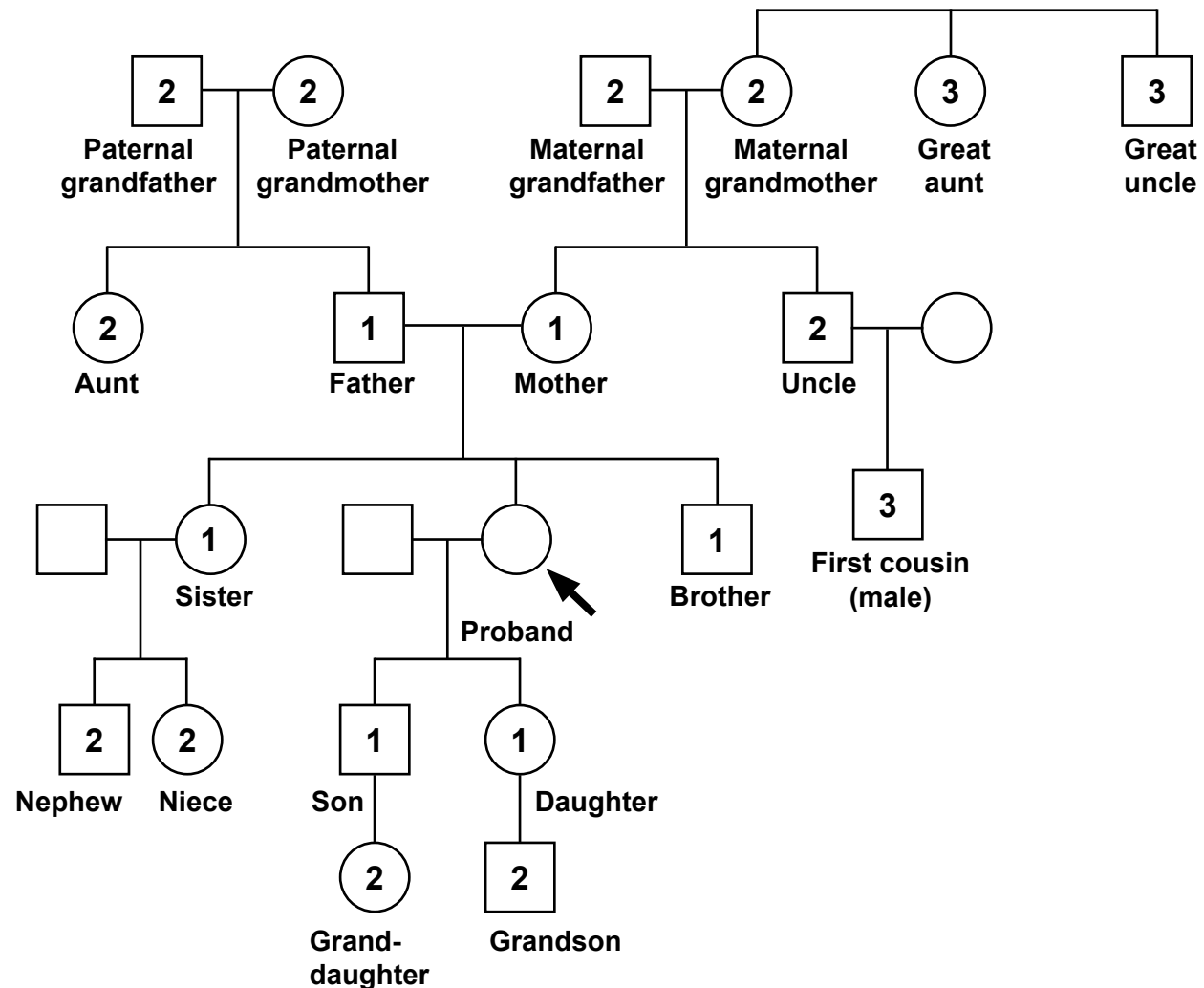
**Note:** All recommendations are category 2A unless otherwise indicated.

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

# NCCN Guidelines Version 1.2017

## Breast and/or Ovarian Cancer Genetic Assessment

### PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND<sup>a</sup>



<sup>a</sup>First-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.

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

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

# NCCN Guidelines Version 1.2017

## BRCA-Related Breast and/or Ovarian Cancer Syndrome

### BRCA1/2 TESTING CRITERIA<sup>a,b</sup>

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of an individual without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing.

- Individual from a family with a known deleterious *BRCA1/BRCA2* gene mutation
- Personal history of breast cancer<sup>b</sup> + one or more of the following:
  - ▶ Diagnosed ≤45 y
  - ▶ Diagnosed ≤50 y with:
    - ◊ An additional breast cancer primary<sup>c</sup>
    - ◊ ≥1 close blood relative<sup>d</sup> with breast cancer at any age
    - ◊ ≥1 close relative with pancreatic cancer
    - ◊ ≥1 relative with prostate cancer (Gleason score ≥7)
    - ◊ An unknown or limited family history<sup>a</sup>
  - ▶ Diagnosed ≤60 y with:
    - ◊ Triple negative breast cancer
  - ▶ Diagnosed at any age with:
    - ◊ ≥2 close blood relatives with breast cancer, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
    - ◊ ≥1 close blood relative<sup>d</sup> with breast cancer diagnosed ≤50 y
    - ◊ ≥1 close blood relative<sup>d</sup> with ovarian<sup>e</sup> carcinoma
    - ◊ A close male blood relative<sup>d</sup> with breast cancer
    - ◊ For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required<sup>f</sup>
- Personal history of ovarian<sup>e</sup> carcinoma
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative<sup>d</sup> with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative<sup>d</sup> with ovarian carcinoma at any age or breast cancer ≤50 y or two relatives with breast, pancreatic cancer, or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer and Ashkenazi Jewish ancestry
- *BRCA1/2* mutation detected by tumor profiling in the absence of germline mutation analysis
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - ▶ First- or second-degree blood<sup>d</sup> relative meeting any of the above criteria
  - ▶ Third-degree blood<sup>d</sup> relative who has breast cancer<sup>b</sup> and/or ovarian<sup>e</sup> carcinoma and who has ≥2 close blood relatives<sup>d</sup> with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian<sup>e</sup> carcinoma

BRCA  
testing  
criteria  
met

[See  
Follow-up  
\(BRCA-2\)](#)

If BRCA  
testing  
criteria  
not met,  
consider  
testing  
for other  
hereditary  
syndromes

If criteria  
for other  
hereditary  
syndromes  
not met,  
then cancer  
screening  
as per  
[NCCN  
Screening  
Guidelines](#)

<sup>a</sup>For further details regarding the nuances of genetic counseling and testing, [see BR/OV-A](#).

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

<sup>c</sup>Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.

<sup>d</sup>Close blood relatives include first-, second-, and third-degree relatives on same side of family. ([See BR/OV-B](#))

<sup>e</sup>Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial non-mucinous histology. Lynch syndrome can be associated with both nonmucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome ([see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#)). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

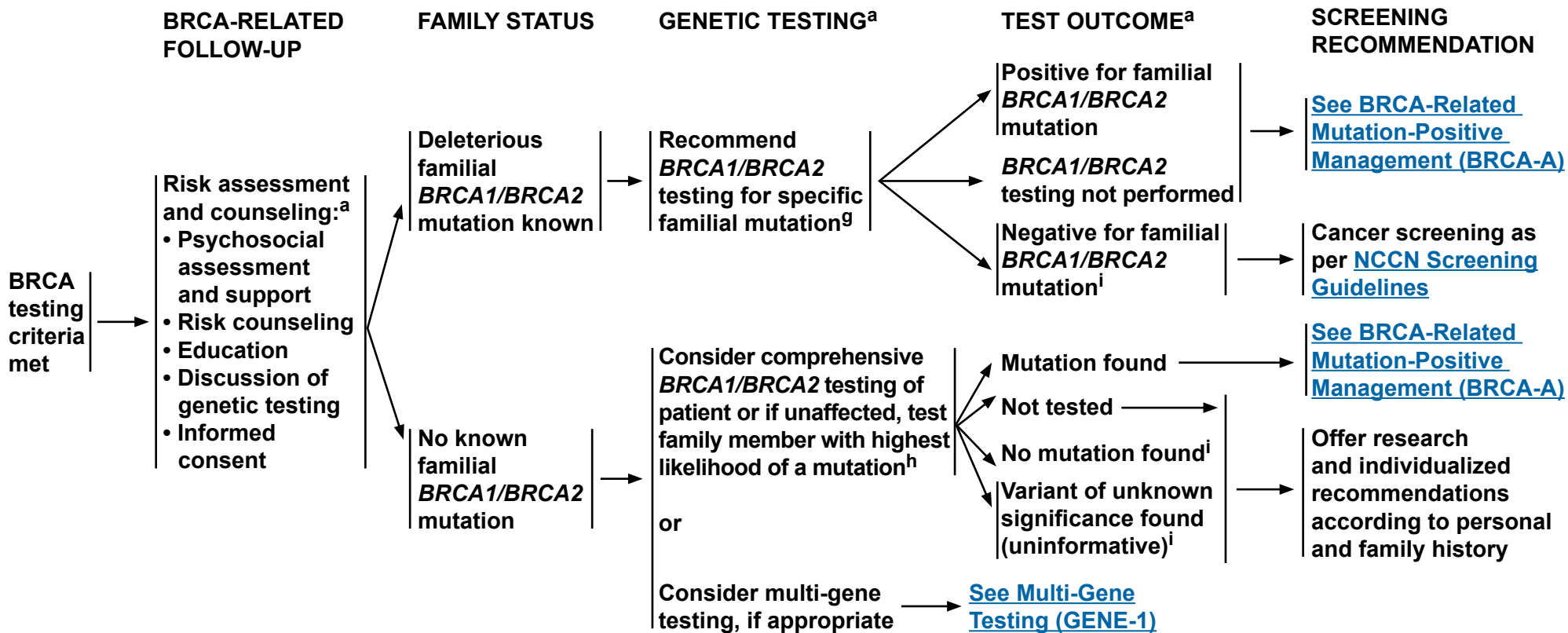
<sup>f</sup>Testing for Ashkenazi Jewish founder-specific mutation(s) should be performed first. Comprehensive genetic testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if other *BRCA*-related criteria are met. Founder mutations exist in other populations.

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

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

# NCCN Guidelines Version 1.2017

## BRCA-Related Breast and/or Ovarian Cancer Syndrome



<sup>a</sup>For further details regarding the nuances of genetic counseling and testing, see [BR/OV-A](#).

<sup>9</sup>If of Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations. Additional testing may be indicated if there is also a significant family history of cancer on the side of the family without the known mutation.

<sup>h</sup>For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, first test for the three common mutations. Then, if negative for the three mutations and ancestry also includes non-Ashkenazi Jewish relatives or other BRCA-related criteria are met, consider comprehensive genetic testing. 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.

<sup>i</sup>If no mutation found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast/ovarian cancer syndromes such as Li-Fraumeni ([LIFR-1](#)) and/or Cowden syndrome ([COWD-1](#)) or multi-gene testing ([GENE-1](#)). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, see [GENE-2](#).

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

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

### BRCA MUTATION-POSITIVE MANAGEMENT

#### WOMEN

- Breast awareness<sup>1</sup> starting at age 18 y.
- Clinical breast exam, every 6–12 mo,<sup>2</sup> starting at age 25 y.
- Breast screening<sup>3,4</sup>
  - ▶ Age 25–29 y, annual breast MRI<sup>5</sup> screening with contrast (preferred), or mammogram if MRI is unavailable or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - ▶ Age 30–75 y, annual mammogram and breast MRI<sup>5</sup> screening with contrast.
  - ▶ Age >75 y, management should be considered on an individual basis.
  - ▶ For women with a *BRCA* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy
  - ▶ Counseling should include a discussion regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy (RRSO),<sup>6</sup> typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* mutations is an average of 8–10 years later than in patients with *BRCA1* mutations, it is reasonable to delay RRSO until age 40–45 y in patients with *BRCA2* mutations who have already maximized their breast cancer prevention (ie, undergone bilateral mastectomy). See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in [NCCN Guidelines for Ovarian Cancer](#)- Principles of Surgery.
  - ▶ 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, and related medical issues.
  - ▶ Salpingectomy alone is not the standard of care for risk reduction although clinical trials are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.
- Address psychosocial, social, and quality-of-life aspects of undergoing risk-reducing mastectomy and/or salpingo-oophorectomy.
- For those patients who have not elected RRSO, transvaginal ultrasound for ovarian cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion starting at age 30–35 y. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.
- Consider risk reduction agents as options for breast and ovarian cancer, including discussing risks and benefits (See Discussion for details). ([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](#)

<sup>1</sup>Women 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.

<sup>2</sup>Randomized 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.

<sup>3</sup>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.

<sup>4</sup>Lehman CD, et al. Screening MRI in women with a personal history of breast cancer. *J Natl Cancer Inst* 2016;108.

<sup>5</sup>High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, radiologists experienced in breast MRI, and regional availability. Breast MRI is performed preferably days 7–15 of menstrual cycle for premenopausal women.

<sup>6</sup>Given 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](#). See [NCCN Guidelines for Ovarian Cancer](#) for treatment of findings.

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

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

### BRCA MUTATION-POSITIVE MANAGEMENT

#### **MEN<sup>7</sup>**

- Breast self-exam training and education starting at age 35 y
- Clinical breast exam, every 12 mo, starting at age 35 y
- Starting at age 45 y: ([See Guidelines for Prostate Early Detection](#))
  - Recommend prostate cancer screening for *BRCA2* carriers
  - Consider prostate cancer screening for *BRCA1* carriers

#### **MEN AND WOMEN**

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

#### **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.
- Biallelic mutations in some genes, such as *BRCA2* and certain other genes included on gene panels, may be associated with rare autosomal recessive conditions. Thus, for these types of genes, consideration would be given to carrier testing the partner for mutations in the same gene if it would inform reproductive decision-making and/or risk assessment and management.<sup>9</sup>

<sup>7</sup>There are only limited data to support breast imaging in men.

<sup>8</sup>Consider full-body skin and eye exam for melanoma and investigational protocols for pancreatic cancer. See [International Cancer of the Pancreas Screening Consortium](#) recommendations.

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

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

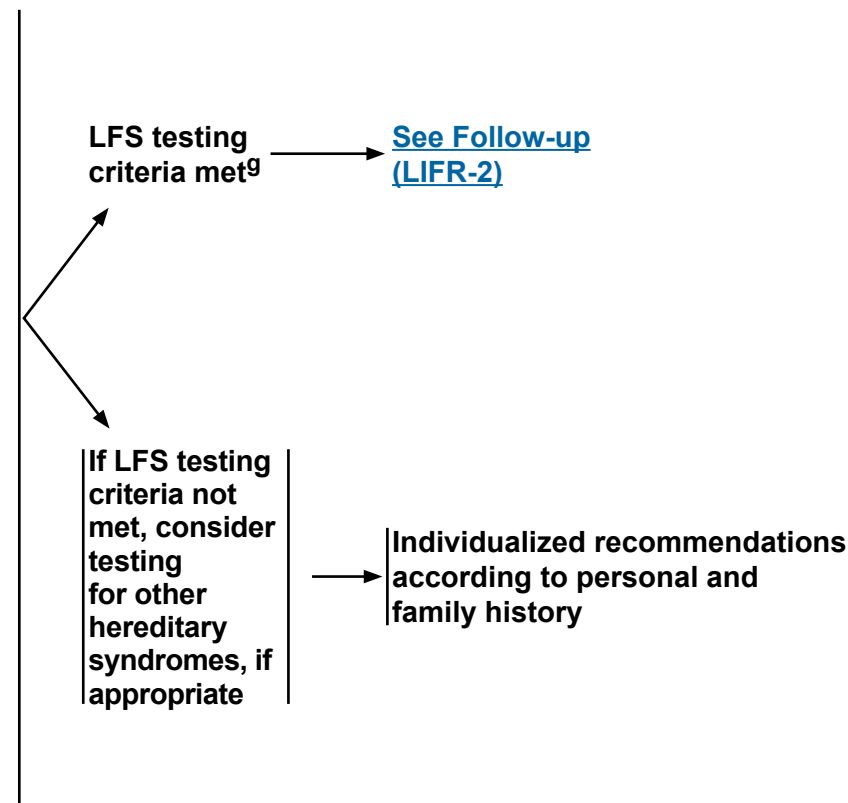
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



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

- Individual from a family with a known *TP53* mutation
- Classic Li-Fraumeni syndrome (LFS) criteria:<sup>b</sup>
  - ▶ Combination of an individual diagnosed age <45 y with a sarcoma<sup>c</sup>  
AND  
A first-degree relative diagnosed age <45 y with cancer  
AND  
An additional first- or second-degree relative in the same lineage with cancer diagnosed age <45 y, or a sarcoma at any age
- Chompret criteria:<sup>d,e,f</sup>
  - ▶ Individual with a tumor from LFS tumor spectrum (eg, soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), 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 y 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 y  
OR
  - ▶ Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of the family history  
OR
  - ▶ Breast cancer before age 31 y

### FOLLOW-UP



<sup>a</sup>For further details regarding the nuances of genetic counseling and testing, [see BR/OV-A](#).

<sup>b</sup>Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 1988;48:5358-5362.

<sup>c</sup>To date, there have been no reports of Ewing sarcoma, GIST, desmoid tumor, or angiosarcoma in *TP53* mutation carriers.

<sup>d</sup>Chompret 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.

<sup>e</sup>Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from *TP53* mutation carriers. *J Clin Oncol* 2015;33:2345-2352.

<sup>f</sup>Leukemia remains a controversial component of LFS, particularly hypodiploid leukemia.

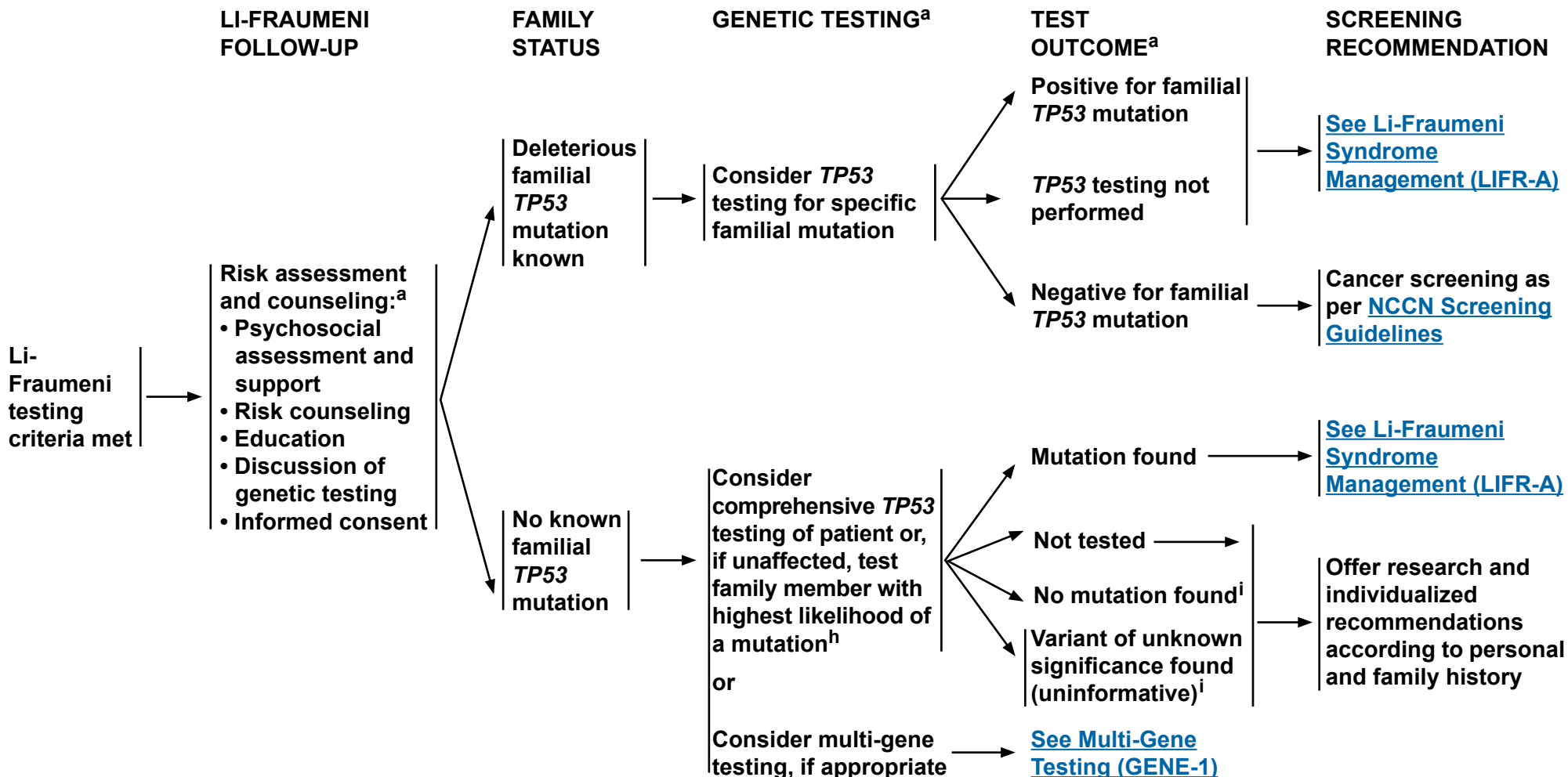
<sup>g</sup>*TP53* testing can be ordered alone, concurrently with *BRCA1/2* testing and/or other gene testing or as a follow-up test after negative *BRCA1/2* testing.

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

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

# NCCN Guidelines Version 1.2017

## Li-Fraumeni Syndrome



<sup>a</sup>For further details regarding the nuances of genetic counseling and testing, [see BR/OV-A](#).

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

<sup>i</sup>If no mutation is found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast cancer syndromes such as BRCA-related ([BRCA-1](#)) and/or Cowden syndrome ([COWD-1](#)) and/or constitutional mismatch repair deficiency (CMMRD) or multi-gene testing ([GENE-1](#)). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, [see GENE-2](#).

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

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

### LI-FRAUMENI SYNDROME MANAGEMENT

#### **BREAST CANCER RISK FOR WOMEN**

- Breast awareness<sup>1</sup> starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 20–25 y<sup>2</sup>
- Breast screening<sup>3</sup>
  - Age 20–29<sup>2</sup> y, annual breast MRI<sup>4</sup> screening with contrast (preferred) or mammogram if MRI is unavailable
  - Age 30–75 y, annual mammogram and breast MRI<sup>4</sup> screening with contrast
  - Age >75 y, management should be considered on an individual basis.
  - For women with a TP53 mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- Discuss option of 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).
- Pediatricians should be apprised of the risk of childhood cancers in affected families.
- Annual comprehensive physical exam with high index of suspicion for rare cancers and second malignancies in cancer survivors: include neurologic examination.
- Therapeutic RT for cancer should be avoided when possible.
- Consider colonoscopy every 2–5 y starting at 25 y or 5 y before the earliest known colon cancer in the family (whichever comes first).
- Perform annual dermatologic examination.
- Perform annual whole body MRI (or equivalent) (category 2B), preferably in context of a longitudinal study.<sup>5</sup>
- The brain may be examined as part of whole body MRI or as a separate exam.<sup>5</sup>
- Provide additional surveillance based on family history of cancer.
- Provide education regarding signs and symptoms of cancer.

[Continued on next page](#)

<sup>1</sup>Women 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.

<sup>2</sup>Or at the age of the earliest diagnosed breast cancer in the family, if below age 20 y.

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

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

<sup>5</sup>Whole body MRI is being evaluated in multiple international trials. Other components of screening are being evaluated in protocols, including regular blood screening for hematologic malignancies, and biochemical screening.

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

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



### LI-FRAUMENI SYNDROME MANAGEMENT

#### **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.

#### **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.

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

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

**COWDEN SYNDROME/PTEN HAMARTOMA TUMOR SYNDROME TESTING CRITERIA<sup>a,b,c,d</sup>**

- Individual from a family with a known *PTEN* mutation
- Individual with a personal history Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria<sup>e</sup> for CS/PHTS
- Individual not meeting clinical diagnostic criteria<sup>e</sup> for CS/PH with a personal history of:
  - ▶ 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 ≥3 minor criteria<sup>f</sup> or
  - ▶ ≥4 minor criteria

**Major criteria:**

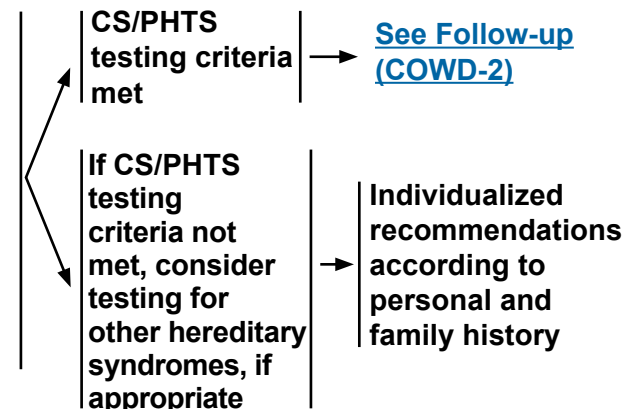
- Breast cancer
- Endometrial cancer
- Follicular thyroid cancer
- Multiple GI hamartomas or ganglioneuromas<sup>g</sup>
- Macrocephaly (megalcephaly) (ie, ≥97%, 58 cm in adult women, 60 cm in adult men)<sup>h</sup>
- Macular pigmentation of glans penis
- Mucocutaneous lesions<sup>i</sup>
  - ▶ One biopsy-proven trichilemmoma
  - ▶ Multiple palmoplantar keratoses
  - ▶ Multifocal or extensive oral mucosal papillomatosis
  - ▶ Multiple cutaneous facial papules (often verrucous)

- At-risk individual with a relative with a clinical diagnosis of CS/PHTS 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

**Minor criteria:<sup>j</sup>**

- Autism spectrum disorder
- Colon cancer
- ≥3 esophageal glycogenic acanthoses
- Lipomas
- Intellectual disability (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)

**FOLLOW-UP**



<sup>a</sup>For further details regarding the nuances of genetic counseling and testing, see [BR/OV-A](#).

<sup>b</sup>These are testing criteria; clinical diagnostic criteria can be found on [COWD-3](#).

<sup>c</sup>If two criteria involve the same structure/organ/tissue, both may be included as criteria.

<sup>d</sup>Current evidence does not support testing for succinate dehydrogenase (*SDH*) gene mutations in patients with PHTS. (Am J Hum Genet 2011;88:674-675).

<sup>e</sup>Pilarski R, Burt R, Kohlmann W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616. See [COWD-3](#).

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

<sup>g</sup>Multiple polyp types are often seen in patients with PHTS, and less commonly may include adenomas, hyperplastic polyps, and other histologies.

<sup>h</sup>Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: Birth to 18 years. Pediatrics 1987;79:706-712.

<sup>i</sup>The 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 CS/PHTS. Clinical judgment should be used.

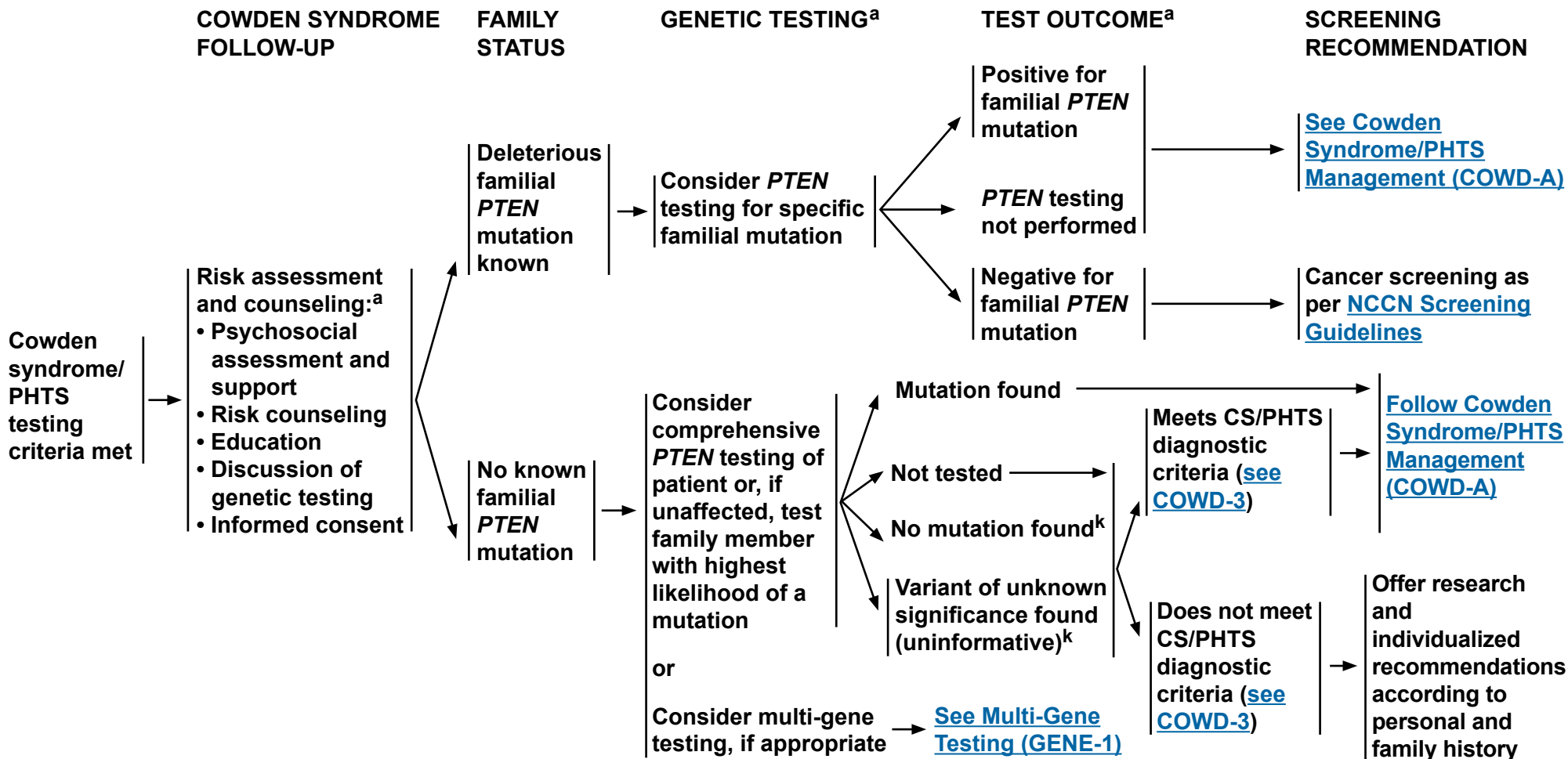
<sup>j</sup>Insufficient evidence exists in the literature to include fibrocystic disease of the breast, fibromas, and uterine fibroids as diagnostic criteria.

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

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

# NCCN Guidelines Version 1.2017

## Cowden Syndrome/PHTS



<sup>a</sup>For further details regarding the nuances of genetic counseling and testing, [see BR/OV-A](#).

<sup>k</sup>If no mutation is found, consider testing another family member with next highest likelihood of having a mutation and/or other hereditary breast cancer syndromes such as BRCA-related ([BRCA-1](#)) and/or Li-Fraumeni syndrome ([LIFR-1](#)) or multi-gene testing ([GENE-1](#)). For additional information on other genetic mutations associated with breast/ovarian cancer risk for which genetic testing is clinically available, [see GENE-2](#).

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

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



### REVISED PTEN HAMARTOMA TUMOR SYNDROME CLINICAL DIAGNOSTIC CRITERIA<sup>1</sup>

#### MAJOR CRITERIA:

- Breast cancer
- Endometrial cancer (epithelial)
- Thyroid cancer (follicular)
- GI hamartomas (including ganglioneuromas, but excluding hyperplastic polyps; ≥3)
- Lhermitte-Duclos disease (adult)
- Macrocephaly (≥97 percentile: 58 cm for females, 60 cm for males)
- Macular pigmentation of the glans penis
- Multiple mucocutaneous lesions (any of the following):
  - ▶ Multiple trichilemmomas (≥3, at least one biopsy proven)
  - ▶ Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)
  - ▶ Mucocutaneous neuromas (≥3)
  - ▶ Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed

#### MINOR CRITERIA:

- Autism spectrum disorder
- Colon cancer
- Esophageal glycogenic acanthoses (≥3)
- Lipomas (≥3)
- Intellectual disability (ie, IQ ≤75)
- Renal cell carcinoma
- Testicular lipomatosis
- Thyroid cancer (papillary or follicular variant of papillary)
- Thyroid structural lesions (eg, adenoma, multinodular goiter)
- Vascular anomalies (including multiple intracranial developmental venous anomalies)

#### Operational diagnosis in an individual (either of the following):

1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or
2. Two major and three minor criteria.

#### Operational diagnosis in a family where one individual meets revised PTEN hamartoma tumor syndrome clinical diagnostic criteria or has a *PTEN* mutation:

1. Any two major criteria with or without minor criteria; or
2. One major and two minor criteria; or
3. Three minor criteria.

<sup>1</sup>Pilarski R, Burt R, Kohlman W, Pho L, Shannon KM, Swisher E. Cowden syndrome and the PTEN Hamartoma Tumor Syndrome: Systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616.

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

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

### COWDEN SYNDROME/PHTS MANAGEMENT

#### WOMEN

- Breast awareness<sup>1</sup> 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 (whichever comes first).
- Breast screening
  - ▶ Annual mammography and breast MRI screening with contrast starting at age 30–35 y or 5–10 y before the earliest known breast cancer in the family (whichever comes first).<sup>2,3</sup>
  - ▶ Age >75 y, management should be considered on an individual basis.
  - ▶ For women with a *PTEN* mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
- For endometrial cancer screening,<sup>4</sup> encourage patient education and prompt response to symptoms (eg, abnormal bleeding). Consider annual random endometrial biopsies and/or ultrasound beginning at age 30–35 y.
- Discuss option of hysterectomy<sup>5</sup> upon completion of childbearing and counsel regarding degree of protection, extent of cancer risk, and reproductive desires.
- Discuss option of risk-reducing mastectomy 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 thyroid exam.
- Annual thyroid ultrasound starting at time of PHTS diagnosis
- Colonoscopy, starting at age 35 y unless symptomatic or if close relative with colon cancer before age 40 y then start 5–10 y before the earliest known colon cancer in the family. Colonoscopy should be done every 5 y or more frequently if patient is symptomatic or polyps are found.
- Consider renal ultrasound starting at age 40 y, then every 1–2 y.
- Dermatologic management may be indicated for some patients.
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms.
- Education regarding the signs and symptoms of cancer.

[Continued on next page](#)

<sup>1</sup>Women 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.

<sup>2</sup>The appropriateness of imaging modalities and scheduling is still under study.

<sup>3</sup>High-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 preferably preformed on days 7–15 of a menstrual cycle for premenopausal women.

<sup>4</sup>There are limited data regarding the lifetime risk of endometrial cancer in CS/PHTS. Surveillance screening and surgical intervention should be on an individual basis.

<sup>5</sup>Oophorectomy is not indicted for CS/PHTS alone but may be indicated for other reasons.

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

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



### COWDEN SYNDROME/PHTS MANAGEMENT

#### **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.

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

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

### MULTI-GENE TESTING

#### Overview of multi-gene testing

- The recent introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Based on next-generation sequencing technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.
- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost-effective.
- There may be a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include “intermediate” penetrant (moderate-risk) genes.<sup>a</sup> For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene tests are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene or gene/environment interactions. In addition, certain mutations in a gene may pose higher or lower risk than other mutations in that same gene. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives.
- In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
- Mutations in many breast cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions.
- There is an increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes.
- It is for these and other reasons that multigene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

#### [References \(GENE-5\)](#)

<sup>a</sup>Research is evolving, and gene carriers should be encouraged to participate in clinical trials or genetic registries.

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

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

# NCCN Guidelines Version 1.2017

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

### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS<sup>a,b</sup>

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
<i>ATM</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider breast MRI with contrast starting at age 40 y<sup>c</sup></li> <li>RRM: Consider based on family history</li> </ul>	<b>No increased risk of OC</b>	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. The 7271T>G missense mutation may act in a dominant-negative fashion, resulting in a lifetime breast cancer risk as high as 60% by age 80 (which is higher than truncating mutations, where risks are in the range of 30-40%). Counsel for risk of autosomal recessive condition in offspring.		
<i>BRCA1</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li><a href="#">See BRCA Mutation-Positive Management</a></li> </ul>	<b>Increased risk of OC</b> <ul style="list-style-type: none"> <li><a href="#">See BRCA Mutation-Positive Management</a></li> </ul>	Prostate cancer <ul style="list-style-type: none"> <li><a href="#">See BRCA Mutation-Positive Management</a></li> </ul>
<i>BRCA2</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li><a href="#">See BRCA Mutation-Positive Management</a></li> </ul>	<b>Increased risk of OC</b> <ul style="list-style-type: none"> <li><a href="#">See BRCA Mutation-Positive Management</a></li> </ul>	Pancreas, Prostate, Melanoma <ul style="list-style-type: none"> <li><a href="#">See BRCA Mutation-Positive Management</a></li> </ul>
<i>BRIP1</i>	<b>No increased risk of BC</b>	<b>Increased risk of OC</b> <ul style="list-style-type: none"> <li>Consider RRSO at 45–50 y</li> </ul>	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in <i>BRIP1</i> appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
<i>CDH1</i>	<b>Increased risk of lobular BC</b> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider breast MRI with contrast starting at age 30 y<sup>c</sup></li> <li>RRM: Consider based on family history</li> </ul>	<b>No increased risk of OC</b>	Diffuse gastric cancer <ul style="list-style-type: none"> <li><a href="#">See NCCN Guidelines for Gastric Cancer</a></li> </ul>

**BC: Breast cancer**  
**OC: Ovarian cancer**  
**RRM: Risk-reducing mastectomy**  
**RRSO: Risk-reducing salpingo-oophorectomy**

<sup>a</sup>Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016;13:581-588.

<sup>b</sup>The following genes and others are found on some of the panels but there is insufficient evidence to make *any* recommendations for breast MRI, RRSO, or RRM: *BARD1*, *FANCC*, *MRE11A*, *MUTYH* heterozygotes, *REQL*, *RAD50*, *RET1*, *SLX4*, *SMARCA4*, or *XRCC2*.

<sup>c</sup>May be modified based on family history or specific gene mutation.

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

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

[Continued](#)

# NCCN Guidelines Version 1.2017

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

### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS<sup>a</sup>

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
<i>CHEK2</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider breast MRI with contrast age 40 y<sup>c</sup></li> <li>RRM: Evidence insufficient, manage based on family history.</li> </ul>	<b>No increased risk of OC</b>	Colon <ul style="list-style-type: none"> <li>See <a href="#">NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</a></li> </ul>
Comments: Risk data are based only on frameshift mutations. The risks for most missense mutations are unclear.			
<i>MSH2</i> , <i>MLH1</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i>	<b>Unknown or insufficient evidence for BC risk<sup>d</sup></b> <ul style="list-style-type: none"> <li>Manage based on family history</li> </ul>	<b>Increased risk of OC</b> <ul style="list-style-type: none"> <li>See <a href="#">NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</a></li> </ul>	See <a href="#">NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</a>
<i>NBN</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider breast MRI with contrast age 40 y<sup>c</sup></li> <li>RRM: Evidence insufficient, manage based on family history</li> </ul>	<b>Unknown or insufficient evidence for OC risk</b>	Unknown or insufficient evidence
Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating mutation. Although risks for other mutations have not been established it is prudent to manage patients with other truncating mutations similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.			
<i>NF1</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li>Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y</li> <li>RRM: Evidence insufficient, manage based on family history.</li> </ul>	<b>No increased risk of OC</b>	<ul style="list-style-type: none"> <li>Malignant peripheral nerve sheath tumors, GIST, others</li> <li>Recommend referral to NF specialist for evaluation and management.</li> </ul>
Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y.			

<sup>a</sup>Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.

<sup>c</sup>May be modified based on family history or specific gene mutation.

<sup>d</sup>There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.

**BC: Breast cancer**

**OC: Ovarian cancer**

**RRM: Risk-reducing mastectomy**

**RRSO: Risk-reducing salpingo-oophorectomy**

[Continued](#)

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

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



# NCCN Guidelines Version 1.2017

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

### BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS<sup>a</sup>

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
<i>PALB2</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li>Screening: Annual mammogram and consider breast MRI with contrast at 30 y</li> <li>RRM: Consider based on family history.</li> </ul>	<b>Unknown or insufficient evidence for OC risk</b>	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
<i>PTEN</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li><a href="#">See Cowden Syndrome Management</a></li> </ul>	<b>No increased risk of OC</b>	<a href="#">See Cowden Syndrome Management</a>
<i>RAD51C</i>	<b>Unknown or insufficient evidence for BC risk</b>	<b>Increased risk of OC</b> <ul style="list-style-type: none"> <li>Consider RRSO at 45–50 y</li> </ul>	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in <i>RAD51C</i> appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
<i>RAD51D</i>	<b>Unknown or insufficient evidence for BC risk</b>	<b>Increased risk of OC</b> <ul style="list-style-type: none"> <li>Consider RRSO at 45–50 y</li> </ul>	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in <i>RAD51D</i> appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
<i>STK11</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li>Screening: <a href="#">See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</a></li> <li>RRM: Evidence insufficient, manage based on family history.</li> </ul>	<b>Increased risk of non-epithelial OC</b> <ul style="list-style-type: none"> <li><a href="#">See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</a></li> </ul>	<a href="#">See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal</a>
<i>TP53</i>	<b>Increased risk of BC</b> <ul style="list-style-type: none"> <li><a href="#">See Li-Fraumeni Syndrome Management</a></li> </ul>	<b>No increased risk of OC</b>	<a href="#">See Li-Fraumeni Syndrome Management</a>

<sup>a</sup>Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol* 2016;13:581-588.

**BC: Breast cancer**  
**OC: Ovarian cancer**

**RRM: Risk-reducing mastectomy**  
**RRSO: Risk-reducing salpingo-oophorectomy**

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

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

### MULTI-GENE TESTING

#### REFERENCES FOR OVERVIEW

1. Bombard Y, Robson M, Offit K. Revealing the incidentalome when targeting the tumor genome. JAMA 2013;310:795-796.
2. Walsh T, Lee MK, Casadei S, et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proc Natl Acad Sci 2010;107:12629-12633.
3. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. JAMA 2006;295:1379-1388.
4. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc Natl Acad Sci 2011;108:18032-18037.
5. Rainville IR, Rana HQ. Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. Curr Oncol Rep 2014;16:371.
6. Cragun D, et al. Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a US laboratory. Clin Genet 2014;86:510-520.
7. Antoniou AC, Casadei S, Heikkinen T, et al. Breast Cancer Risks in Families with Mutations in PALB2. N Engl J Med 2014;7:497-506.
8. Laduca H, Laduca H, Stuenkel AJ, et al. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. Genet Med 2014;16:830-837.
9. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. Cancer 2015;121:25-33.
10. Castéra L, Krieger S, Rousselin A, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate gene. Eur J Hum Genet 2014; 22:1305-1313.
11. Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol 2014;32:2001-2009.
12. Mauer CB, Pirzadeh-Miller SM, Robinson LD, Euhus DM. The integration of next-generation sequencing panels in the clinical cancer genetics practice: an institutional experience. Genet Med 2014;16:407-412.

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

**Clinical Trials:** NCCN believes that the best management of any patient with cancer 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 03/15/16

### 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.**

## Table of Contents

Overview.....	MS-2
Literature Search Criteria and Guidelines Update Methodology....	MS-3
Hereditary Breast or Breast/Ovarian Cancer Syndromes .....	MS-3
BRCA-Related Breast/Ovarian Cancer Syndrome.....	MS-4
Li-Fraumeni Syndrome .....	MS-10
Cowden Syndrome/ <i>PTEN</i> Hamartoma Tumor Syndrome .....	MS-13
Other Genetic Mutations Associated with Breast/Ovarian Cancer .....	MS-16
Initial Risk Assessment.....	MS-18

Formal Risk Assessment and Genetic Counseling.....	MS-19
Risk Assessment.....	MS-19
Genetic Counseling .....	MS-21
Genetic Testing .....	MS-22
Risk Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome .....	MS-26
Screening Recommendations.....	MS-27
Risk Reduction Surgery.....	MS-29
Chemoprevention .....	MS-32
Reproductive Options.....	MS-33
Risk Assessment, Counseling, and Management: Li-Fraumeni Syndrome .....	MS-34
Risk Assessment, Counseling, and Management: Cowden Syndrome/ <i>PTEN</i> Hamartoma Tumor Syndrome .....	MS-37
Testing Criteria.....	MS-37
Genetic Testing .....	MS-38
Clinical Diagnostic Criteria .....	MS-38
Screening Recommendations.....	MS-39
Table 1. Glossary of Relevant Genetic Terms (from the National Cancer Institute [NCI]) .....	MS-41
Table 2. Genetic Test Results to Determine the Presence of a Cancer-Predisposing Gene .....	MS-42
References .....	MS-43

## 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,<sup>1,2</sup> although not all of these mutations are inherited from a parent. For example, sporadic mutations can occur in somatic/tumor cells only, and de novo mutations can occur for the first time in a germ cell (ie, egg or sperm) or in the fertilized egg itself during early embryogenesis. However, family studies have long documented an increased risk for several forms of cancer among first-degree relatives (ie, parents, siblings, children) and second-degree relatives (ie, grandparents, aunts or uncles, grandchildren, nieces or nephews) of affected individuals. These individuals may have an increased susceptibility to cancer as the result of one or more gene mutations present in parental germline cells; cancers developing in these individuals may be classified as hereditary or familial cancers.

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

An individual suspected of being at risk for hereditary cancer should be offered genetic counseling.<sup>9,10</sup> This is consistent with recommendations from the US Preventive Services Task Force.<sup>11</sup> Assessment of an individual's risk for familial or hereditary cancer is based on a thorough evaluation of the family history. With respect to hereditary cancers, advances in molecular genetics have identified a number of genes associated with inherited susceptibility to breast and/or ovarian cancers (eg, *BRCA1/2*, *TP53*, *CDH1*) and provided a means of characterizing the specific gene mutation or mutations present in certain individuals and families exhibiting an increased risk for cancer. The field of cancer genetics has implications for all aspects of cancer management of individuals with hereditary or familial cancers, including prevention, screening, and treatment.<sup>12</sup>

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: 1) serve as a resource for health care providers to identify individuals who may benefit from cancer risk assessment and genetic counseling; 2) 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 3) facilitate a multidisciplinary approach in the management of individuals at increased risk for hereditary breast and/or ovarian cancer. Although cancers other than breast and ovarian cancers are associated with these hereditary syndromes, the main focus of these NCCN



Guidelines® is on the management of breast and ovarian cancer risk in these individuals. During the last few years, a number of genetic aberrations that may contribute to increased risks for development of breast and/or ovarian cancers have been identified. The current NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian focus primarily on assessment of mutations in *BRCA1/2*, *TP53*, and phosphatase and tensin homolog (*PTEN*), and recommended approaches to genetic testing/counseling and management strategies in individuals with these genetic mutations. Where possible, mutations in more recently identified genes have been addressed to the extent possible given the limited information available.

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

### Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian, an electronic search of the PubMed database was performed to obtain key literature published between November 14, 2014 and September 30, 2015, using the following search terms: (hereditary breast cancer) or (familial breast cancer) or (hereditary ovarian cancer) or (familial ovarian cancer) or (Li-Fraumeni syndrome) or (Cowden syndrome) or (pten hamartoma tumor syndrome). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.<sup>13</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guidelines; Randomized Controlled Trials; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 40 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website ([www.NCCN.org](http://www.NCCN.org)).

### Hereditary Breast or Breast/Ovarian Cancer Syndromes

Breast cancer is the most prevalent type of cancer in women in the United States and is the second leading cause of cancer death in women.<sup>14</sup> In the United States, approximately 234,190 new cases of breast cancer and 40,730 deaths are estimated for 2015 (estimated figures include both genders).<sup>14</sup> Up to 10% of breast cancers are due to specific mutations in single genes that are passed down in a family.<sup>6,8</sup> Specific patterns of hereditary breast/ovarian cancers are linked to mutations in the *BRCA1/2* genes.<sup>15,16</sup> In addition, two very rare hereditary cancer syndromes exhibiting an increased risk for breast cancer are Li-Fraumeni syndrome (LFS) and Cowden syndrome, which are related to germline mutations in the *TP53* and *PTEN* genes, respectively.<sup>17,18</sup> Similar to the *BRCA1/2* 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.<sup>19</sup> In an analysis of 4 predominantly gastric cancer pedigrees from Newfoundland with a specific *CDH1* mutation, the cumulative risk for female lobular breast cancer by the age of 75 was estimated to be as high as 52%.<sup>20,21</sup> Furthermore, germline *CDH1* mutations may be associated with lobular breast cancer in the absence of diffuse gastric cancer.<sup>22</sup> More information about HDGC can be found in the NCCN Guidelines for Gastric Cancer (available at [www.NCCN.org](http://www.NCCN.org)).

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 for 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 or silencing in the second copy of the gene without the hereditary mutation is believed to be necessary for the initiation of cancer development (ie, 2-hit hypothesis).<sup>23,24</sup> In addition, the manifestations (ie, expression) of these hereditary syndromes are often variable in individuals within a single family (eg, age of onset, tumor site, number of primary tumors). The risk of developing cancer in individuals with one of these hereditary syndromes depends on numerous variables including the gender and age of the individual.

### BRCA-Related Breast/Ovarian Cancer Syndrome

The overall prevalence of disease-related mutations in *BRCA1/2* genes has been estimated as 1 in 300 and 1 in 800, respectively.<sup>25,26</sup> 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, ostensibly 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.<sup>6,27</sup> Certain founder mutations have also been identified in other populations.<sup>25,28-33</sup>

It has been estimated that over 90% of hereditary families with both breast and ovarian cancers are caused by mutation(s) in the *BRCA1/2* genes.<sup>34</sup> 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 and is believed to be involved in both DNA repair and the regulation of cell-cycle checkpoints in response to DNA damage. However, the molecular mechanism through which *BRCA1* functions to preserve genomic stability remains unclear.<sup>35</sup> The *BRCA2* gene, located on chromosome 13, is involved in repair of replication-mediated double-strand DNA breaks.<sup>36,37</sup>

Mutations in the *BRCA1/2* genes can be highly penetrant (for definition, see Table 1), although the probability of cancer development in carriers of *BRCA1/2* mutations is variable, even within families with the same mutation.<sup>38-40</sup> Estimates of penetrance range from 41% to 90% lifetime



risk for breast cancer, with an increased risk for contralateral breast cancer.<sup>41-48</sup> In addition, female carriers of these genes have an estimated 8% to 62% lifetime risk for ovarian cancer, depending on the population studied.<sup>42-54,43-47,49,50</sup> In a 2007 meta-analysis of published data that evaluated *BRCA1/2* penetrance, estimates for mean cumulative risks for breast and ovarian cancer by age 70 years for *BRCA1* mutation carriers were 57% and 40%, respectively.<sup>43</sup> The corresponding estimates for *BRCA2* mutation carriers were 49% and 18%, respectively. In a recent prospective analysis of risk estimates from individuals with *BRCA1/2* mutations in the United Kingdom (N = 1887), estimates for mean cumulative risks for breast cancer and ovarian cancer by age 70 years for *BRCA1* mutation carriers were 60% and 59%, respectively.<sup>46</sup> The corresponding estimates for *BRCA2* mutation carriers were 55% and 16.5%, respectively. Among the patients diagnosed with unilateral breast cancer (n = 651), the mean cumulative risks for contralateral breast cancer by age 70 years were estimated to be 83% for *BRCA1* carriers and 62% for *BRCA2* carriers.<sup>46</sup> An international study including 19,581 *BRCA1* mutation carriers and 11,900 *BRCA2* mutation carriers showed that 46% of the *BRCA1* mutation carriers and 52% of the *BRCA2* mutation carriers eventually developed breast cancer, and 12% of the *BRCA1* mutation carriers and 6% of the *BRCA2* mutation carriers eventually developed ovarian cancer.<sup>51</sup> At present, it is unclear whether penetrance is related only 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 *BRCA1/2* 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 (ie, “triple negative”).<sup>52-57</sup> Studies have reported *BRCA1* mutations in 8.5% to 28% of patients with triple-negative breast cancer.<sup>57-63</sup> A recent meta-analysis examining 12 studies with 2,533 breast cancer patients showed that women with triple-negative breast cancer are more likely to be carriers of a *BRCA1* mutation, relative to women with breast cancer that is not classified as triple-negative (relative risk [RR] = 5.65, 95% CI = 4.15–7.69).<sup>64</sup> Several reports have also suggested the role of *BRCA2* mutations in triple-negative breast cancer. The incidence of *BRCA2* mutations range from 3% to 17% in studies of triple-negative breast cancer cases unselected for age or family history.<sup>58,63,65</sup>

An increased incidence of *BRCA1/2* mutations was reported in triple-negative breast cancer cases from at-risk populations. Among Ashkenazi Jewish women with breast cancer unselected for family history (N = 451), triple-negative disease was observed in 14% of patients and *BRCA* founder mutations were found in 11% of patients.<sup>66</sup> Among the subgroup with triple-negative breast cancer (n = 65), the incidence of *BRCA* mutations was 39% (*BRCA1* mutation in 30%; *BRCA2* mutation in 9%).<sup>66</sup> In addition, it appears that among patients with triple-negative disease, *BRCA* mutation carriers were diagnosed at a younger age compared with non-carriers.<sup>60,67</sup> In a study of a large cohort of patients with triple-negative breast cancer (N = 403), the median age of diagnosis among carriers of *BRCA1* mutations (n = 65) was 39 years.<sup>59</sup> Patients in this population-based study were unselected for family history or age. Among the group of patients with early-onset (age at diagnosis <40 years) triple-negative breast cancer (n = 106), the incidence of *BRCA1* mutations was 36%; the incidence was 27%

among those diagnosed before age 50 years ( $n = 208$ ). For patients with triple-negative breast cancer with a family history of breast and/or ovarian cancer ( $n = 105$ ), *BRCA1* mutations were found in 48% of patients.<sup>59</sup>

Male carriers of a *BRCA1/2* mutation also have a greater risk for cancer susceptibility.<sup>68</sup> In one study of 26 high-risk families with at least one case of male breast cancer, 77% demonstrated a *BRCA2* mutation.<sup>34</sup> Among male patients with breast cancer who were not selected on the basis of family history, 4% to 14% tested positive for a germline *BRCA2* mutation.<sup>69-72</sup> In a series of male breast cancer cases ( $N = 115$ ; primarily from cancer registry data), *BRCA2* mutations were detected in 16% of cases; the incidence of *BRCA2* mutations was 40% among patients selected for family history of breast cancer and 13% among those unselected for family history.<sup>71</sup> For males with a *BRCA2* mutation, the cumulative lifetime risk for breast cancer has been estimated at 7% to 8%.<sup>73,74</sup> The cumulative lifetime risk for *BRCA1* mutation carriers is 1.2%.<sup>74</sup> In contrast, for men without a *BRCA1/2* mutation, the lifetime risk for breast cancer has been estimated at approximately 0.1% (1 in 1,000).<sup>71,75</sup>

Relatively few studies have examined *BRCA1/2* mutation rates in black women. An observational study including 396 black women who were diagnosed with invasive breast cancer before age 50 showed that 12.4% were carriers of a *BRCA1/2* mutation.<sup>76</sup> Carriers of a *BRCA1/2* mutation were also significantly more likely to have triple-negative disease ( $P < .001$ ), a family history of breast and/or ovarian cancer ( $P < .001$ ), and a diagnosis before age 45 ( $P < .05$ ). Based on these findings, study authors suggested that black women diagnosed with invasive breast cancer at a young age (ie, younger than 50 years) should be considered for *BRCA* testing.

The evidence that a *BRCA1/2* mutation is associated with poor survival outcomes for breast cancer has been inconsistent.<sup>77,78</sup> A meta-analysis including 13 studies showed that *BRCA1* mutation carriers with breast cancer had worse OS, compared to those without a *BRCA* mutation (hazard ratio [HR], 1.50; 95% CI, 1.11—2.04), while harboring a *BRCA2* mutation was not significantly associated with worse survival.<sup>79</sup> Another recent meta-analysis including 66 studies showed that a *BRCA2* mutation was associated with worse breast cancer-specific survival (HR, 1.57; 95% CI, 1.29—1.86), but study results were too heterogeneous for the analysis to be conclusive.<sup>80</sup> An analysis of 119 Swedish women who were diagnosed with early-onset breast cancer showed that not receiving chemotherapy treatment was associated with poor survival in *BRCA1/2* mutation carriers (HR, 3.0; 95% CI, 1.2—7.7;  $P = .014$ ).<sup>81</sup> Carrying a *BRCA1/2* mutation is not significantly associated with nodal metastasis.<sup>82</sup>

Increased risks for cancers of the ovary, fallopian tube, and peritoneum are observed in carriers of *BRCA1/2* mutations.<sup>83,84</sup> Germline mutations in *BRCA1/2* are responsible for at least 10% of epithelial ovarian cancers.<sup>85,86</sup> An analysis of 2,222 epithelial ovarian cancer patients showed that 11% carried a *BRCA1/2* mutation when disease was high-grade serous.<sup>87</sup> In the setting of an invasive ovarian cancer diagnosis, as many as 13% to 20% of women have a germline *BRCA1/2* mutation.<sup>47,88-90</sup> However, it has been reported that about half of families showing a genetic predisposition to ovarian cancer do not have identifiable *BRCA1/2* mutations.<sup>91</sup> Hence, other gene mutations predisposing a patient to ovarian cancer are likely to exist.<sup>92</sup> Of note, ovarian cancer is a component tumor of Lynch syndrome that is associated with germline mutations in mismatch repair genes.<sup>93</sup> Interestingly, results from a prospective study suggest that women from families at increased risk for hereditary breast cancer without site-

specific *BRCA* mutations are not at increased risk for ovarian cancer. However, these results may have been confounded by the ethnic characteristics and size of the study population.<sup>94</sup>

Several studies have reported more favorable survival outcomes among *BRCA1/2* mutation carrier patients with ovarian cancer compared with non-carrier patients.<sup>95-100</sup> In a case-control study of patients with epithelial ovarian cancer (N = 66), patients with a *BRCA1/2* mutation 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;  $P < .002$ ).<sup>99</sup> In a large case-control study of Jewish patients with epithelial invasive ovarian cancer (N = 779), patients with a *BRCA1/2* mutation had significantly longer median survival compared with non-carrier patients (54 months vs. 38 months;  $P = .002$ ).<sup>98</sup> Results from a 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 a *BRCA1/2* mutation.<sup>96</sup> 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 (HR, 0.78; 95% CI, 0.68–0.89;  $P < .001$ ) and *BRCA2* mutation carriers (HR, 0.61; 95% CI, 0.50–0.76;  $P < .001$ ).<sup>96</sup> In a population-based case-control study of women with invasive epithelial (nonmucinous) ovarian cancer (N = 1001) from the Australian Ovarian Cancer Study Group, *BRCA1/2* mutation carriers had improved survival outcomes compared with non-carriers in terms of median progression-free survival (20 months vs. 16 months; not statistically significant) and median survival (62 months vs. 55.5 months;  $P = .031$ ).<sup>95</sup> Moreover, *BRCA1/2* mutation carriers appeared to be more responsive to cytotoxic

chemotherapy (regardless of class of agent) compared with non-carrier patients.

Survival outcomes appear to be most favorable for *BRCA2* mutation carriers; in a subgroup of patients with *BRCA2* mutations (n = 53), the median survival was 70 months.<sup>95</sup> In an observational study of patients with high-grade serous ovarian cancer (N = 316), patients with *BRCA2* mutations had significantly favorable survival outcomes (HR, 0.33; 95% CI, 0.16–0.69;  $P = .003$ ; 5-year rate: 61% vs. 25%) and progression-free survival (HR, 0.40; 95% CI, 0.22–0.74;  $P = .004$ ; 3-year rate: 44% vs. 16%) compared with non-carrier patients (having wild-type *BRCA*).<sup>100</sup> An observational study including 1,345 women with ovarian cancer who participated in clinical trials from the Gynecologic Oncology Group showed that *BRCA2* mutation carriers had significantly longer progression-free survival (HR, 0.60; 95% CI, 0.45–0.79;  $P < .001$ ) and overall survival (HR, 0.39; 95% CI, 0.25–0.60;  $P < .001$ ), relative to those without mutations.<sup>86</sup> 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.<sup>100</sup>

The histology of ovarian cancers in carriers of a *BRCA1/2* 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 also have been reported in the former population.<sup>85,89,101-104</sup> Mutations are also associated with non-mucinous ovarian carcinoma as opposed to mucinous.<sup>88,90</sup> Mucinous epithelial ovarian carcinomas may be associated with other gene mutations, such as *KRAS* and *TP53* mutations.<sup>105</sup> *TP53* mutations are implicated in LFS (see below). Non-epithelial ovarian carcinomas (eg, germ cell and sex cord stromal tumors) are not significantly associated



with a *BRCA1/2* mutation,<sup>106</sup> but they may be associated with other cancer genetic syndromes. For example, sex cord tumors may be associated with Peutz-Jeghers syndrome (see below), while Sertoli-Leydig tumors are associated with both Peutz-Jeghers syndrome and DICER1-related disorders.<sup>107-112</sup> Current data show that ovarian low malignant potential tumors (ie, borderline epithelial ovarian tumors) are also not associated with a *BRCA1/2* mutation.<sup>88</sup> Therefore, the panel does not consider the presence of an ovarian low malignant potential tumor to be a criterion for genetic testing.

In studies of women with a *BRCA1/2* mutation who underwent risk-reducing salpingo-oophorectomy (RRSO), occult gynecologic carcinomas were identified in 4.5% to 9% of cases based on rigorous pathologic examinations of the ovaries and fallopian tubes.<sup>113-115</sup> 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% to 8% of cases from patients with a *BRCA1/2* mutation who underwent RRSO.<sup>113,116,117</sup> 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.<sup>113,117,118</sup> Although TIC appeared to present more frequently among *BRCA1/2* mutation carriers compared with non-carriers undergoing RRSO,<sup>117,118</sup> TIC has also been documented among patients with serous carcinomas unselected for family history or *BRCA* mutation status.<sup>119</sup> Because TIC was identified in individuals who underwent surgery for risk reduction (for *BRCA1/2* mutation carriers) or other gynecologic 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 gynecologic indications.

An increased frequency of other malignancies has been reported in families with mutations in the *BRCA1/2* genes.<sup>44,68,120</sup> Germline *BRCA1/2* mutations have been associated with an increased risk for prostate cancer in numerous reports.<sup>44,68,120-126</sup> In particular, *BRCA2* mutations have been associated with a 2- to 6-fold increase in risk for prostate cancer,<sup>121-123,126-128</sup> while increased risks were not observed for *BRCA1* mutation carriers in some studies.<sup>121-123,127,128</sup> An analysis of 1,522 *BRCA1/2* male mutation carriers undergoing prostate-specific antigen (PSA) testing showed that 2.3% of *BRCA1* carriers and 3.3% of *BRCA2* carriers had a detected prostate cancer based on biopsy results.<sup>129</sup> Prostate cancers with germline *BRCA1/2* mutations appear to have a more aggressive phenotype (eg, more frequently associated with Gleason score  $\geq 8$ ) than tumors from non-carrier patients.<sup>130,131</sup> A recent study in a large cohort of patients from Spain with prostate cancer (N = 2019) showed that the group of patients with *BRCA1/2* mutations had significantly higher rates of aggressive prostate cancer (Gleason score  $\geq 8$ ), nodal involvement, and distant metastasis compared with non-carriers.<sup>130</sup> Moreover, cause-specific survival outcome was significantly poorer in *BRCA1/2* mutation carriers compared with non-carriers (median survival 8.6 years vs. 15.7 years;  $P = .015$ ). Subgroup analysis by mutation type showed poor outcomes in patients with *BRCA2* mutations (n = 61); the role of *BRCA1* mutations was not well defined, possibly due to the small patient size (n = 18) and limited follow-up in this subgroup.<sup>130</sup> Prostate cancer in patients with *BRCA2* mutations has also been associated with a higher histologic grade in other studies.<sup>121,122</sup> In addition, 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.<sup>132-134</sup> 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*) (2 years vs. 12 years;  $P < .001$ ).<sup>134</sup> 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 y vs. 8 y;  $P < .01$ ).<sup>132</sup>

*BRCA2* mutation carriers have also been reported to have a higher risk for pancreatic cancer and melanoma.<sup>68,120,126,128,135,136</sup> An analysis of 490 families with *BRCA1/2* mutations showed an increased risk for ocular melanoma in *BRCA2* carriers (RR, 99.4; 95% CI, 11.1–359.8).<sup>127</sup> Both *BRCA1* and *BRCA2* mutations have been associated with increased propensity for developing pancreatic cancer.<sup>126,136–141</sup> In an analysis of samples taken from patients with familial pancreatic cancer (kindreds in which  $\geq 3$  family members had pancreatic cancer, at least 2 of who were first-degree relatives), *BRCA2* mutations were detected in 17% of patient samples.<sup>139</sup> A recent analysis including 727 unrelated probands with a family history of pancreatic cancer showed that 1.2% tested positive for a *BRCA1* mutation, and 3.7% tested positive for a *BRCA2* mutation.<sup>142</sup>

An analysis of 159 patients with pancreatic adenocarcinoma showed that 8% harbored a *BRCA2* mutation.<sup>140</sup> However, it is important to note that participants of this study were not unselected pancreatic cancer patients; they were presenting for genetic counseling, and, thus, were weighted towards stronger family histories. Also, 56% of the sample was Ashkenazi Jewish. Pancreatic cancer patients with Ashkenazi Jewish ancestry may have a greater likelihood of testing positive for a *BRCA1/2* mutation, with prevalence of detected mutations in this group ranging from 5.5% to 19%, with mutations being more common for *BRCA2*.<sup>135,140,141,143</sup> In 211 Ashkenazi Jewish breast cancer patients with

a family history of pancreatic cancer, 6.6% had a *BRCA1* mutation and 7.6% had a *BRCA2* mutation.<sup>144</sup>

Some data related to cancer risk in *BRCA1/2* mutation carriers at some sites other than the breast/ovary are contradictory.<sup>145</sup> For example, it has been suggested that the increased risk for endometrial cancer observed in some *BRCA1/2* mutation carriers is mainly due to the use of tamoxifen therapy by these women rather than the presence of a gene mutation.<sup>146</sup>

### NCCN Recommendations

The NCCN Panel recommends that individuals from a family with a known deleterious *BRCA1/2* mutation be considered for testing (see *BRCA1/2 Testing Criteria* in the algorithm). In individuals from a family without a known deleterious *BRCA1/2* mutation, testing should be considered for those individuals who meet the testing criteria discussed below. Meeting one or more criteria warrants further personalized risk assessment, genetic counseling, and, often, genetic testing and management. The probability of mutation detection will vary based on family structure. In evaluating risks based on family history factors, the maternal and paternal sides should be considered independently. For the testing criteria mentioned below, “close relatives” pertain to first-, second-, or third-degree blood relatives on the same side (either maternal or paternal side) of the family. Individuals with a limited or unknown family history (eg, having fewer than 2 first- or second-degree female relatives surviving beyond 45 years of age on either the maternal or paternal side) may have an underestimated probability of a familial gene mutation detection. The likelihood of mutation detection may be very low in families with a large number of unaffected female relatives. Clinical judgment should be used to determine the appropriateness of genetic testing.

The panel recommends that patients with a personal history of breast cancer *in addition to* one or more of the following criteria be considered for *BRCA1/2* testing:

- Diagnosed at age 45 years or younger;
- Diagnosed with at least two breast cancer primaries (ie, bilateral tumors or 2 or more clearly separate ipsilateral tumors, occurring synchronously or asynchronously), the first at age 50 years or younger;
- Diagnosed at age 50 years or younger with 1 or more close relatives with breast cancer at any age (or with an unknown or limited family history), 1 or more close relatives with pancreatic cancer, or 1 or more close relatives with prostate cancer (Gleason score  $\geq 7$ );
- Diagnosed with triple-negative breast cancer at age 60 years or younger;
- Diagnosed at any age with 1 or more close relatives with breast cancer diagnosed at age 50 years or younger;
- Diagnosed at any age with 2 or more close relatives with breast cancer at any age;
- Diagnosed at any age with 1 or more close relatives with ovarian carcinoma (including fallopian tube and primary peritoneal cancers) diagnosed at any age;
- Diagnosed at any age with 2 or more close relatives with pancreatic cancer and/or prostate cancer (Gleason score  $\geq 7$ ) at any age; or
- Having a close male relative with breast cancer at any age.

In patients with a personal history of breast cancer and Ashkenazi Jewish heritage, no additional family history may be needed to meet testing criteria. In addition, the NCCN Panel recommends testing for

patients with a personal history of ovarian carcinoma or male breast cancer, either diagnosed at any age.

Testing is recommended for those with a personal history of prostate cancer (Gleason score  $\geq 7$ ) diagnosed at any age, with a family history of at least one relative with ovarian carcinoma at any age or breast cancer younger than age 50 or two relatives with breast, pancreatic, or prostate cancer (Gleason score  $\geq 7$ ) diagnosed at any age. Those with a personal history of pancreatic cancer should meet the same testing criteria. Further, a personal history of pancreatic cancer combined with Ashkenazi Jewish ancestry warrants testing.

In individuals with a family history only (ie, no personal history of breast or ovarian cancer), significant limitations of interpreting test results should be discussed prior to any testing. Moreover, testing of individuals without a cancer diagnosis should only be considered when an appropriate affected family member is unavailable for testing. When evaluating an individual without a cancer diagnosis for his or her likelihood of carrying a *BRCA1/2* mutation, clinical judgment should be made based on factors such as the individual's current age and the age of unaffected female relatives who link the individual with an affected close relative.

For individuals not meeting testing criteria for *BRCA1/2* mutations, testing should be considered for other hereditary syndromes. If criteria for other hereditary syndromes are not met, then the panel recommends screening as per the NCCN Screening Guidelines (available at [www.NCCN.org](http://www.NCCN.org)).

### Li-Fraumeni Syndrome

LFS is a rare hereditary cancer syndrome associated with germline *TP53* gene mutations.<sup>18</sup> It has been estimated to be involved in only



about 1% of hereditary breast cancer cases,<sup>147</sup> although results from other studies suggest that germline *TP53* gene mutations may be more common than previously believed, with estimates of 1 in 5,000 to 1 in 20,000.<sup>148,149</sup> There are only about 300 families reported in an LFS registry maintained by an NCCN Member Institution and the National Cancer Institute.<sup>150</sup> The tumor suppressor gene, *TP53*, is located on chromosome 17,<sup>151,152</sup> and the protein product of the *TP53* gene (ie, p53) is located in the cell nucleus and binds directly to DNA. It has been called the “guardian of the genome” and plays important roles in controlling the cell cycle and apoptosis.<sup>151-153</sup> 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 Li-Fraumeni Syndrome Testing Criteria in the algorithm).<sup>18,148,154</sup> Additional studies are needed to investigate the possibility of other gene mutations in families meeting these criteria not carrying germline *TP53* mutations.<sup>155</sup>

LFS, a highly penetrant cancer syndrome associated with a high life-time risk for cancer, is characterized by a wide spectrum of neoplasms occurring at a young age. It is associated with soft tissue sarcomas, osteosarcomas (although Ewing’s sarcoma is less likely to be associated with LFS), premenopausal breast cancer, acute leukemia, colon cancer, adrenocortical carcinoma, and brain tumors.<sup>18,148,153,156-161</sup> 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.<sup>148</sup> Interestingly, two 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 suggests that amplification of HER2 may arise in conjunction with *TP53* mutations.<sup>162,163</sup> 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 (eg, soft tissue sarcomas, brain tumors, adrenocortical carcinomas) in early childhood,<sup>158</sup> and have an increased risk of developing multiple primary cancers during their lifetimes.<sup>164</sup> 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 45 and 70 years, respectively.<sup>165</sup> 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.<sup>148</sup> 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: a member of a kindred with a known *TP53* mutation; a 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 younger than 45 years or a sarcoma diagnosed at any age (see Li-Fraumeni Syndrome Testing Criteria in the algorithm). 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%).<sup>148</sup> Thus, it is not uncommon for individuals with patterns of cancer outside of these criteria to be carriers of germline *TP53* mutations.<sup>161,166</sup> Classic LFS criteria make up one set of criteria included in the guidelines to guide selection of individuals for *TP53* gene mutation testing (see Li-Fraumeni Syndrome Testing Criteria in the algorithm).

Other groups have broadened the classic LFS criteria to facilitate identification of individuals with LFS.<sup>156,167-169</sup> 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 is included.<sup>148,156</sup> Individuals with de novo germline *TP53* mutations (no mutation in either biological parent) have also been identified.<sup>148,149,157</sup> These cases would not be identified as *TP53* testing candidates based on 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 (ie, 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 Li-Fraumeni Syndrome Testing Criteria in the algorithm).<sup>168</sup> The Chompret criteria have an estimated positive predictive value of 20% to 35%,<sup>148,168</sup> and, when incorporated as part of *TP53* testing criteria in conjunction with classic LFS criteria have been shown to improve the sensitivity to 95% (ie, the Chompret criteria added to classic LFS criteria detected 95% of patients with *TP53* mutations).<sup>148</sup> 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 adopting the 2015 Revised Chompret Criteria and testing individuals with choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype diagnosed at any age and regardless of family history (for inclusion in criterion 3), based on reports of considerable incidence of *TP53* mutations found in patients with these rare forms of cancer.<sup>148,157,170-172</sup> The panel supports the broader age cut-offs proposed by Tinat et al, based on a study in a large number of families, which detected germline *TP53* mutations in affected individuals with later tumor onsets.<sup>170,172</sup>

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.<sup>171</sup> Several studies have investigated the likelihood of a germline *TP53* mutation in this population.<sup>148,170,173-176</sup> In a study of *TP53* mutations evaluated at a single reference laboratory, Gonzalez et al found that all women younger than 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.<sup>148</sup> In an analysis of patients with early-onset breast cancer (age of diagnosis <30 years) tested for *TP53* mutation at a single institution (N = 28), 6 patients (33%) were found to have *TP53* mutations.<sup>177</sup> Among the patients who were tested, a *TP53* mutation was found in approximately 8% who did not meet traditional LFS criteria for testing. In another study in patients with *BRCA1/2* mutation-negative early-onset breast cancer (age of diagnosis ≤35 years) tested for *TP53* mutation at a single institution (N = 83), approximately 5% were found to have *TP53* mutations.<sup>175</sup> Deleterious *TP53* mutations were identified in 3 of 4 patients (75%) with a family history of at least 2 LFS-associated tumors (breast cancer, bone or soft

tissue sarcoma, brain tumors or adrenocortical carcinoma) and in 1 of 17 patients (6%) with a family history of breast cancer only.<sup>175</sup> Among women <30 years of age with breast cancer and without a family history, the incidence of *TP53* mutations has been reported at 3% to 8%.<sup>148,174,176,177</sup> 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.<sup>170</sup> Furthermore, Ginsburg and colleagues found no germline *TP53* mutations in 95 unselected women with early-onset breast cancer who previously tested negative for *BRCA1/2* mutations.<sup>173</sup>

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. Individuals not meeting testing criteria should be followed according to recommendations tailored to his/her personal cancer history and family history.

### **Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome**

The spectrum of disorders resulting from germline mutations in *PTEN*<sup>178</sup> are referred to as the *PTEN* hamartoma tumor syndrome (PHTS). The spectrum of PHTS includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Adult Lhermitte-Duclos disease (LDD), Proteus-like syndrome,<sup>17,179,180</sup> and autism spectrum disorders with macrocephaly.<sup>17,180,181</sup>

The estimated penetrance of *PTEN* mutation is high, at approximately 80%.<sup>182</sup> 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.<sup>183,184</sup> Cowden syndrome is an autosomal dominant disorder, and most cases are associated with germline mutations in the *PTEN* gene, though one

study found that germline *KILLIN* methylation may also be associated with this syndrome.<sup>185</sup>

Hamartomas (benign tumors resulting from an overgrowth of normal tissue) are a common manifestation of the PHTS syndromes. 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.<sup>17,186</sup> However, it has been suggested that patients with other PHTS diagnoses associated with *PTEN* mutations should be assumed to have Cowden syndrome-associated cancer risks.

The lifetime risk for breast cancer for women diagnosed with Cowden syndrome has been estimated at 25% to 50%, with an average age of 38 to 50 years at diagnosis.<sup>17,186-188</sup> Some studies (as discussed above) have reported a higher cumulative lifetime risk for breast cancer (77%–85%) in individuals with Cowden syndrome or *PTEN* mutations.<sup>189-191</sup> There have been only 2 cases of breast cancer reported in men with Cowden syndrome.<sup>188</sup> Although many women with Cowden syndrome experience benign breast disease,<sup>17</sup> there is no evidence that the rate is higher than in the general population.<sup>188</sup>

Thyroid disease, including benign multinodular goiter, adenomatous nodules, and follicular adenomas, has been reported to occur in approximately 30% to 68% of adults with *PTEN* mutations,<sup>180,192</sup> and the lifetime risk for thyroid cancer (follicular or papillary) has been estimated at 3% to 10%.<sup>17,193</sup> However, data tend to be aggregated, so it is difficult to calculate rates for multinodular goiter vs. solitary nodules.<sup>188</sup>

As in many other hereditary cancer syndromes, affected individuals are more likely to develop bilateral and multifocal cancer in paired organs.<sup>182</sup> Although not well defined, women with Cowden syndrome may have a



5% to 10% risk for endometrial cancer.<sup>17,194 188</sup> While many women with Cowden syndrome may also have uterine fibroids, this risk is not likely to be much greater than in women without Cowden syndrome or *PTEN* mutation.<sup>188</sup>

In addition, 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.<sup>17,188</sup> It is important to note, however, that most of the data on the frequencies of the clinical features of Cowden syndrome are from compilations of case reports of relatively young individuals who may have subsequently developed additional signs of the disease (ie, new cancerous lesions), and these data are also likely to be confounded by selection bias.<sup>17</sup> 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.<sup>17,195</sup>

Benign skin lesions are experienced by most to all Cowden syndrome patients.<sup>180,186</sup> Skin lesions associated with Cowden syndrome include trichilemmomas (ie, benign tumors derived from the outer root sheath epithelium of a hair follicle), oral papillomas, mucocutaneous neuromas (hamartoma of the peripheral nerve sheath), palmoplantar keratoses, penile pigmentation in men, lipomas and vascular anomalies, and fibromas.<sup>188,196</sup> Trichilemmomas associated with Cowden syndrome tend to appear on the face, particularly the eyes, mouth, nose, and forehead.<sup>188</sup> 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, showing nearly complete penetrance, although this may be a

reflection of selection bias in the cases reported.<sup>85,179</sup> The presence of three or more mucocutaneous neuromas is considered a major diagnostic criterion of PHTS,<sup>188</sup> while the presence of 2 or more trichilemmomas has been reported to be pathognomonic for Cowden syndrome.<sup>197,198</sup> However, since most of the evidence regarding trichilemmomas is from the older literature, it is possible that the association with Cowden syndrome is somewhat overestimated.<sup>17</sup> There are reports of individuals with a solitary trichilemmoma who do not have Cowden syndrome.<sup>197,198</sup> 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 was previously estimated that about half of individuals with Cowden syndrome have gastrointestinal polyps.<sup>199</sup> However, this was almost certainly an underestimate.<sup>199,200</sup> In an analysis of 67 *PTEN* mutation carriers undergoing colonoscopy, colorectal polyps were found in 92.5% of patients.<sup>199</sup> About half of the patients undergoing colonoscopy had hyperplastic polyps, and about 25% each had polyps that were hamartomatous, ganglioneuromatous, or adenomatous.<sup>199</sup>

Adenomatous or hyperplastic polyps were associated with development of colorectal cancer in this sample. Out of 39 *PTEN* mutation carriers undergoing esophagogastroduodenoscopy, upper gastrointestinal polyps were found in 67% of patients.<sup>199</sup> A systematic review of published case series (N = 102) regarding gastrointestinal manifestations in PHTS and component syndromes showed that 92.5% of these patients had polyps, with 64% having 50 or more.<sup>201</sup> Histologies were described as: hyperplastic (44%), adenomatous (40%), hamartomatous (38%), ganglioneuroma (33%), and inflammatory (24.5%). Other studies have also reported ganglioneuromatous polyps

(ie, rare, benign peripheral nervous system tumors) in this population.<sup>188,202</sup> 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.<sup>199</sup> The lifetime risk for colorectal cancer has been estimated as 9% to 16%.<sup>190,191</sup>

Several studies have projected lifetime estimates of cancer risk that are significantly higher than previously estimated. In a study of patients meeting diagnostic criteria for Cowden syndrome (N = 211; identified from published literature and records from a single institution), the cumulative lifetime risk for any cancer was 89%.<sup>190</sup> *PTEN* mutations had been identified in 97 of 105 patients (92%) who underwent testing. The cumulative lifetime cancer risks for all evaluable patients (n = 210) were 81% for female breast cancer, 21% for thyroid cancer, 19% for endometrial cancer, 15% for renal cancer, and 16% for colorectal cancer.<sup>190</sup> In a prospective study that evaluated genotype-phenotype associations between *PTEN* mutations and cancer risks,<sup>191</sup> deleterious germline mutations in *PTEN* were identified in 368 patients. Calculation of age-adjusted standardized incidence ratios (SIRs) using cancer incidence data from the SEER database showed elevated SIRs among individuals with *PTEN* mutations for breast cancer (25), thyroid cancer (51), endometrial cancer (43), colorectal cancer (10), renal cancer (31), and melanoma (8.5). The estimated cumulative lifetime cancer risks were 85% for breast, 35% for thyroid, 28% for endometrial, 9% for colorectal, 34% for renal, and 6% for melanoma.<sup>191</sup> In another study in individuals with PHTS found to have deleterious germline *PTEN* mutations (N = 154; detailed information available in n = 146), age- and gender-adjusted SIRs were elevated for female breast cancer (39), endometrial cancer (49), female thyroid cancer (43), male thyroid cancer (199.5), female melanoma (28), and male melanoma (39).<sup>189</sup>

The cumulative lifetime risks in these individuals were 77% for female breast cancer and 38% for thyroid cancer. The cumulative lifetime risk for any cancer was 85% overall, and women with PHTS were found to have a 2-fold greater cancer risk compared with men with PHTS.<sup>189</sup> It is important to note, however, that all three of these studies suffer from significant ascertainment biases, in that patients were usually selected for *PTEN* testing based on the presence of these malignancies, which would inflate the projected lifetime cancer estimates. An observational study of 180 patients with *PTEN* mutations used Kaplan-Meier methods to estimate that female carriers (n = 99) have an 87% cumulative risk of developing any cancer and/or LDD by age 60, while male carriers have a cumulative risk of 56%.<sup>203</sup>

Adult LDD and autism spectrum disorder characterized by macrocephaly are strongly associated with Cowden syndrome.<sup>179,182,190,204</sup> A rare, slow growing, benign hamartomatous lesion of the brain, LDD, is a dysplastic gangliocytoma of the cerebellum.<sup>17,190</sup> In a multicenter prospective study examining 3042 probands who met clinical criteria for Cowden syndrome, 6% met criteria for LDD.<sup>192</sup> In a study of individuals meeting the diagnostic criteria for Cowden syndrome, the cumulative lifetime risk for LDD was reported to be 32%.<sup>190</sup> The preponderance of evidence supports a strong association between adult-onset LDD and the presence of a *PTEN* gene mutation,<sup>182,205</sup> although exceptions have been reported.<sup>206</sup> In addition, there is a relatively large body of evidence to support that 10% to 20% of individuals with autism spectrum disorder and macrocephaly carry germline *PTEN* mutations.<sup>181,207-210</sup> Macrocephaly (defined as head circumference greater than the 97<sup>th</sup> percentile)<sup>211</sup> is a common finding in patients with Cowden syndrome. It has been estimated that approximately 80% to 100% of individuals with this syndrome will exhibit this clinical finding.<sup>188</sup>

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,<sup>212</sup> 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.<sup>213</sup> 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.<sup>204</sup>

### Other Genetic Mutations Associated with Breast/Ovarian Cancer

In the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian, the panel specifically focuses on assessment of known high-penetrance mutations (ie, *BRCA1/2*, *TP53*, *PTEN*) and recommendations for genetic testing, counseling, and management strategies in individuals with these mutations. Below is a description of additional gene mutations that the panel argues warrants additional screening beyond what is recommended in the general population (ie, those without the specific gene mutation). These include mutations for *CDH1*, *STK11*, *CHEK2*, *PALB2*, *ATM*, *BRIP1*, and *RAD51C* and *RAD51D*. Risk management for genetic mutations associated with Lynch syndrome is also described. Risk management recommendations within each gene mutation may be modified based on family history. A retrospective analysis of 337 patients who met NCCN criteria for *BRCA1/2* mutation testing and underwent multigene testing showed that 25 patients (7.4%) had non-*BRCA* mutations.<sup>214</sup> The most common of these mutations were *PALB2* (23%), *CHEK2* (15%), and *ATM* (15%).

Germline mutations in *CDH1* are associated with HDGC and lobular breast cancer, and studies have reported a cumulative lifetime risk for breast cancer of 39% to 52% among women who carry *CDH1*

mutations.<sup>20,215</sup> Given the considerable risk for breast cancer in women with a *CDH1* mutation, the panel recommends screening with breast MRI, and the option of risk-reducing mastectomy should be discussed.

Germline mutations in *STK11* are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by gastrointestinal polyps, mucocutaneous pigmentation, and elevated risk for gastrointestinal cancers as well as breast or non-epithelial ovarian cancers. Breast cancer risk in women with Peutz-Jeghers syndrome is 8% at age 40, 13% at age 50, 31% at age 60, and 45% at age 70.<sup>216</sup> The panel recommends breast MRI screening for women with this syndrome. Further information on Peutz-Jeghers syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at [www.NCCN.org](http://www.NCCN.org)).

Another breast cancer susceptibility gene that has been identified is *CHEK2*. In a study of breast cancer patients in the United States with a strong family history of breast or ovarian cancer but who tested negative for a *BRCA1/2* mutation, 5% had *CHEK2* mutations.<sup>217</sup> Deleterious *CHEK2* mutations have been reported to occur with a higher frequency in Northern and Eastern European countries compared with North America.<sup>218-221</sup> The cumulative lifetime risk for breast cancer in women with *CHEK2* mutations and familial breast cancer has been estimated to range from approximately 28% to 37%, and is higher in women with stronger family histories of breast cancer than those without.<sup>222,223</sup> The panel recommends breast MRI screening for women with this gene mutation.

*PALB2* (partner and localizer of *BRCA2*) is a Fanconi anemia gene. Mutations in this gene are associated with increased risk for breast cancer, with studies including women with breast cancer showing that 1% to 3% harbor a pathogenic *PALB2* mutation.<sup>63,224-226</sup> In a study of 115



men with breast cancer, a pathogenic *PALB2* mutation was detected in 1% to 2% of men who tested negative for a *BRCA2* mutation.<sup>71</sup> Breast cancer risk increases with age in women with a *PALB2* mutation, with a 14% lifetime risk by age 50 and a 35% lifetime risk by age 70.<sup>227</sup> The risk also increases with increasing number of relatives affected with breast cancer. Lifetime breast cancer risk for those with two first-degree relatives with breast cancer is 58% by age 70.<sup>227</sup> The panel recommends breast MRI screening for women with this gene mutation, and risk-reducing mastectomy should be considered. Though some studies suggest that there may be an association between *PALB2* and increased ovarian cancer risk,<sup>86,228</sup> there is currently insufficient evidence to recommend RRSO in these mutation carriers.

Mutations in the *ATM* (ataxia-telangiectasia mutated) gene may also increase risk for breast cancer. An analysis of 82 Dutch patients with early-onset breast cancer showed that 8.5% (n = 7) of the patients had a detected *ATM* mutation.<sup>229</sup> The presence of *ATM* heterozygotes was associated with a 9-fold increased risk for early-onset breast cancer and frequent bilateral occurrence. This study also showed an association between *ATM* heterozygotes and longer survival. However, the association between other *ATM* genetic variants and breast cancer susceptibility is less clear.<sup>230-233</sup> An analysis of 2,570 women with breast cancer estimated that carriers of a mutated *ATM* gene have a 60% lifetime risk for breast cancer by age 80 (HR, 6.88; 95% CI, 2.33–20.3; *P* < .001), with an even greater risk for those with the c.7271T > G variant (HR, 8.0; 95% CI, 2.3–27.4; *P* < .001).<sup>234</sup> The panel recommends breast MRI screening for women with a mutated *ATM* gene.

Lynch syndrome is a hereditary syndrome that usually results from a germline mutation in 1 of 4 DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), though deletions in the *EPCAM* gene have also been

found to be associated.<sup>235,236</sup> Lynch syndrome is most commonly associated with increased risk for colorectal cancer, but women with Lynch syndrome are at an increased risk for endometrial and ovarian cancer (up to 60% and 24%, respectively).<sup>237-241</sup> Ovarian cancers in Lynch syndrome are not associated with a specific histology; that is, they may be mucinous or non-mucinous.<sup>242</sup> Total abdominal hysterectomy and bilateral salpingo-oophorectomy are risk-reducing options that should be considered for women who have completed childbearing and carry an *MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6* mutation.<sup>243-245</sup> Annual endometrial sampling is an option for carriers of mutations associated with Lynch syndrome,<sup>243,246-248</sup> but there is no clear evidence to support routine screening for gynecologic cancers, like routine transvaginal ultrasound and serum CA-125 testing.<sup>243,246-248</sup> Female *MLH1* mutation carriers have been suggested to be at increased risk for breast cancer, with one study estimating a cumulative risk to age 70 being 18.6% (95% CI, 11.3–25.9).<sup>249</sup> However, there is currently not enough evidence for the panel to recommend breast screening for women with Lynch syndrome beyond that which is recommended for the average-risk population. More information regarding Lynch syndrome can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at [www.NCCN.org](http://www.NCCN.org)).

In an observational study including 1,915 unselected ovarian cancer cases, 1.4% of patients had a mutation in the *BRCA1* interaction protein C-terminal helicase 1 gene (*BRIP1*),<sup>86</sup> which is a Fanconi anemia gene. An analysis of 3,236 women with epithelial ovarian cancer, 3,431 controls, and 2,000 unaffected high-risk women from an ovarian cancer screening trial (UKFOCSS) showed that *BRIP1* is associated with an increased risk for ovarian cancer (*P* < .001), with the RR for invasive epithelial ovarian cancer being 11.22 (95% CI, 3.22–34.10, *P* < .001)

and 14.09 for high-grade serous disease (95% CI, 4.04–45.02,  $P < .001$ ).<sup>250</sup> An analysis of an Icelandic population (656 ovarian cancer cases, 3,913 controls) also showed an association between *BRIP1* and increased risk of ovarian cancer (OR, 8.13; 95% CI, 4.74–13.95;  $P < .001$ ).<sup>251</sup> The panel recommends that RRSO be considered in women with a *BRIP1* mutation.

Genes in the *RAD51* protein family are involved in homologous recombination and DNA repair. *RAD51C* and *RAD51D* have been shown to be associated with increased risk of ovarian cancer. In an observational study including 1,915 unselected ovarian cancer cases, 1.1% of patients had either a *RAD51C* or *RAD51D* mutation.<sup>86</sup> In a comparison of 1,132 probands with a family history of ovarian cancer and 1,156 controls, *RAD51C* was associated with an increased risk of ovarian cancer (RR, 5.88; 95% CI, 2.91–11.88;  $P < .001$ ).<sup>252</sup> Analyses from the same trial (911 probands and 1,060 controls) also showed an association between *RAD51D* and increased risk of ovarian cancer (RR, 6.30; 95% CI, 2.86–13.85;  $P < .011$ ).<sup>253</sup> An analysis of 409 unselected cases of ovarian cancer in Finland also showed an association between *RAD51C* and increased risk of ovarian cancer (OR, 6.31; 95% CI, 1.15–34.6;  $P = .033$ ), with higher prevalence in patients with familial ovarian cancer but without a family history of breast cancer (OR, 33.8; 95% CI, 5.15–221.0;  $P = .005$ ).<sup>254</sup> In another study from Finland, a non-significant association was found between *RAD51D* and increased risk for ovarian cancer ( $n = 541$ ,  $P = .08$ ), but a significant association was found among those with a family history of breast and ovarian cancer ( $n = 105$ ; OR, 37.83; 95% CI, 3.90, 366.91;  $P = .002$ ).<sup>255</sup> In a case-control analysis of 3,429 women with epithelial ovarian cancer and 2,772 controls, both *RAD51C* (OR, 5.2; 95% CI, 1.1–24;  $P = .035$ ) and *RAD51D* (OR, 12.0; 95% CI, 1.5–90;  $P = .019$ ) were associated with an increased risk for ovarian cancer.<sup>256</sup> The panel

recommends that RRSO be considered in women with these gene mutations. There is currently insufficient evidence to recommend routine breast screening in carriers of these gene mutations.

The gene mutations noted above may be tested for concurrently using panel testing (see *Multi-Gene Testing* below). Lower penetrance genes for which there is currently insufficient evidence to recommend breast MRI, risk-reducing mastectomy, or RRSO include, but are not limited to: *BARD1*, *FANCC*, *MRE11A*, *MUTYH*, *NF1*, *NBN*, *RAD50*, *SMARCA*, and *XRCC2*. Risk management recommendations should take into account family history and other clinical factors. A more comprehensive review of these lower-penetrance genes is included in a recent publication.<sup>218</sup>

### Initial Risk Assessment

For a patient concerned about or suspected of having a hereditary propensity for 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 Criteria for Further Genetic Risk Evaluation in the algorithm). 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.<sup>257,258</sup> The magnitude of the risk increases with the number of affected relatives in the family and the closeness of the relationship, and is affected by the age at which the affected relative was diagnosed.<sup>259,260</sup> The younger the age at diagnosis, the more likely it is that a genetic component is present. When assessing a family history for a hereditary pattern, the equal likelihood of paternal or maternal transmission of a gene that predisposes to breast cancer must also be kept in mind.

If an individual or a close family member of that individual meets any one of the criteria presented in the NCCN Guidelines (see Criteria for

Further Genetic Risk Evaluation in the algorithm), 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, medical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved in this process.<sup>9</sup> Those not meeting criteria for testing who are still considered at increased risk for familial breast cancer are also likely to benefit from appropriate risk-reduction strategies (eg, a change in the frequency of, or modalities used for, breast cancer screening).<sup>5</sup> The panel recommends that these individuals follow recommendations in the NCCN Guidelines for Breast Cancer Screening and Diagnosis (available at [www.NCCN.org](http://www.NCCN.org)).

## 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 for 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.<sup>261</sup> The Gail model was also developed to assess risk for breast cancer.<sup>262</sup> The modified model is a computer-based, multivariate, logistic regression model that uses age, race, age at menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous breast biopsies, and histology of the breast biopsies to produce actuarial estimates of future breast cancer risk.<sup>263-265</sup> This model considers only family history of breast cancer in first-degree relatives<sup>266</sup> and is heavily weighted by benign breast disease. Therefore, the Gail model may underestimate breast cancer risk for women with a significant family history and should not be used for women suspected of having a hereditary syndrome associated with increased risk for breast cancer.<sup>266</sup>

Decision models developed to estimate the likelihood that a *BRCA1/2* mutation is present include BRCAPRO<sup>267,268</sup> and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).<sup>267</sup> A lifetime risk for breast cancer of 20% to 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 for breast cancer. For example, this risk threshold was used in updates to the American Cancer Society (ACS) guidelines on breast screening, which incorporates MRI.<sup>269,270</sup>



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 an 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.<sup>271</sup> This is a situation that can interfere with the adoption of appropriate health behaviors. In addition, the patient's knowledge about the benefits, risks, and limitations of genetic testing should be assessed 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 individual diagnosed with cancer and proceeding outward to include first-, second-, and third-degree relatives on both the maternal and paternal sides. Standardized pedigree nomenclature should be used.<sup>272,273</sup> Unaffected family members, both living and deceased, are also included, as their histories also provide information about the magnitude of genetic risk.

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

by obtaining medical records, pathology reports, or death certificates. This is particularly important in the case of a report of an "abdominal" cancer in a female relative—a situation in which cancers of the cervix, uterus, ovary, and/or colon are often confused. It is also important to know the ancestry/ethnicity of the individual, since members of certain groups (eg, Ashkenazi Jewish) have increased risks of carrying mutations for specific diseases. Any family members who received genetic testing should also be noted, as well as testing results.

Other medical conditions that may be associated with or predispose an individual to breast and/or ovarian cancer should also be noted. Family history data are then graphically represented on a pedigree that follows standard nomenclature to illustrate family relationships and disease information. Factors that limit the informativeness of the pedigree are small family size, a small number of individuals of the susceptible gender for sex-limited cancers, reduced penetrance, early deaths in family members (which precludes the possibility that they will develop adult diseases), prophylactic surgeries that remove an organ from subsequent risk for cancer (eg, hysterectomy for uterine fibroids in which the ovaries are also removed), adoptions, and inaccurate or incomplete information on family members.<sup>5,274</sup>

A 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* mutation based on models dependent on family history.<sup>275</sup>

**Medical and Surgical History**

The collection of a detailed medical and surgical history from the proband allows the counselor to estimate the contribution of other risk factors that may interact with or modify family history to determine the risk for cancer. Any personal cancer history should include age of diagnosis, histology, and laterality. A history of previous breast biopsies and pathology results, especially those in which the pathology revealed atypical hyperplasia or lobular carcinoma in situ (LCIS), is associated with an increased risk for breast cancer.<sup>276,277</sup> Pathologic verification of these diagnoses is encouraged. History of salpingo-oophorectomy and potential exposure to carcinogens (eg, 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 (see section below on *Focused Physical Examination*).

Reproductive variables are important determinants of risk for both breast and ovarian cancer, suggesting a significant contribution of hormones to the etiology of these cancers. This possible link is supported by the increased breast cancer risk seen among women who have had prolonged exposure to exogenous estrogens and progestins and the reduction in risk for ovarian cancer observed among women who report using oral contraceptives.<sup>278-281</sup>

**Focused Physical Examination**

A physical examination performed by a qualified clinician (when available) should 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, as discussed earlier; a focused physical examination for Cowden syndrome should include a

comprehensive dermatologic examination (including oral mucosa), evaluation of head circumference (to determine presence of macrocephaly), and palpation of the thyroid (see section above on *Cowden Syndrome*).

**Genetic Counseling**

Genetic counseling is a critical component of the cancer risk assessment process. Many patients undergoing genetic testing do not receive proper counseling. In the national ABOUT study, patients undergoing genetic testing ( $N = 3,628$ ) completed a survey regarding their experience. About 37% of respondents reported receiving counseling prior to testing.<sup>282</sup>

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 for disease to help them derive personal meaning from cancer genetic information, and to 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 testing 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.<sup>7</sup>

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.<sup>7</sup> The

foundation of pre-test genetic counseling is based on the principle of informed consent.<sup>9</sup> 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 *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, the potential significance of the test results for family members, and other topics.<sup>7</sup> The patient should be educated regarding inheritance patterns, penetrance, variable expressivity, and the potential for genetic heterogeneity. A discussion of confidentiality issues should include an explanation of the federal Genetic Information Nondiscrimination Act (GINA) enacted in 2008, which prohibits most health insurers and employers from discrimination on the basis of genetic test results.<sup>283</sup>

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.<sup>9</sup> 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.<sup>7</sup> It may also be appropriate to offer genetic testing to both parents of an individual who tests positive for one of these gene mutations to confirm which side of the family carries the mutation and is at increased risk. Counseling should also include making the individual aware of any available resources, such as disease-specific support groups, advocacy groups, and research studies.<sup>284</sup> Individuals who have tested positive for

a mutation may have greater distress than anticipated, so provisions for supportive interventions should be provided.

### 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 and Genomic Testing for Cancer Susceptibility from ASCO updated in 2003, genetic testing is recommended when: 1) there is a personal or family history suggesting genetic cancer susceptibility; 2) the test can be adequately interpreted; and 3) the results will aid in the diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk for cancer.<sup>285</sup> 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).<sup>286</sup>

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.<sup>287,288</sup> 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 (ie, *BRCA1/2*, *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 (ie, 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, even if a mutation has already been identified in a relative.

In the situation of an unaffected individual with a significant family history, the testing of the unaffected individual (or of unaffected family members) should only be considered when no affected family member is available for testing. In such cases, the unaffected individual or unaffected close relative 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 individuals (in the absence of having tested affected family members), significant limitations may exist in interpreting the test results, and testing multiple family members may be indicated.

In the case of *BRCA*-related breast/ovarian cancer, if no family member with breast or ovarian cancer is living, consideration can be given to testing first- or second-degree family members affected with cancers thought to be related to the deleterious mutation in question (eg, prostate or pancreatic cancer). Importantly, the significant limitations of interpreting testing results for an unaffected individual should be discussed prior to testing.

Another counseling dilemma is posed by the finding of a variant of unknown significance (VUS) (see Table 2), a genetic alteration 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. Clinicians and scientists should work together to develop a VUS classification system as more information is discovered in research studies.<sup>289</sup>

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.<sup>290-293</sup> For example, there are tests that detect rare, large cancer-associated rearrangements of DNA in the *BRCA1/2* 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.

Following testing, the proband should be advised regarding possible inherited cancer risk to relatives and his/her options for risk assessment and management. The counselor should recommend genetic counseling and testing for at-risk relatives.

### Multi-Gene Testing

Next-generation sequencing allows for the sequencing of multiple genes simultaneously. This is referred to as multi-gene testing. The NCCN Guidelines Panel added information regarding multi-gene testing for the 2014 update. The recent introduction of multi-gene testing for hereditary

forms of cancer has rapidly altered the clinical approach to testing at-risk patients and their families. Multi-gene testing simultaneously analyzes a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.

Multiple studies have shown that this approach may detect mutations not found in single-gene testing. In a study of 300 probands who tested negative for a *BRCA1/2* mutation (wild-type) in a commercially available single-gene test, multi-gene testing revealed that 12% had detected *BRCA1/2* genomic rearrangements, 5% had detected *CHEK2* mutations, and 1% had *TP53* mutations. Multiple DNA- and RNA-based methods were used.<sup>217</sup> A study of 198 women referred for *BRCA1/2* testing who underwent multi-gene testing showed 16 deleterious mutations out of 141 women who tested negative for *BRCA1/2* (11.4%, 95% CI = 7.0–17.7).<sup>294</sup> The discovery of these mutations led to recommendations for further screening. Therefore, findings from multi-gene testing have the potential to alter clinical management.<sup>295</sup>

Multi-gene testing could include only high-penetrance genes associated with a specific cancer, or both high- and moderate-penetrance genes. Comprehensive cancer risk panels, which include a large number of genes associated with a variety of cancer types, are also available.<sup>296</sup> The decision to use multi-gene testing for patient care should be no different than the rationale for testing a single gene known to be associated with the development of a specific type of cancer. Testing is focused on identifying a mutation known to be clinically actionable; that is, whether the management of an individual patient is altered based on the presence or absence of a mutation. Multi-gene testing may be most useful when more than one gene can explain an inherited cancer syndrome. For example, though ovarian cancer is mainly associated with *BRCA1/2* mutations, it may also be associated with mutations in the following genes: *BARD1*, *BRIP1*, *CHEK2*, *MRE11A*, *MSH6*, *NBN*,

*PALB2*, *RAD50*, *RAD51C*, and *TP53*.<sup>297</sup> Highly penetrant genes associated with hereditary breast cancer include the following that could potentially be included in a multi-gene test: *BRCA1/2*, *PALB2*, *TP53*, *PTEN*, *STK11*, and *CDH1*.<sup>10,294,298-300</sup> In these cases where more than one gene mutation could potentially influence a condition, multi-gene testing may be more efficient and/or cost-effective.<sup>296</sup> Multi-gene testing may also be considered for those who tested negative (indeterminate) for one particular syndrome, but whose personal and family history is strongly suggestive of an inherited susceptibility.<sup>296,301</sup>

There are several issues to consider regarding multi-gene testing. First, commercially available tests may differ significantly on a number of factors, such as number of genes analyzed, turn-around time, and insurance coverage, among others. Tests requiring a longer turn-around time may not be suitable for patients who need rapid results. The specific laboratory and multi-gene test should be chosen carefully.<sup>296</sup> Second, in some cases, next-generation sequencing may miss some mutations that would have been detected with traditional single-gene analysis.<sup>296</sup> Third, mutations identified for more than one gene add complexity that may lead to difficulty in making risk management recommendations.<sup>301</sup> A management plan should only be developed for identified gene mutations that are clinically actionable.

A major dilemma regarding multi-gene testing is that there are limited data and a lack of clear guidelines regarding degree of cancer risk associated with some of the genes assessed in multi-gene testing, and how to communicate and manage risk for carriers of these genes.<sup>299,301,302</sup> This issue is compounded by the low incidence rates of hereditary disease, leading to a difficulty in conducting adequately powered studies.<sup>302</sup> Some multi-gene tests may include moderate-penetrance genes, for which there are little available data regarding degree of cancer risk and guidelines for risk management.<sup>296,299,303-305</sup>

Further, it is possible that the risks associated with these genes may not entirely be due to that gene only, but may be influenced by gene/gene or gene/environment interactions. Also, certain mutations in a gene may be associated with a different degree of risk than other mutations in that gene. For example, the presence of certain *ATM* mutations is associated with an increased risk for early-onset breast cancer and frequent bilateral occurrence, but the association between other *ATM* genetic variants and breast cancer susceptibility is less clear.<sup>230-233</sup>

As a result of these dilemmas, risk management following detection of a mutation for a moderate-risk gene, and how risk should best be communicated to relatives, is currently unknown.<sup>305</sup> Further, the information gained from testing for moderate-penetrance genes may not change risk management recommendations significantly compared to that based on family history only. Multi-gene tests also increase the likelihood of detecting a VUS.<sup>214,294,296,299-301,305</sup> In a multi-gene analysis of 2,158 DNA samples from individuals with breast cancer, a VUS was found in about 40% of individuals.<sup>300</sup> Another multi-gene sequencing analysis that included 42 genes in 192 women showed a VUS identified in 88% of participants.<sup>294</sup> The considerable possibility of detecting a VUS adds to the complexity of counseling following multi-gene testing. However, as multi-gene testing is increasingly used, the frequency of a VUS being detected is expected to decrease.

Multi-gene testing is a new and rapidly growing field, but there is currently a lack of evidence regarding proper procedures and risk management strategies that should follow testing, especially when mutations are found for moderate-penetrance genes and when a VUS is found. For this reason, the NCCN Panel recommends that multi-gene testing be offered in the context of professional genetic expertise, with pre- and post-test counseling being offered. Panel recommendations are in agreement with recommendations by ASCO, who issued an



updated statement regarding genetic testing in 2015.<sup>306</sup> Carriers of a genetic mutation should be encouraged to participate in clinical trials or genetic registries.

### Risk Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome

Detailed in the NCCN Guidelines is a set of specific risk assessment criteria that form part of the decision-making process in evaluating whether an individual suspected of being a carrier of a *BRCA1/2* mutation should be considered for genetic testing (see *BRCA1/2 Testing Criteria* in the algorithm). Following risk assessment and counseling, genetic testing should be considered for individuals for whom hereditary breast/ovarian cancer syndrome testing criteria are met. Testing is generally not recommended in children less than 18 years of age, since conditions associated with *BRCA1/2* mutations generally have an adult onset.<sup>307</sup>

Individuals from a family with a known deleterious *BRCA1/2* mutation should be tested for this mutation. For individuals from a family without a known *BRCA1/2* mutation (and who meet testing criteria), genetic testing should be comprehensive, including full sequencing of *BRCA1/2*, and testing for large genomic rearrangements. Individuals from a family with a known deleterious *BRCA1/2* mutation who test positive for the familial mutation, or for whom *BRCA1/2* mutation testing is not performed, should follow the screening recommendations outlined in *BRCA Mutation-Positive Management* in the algorithm (and discussed below).

For individuals of Ashkenazi Jewish descent with no known familial *BRCA1/2* mutations, one approach is to first test for the three known founder mutations; if the tests are negative for founder mutations, and if the individual's ancestry also included non-Ashkenazi ethnicity (or if

other *BRCA1/2* testing criteria are met), comprehensive genetic testing should be considered. However, with new panels available, many clinicians are moving away from this stepped approach and are increasingly using comprehensive testing (see *Multi-Gene Testing*). Additional testing may also be considered if there is a significant family history of cancer on the side of the family without the known mutation.

Whenever possible, an affected family member with the highest likelihood of carrying the *BRCA1/2* mutation should be tested first. If more than one family member is affected, members with the following factors should be considered for testing first: youngest age at diagnosis; having bilateral disease or multiple primaries; having other associated cancers (eg, ovarian); and most closely related to the proband. If no living family member with breast or ovarian cancer exists, consider testing first- or second-degree family members affected with cancer thought to be related to deleterious *BRCA1/2* mutations (eg, prostate cancer, pancreatic cancer, melanoma). The same principles apply when considering genetic testing for Li-Fraumeni syndrome and Cowden syndrome (see below).

As previously discussed, testing of unaffected individuals should only be considered when an appropriate affected family member is not available for testing. Individuals who test positive for a mutation should follow the screening recommendations outlined in *BRCA Mutation-Positive Management* in the algorithm (and discussed below). Alternatively, testing another family member with the next highest likelihood of having a mutation may also be considered. For individuals who have not been tested or for those in whom variants of unknown significance are found (uninformative testing results), participation in a research program or individualized recommendations based on personal history and family history should be offered.

Counseling issues specific for both female and male carriers of a *BRCA1/2* mutation include the increased incidence of pancreatic cancer and melanoma. In addition, the risks to family members of individuals with a known *BRCA1/2* gene mutation (see *Risk Assessment* and *Genetic Testing*) 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 for prostate cancer and pancreatic cancer in male carriers of a *BRCA1/2* mutation.<sup>308-310</sup>

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 for 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 (available at [www.NCCN.org](http://www.NCCN.org)).

### 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.<sup>311</sup> For a woman who is a carrier of a *BRCA1/2* mutation, training in breast awareness with regular monthly practice should begin at age 18 years, and semiannual clinical breast examinations should begin at age 25 years. Between the ages of 25 and 29 years, the woman should have annual breast MRI screening (to be performed on days 7–15 of menstrual cycle for premenopausal

women) or annual mammograms if MRI is not available. The age to begin screening can be individualized if the family history includes a breast diagnosis prior to age 30.<sup>269,311-314</sup> Breast MRI screening is preferred over mammogram in the 25- to 29-year age group. High-quality breast MRI screening should consist of the following: dedicated breast coil, ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Between ages 30 and 75, annual mammogram and breast MRI should both be done. After age 75, management should be considered on an individual basis. In women treated for breast cancer, mammography and breast MRI screening should be done on remaining breast tissue.

Mammography has served as the standard screening modality for detection of breast cancer during the last few decades. There are currently no data indicating that mammography on its own reduces mortality in women with genetically increased risk for breast cancer.<sup>315</sup> Also, false-negative mammography results are common and have been correlated with factors such as presence of a *BRCA1/2* mutation and high breast tissue density,<sup>316-319</sup> both of which may occur more frequently among younger women. Rapidly growing or aggressive breast tumors—also more common among younger women—have also been associated with decreased sensitivity of mammographic screening methods.<sup>316,320</sup> Prospective studies on comparative surveillance modalities in women at high risk for familial breast cancer (ie, confirmed *BRCA1/2* mutation or suspected mutation based on family history) have consistently reported higher sensitivity of MRI screening (77%–94%) compared with mammography (33%–59%) in detecting breast cancers. False-positive rates were higher with MRI in some reports, resulting in a slightly lower or similar specificity with MRI screening (81%–98%) compared with mammography (92%–100%).<sup>311-313,321-323</sup> The sensitivity with ultrasound screening (33%–65%) appeared similar to that of

mammography in this high-risk population.<sup>311,321-323</sup> In a prospective screening trial (conducted from 1997–2009) that evaluated the performance of annual MRI and mammography in women (age 25–65 years; N = 496) with confirmed *BRCA1/2* mutation, sensitivity with MRI was significantly higher compared with mammography during the entire study period (86% vs. 19%;  $P < .0001$ ).<sup>324</sup> Sensitivity with MRI was higher during the early years (1997–2002; 74% vs. 35%) as well as the later years of the study (2003–2009; 94% vs. 9%). Factors such as age, mutation type, or invasiveness of the tumor did not significantly influence the relative sensitivity of the 2 screening modalities. Importantly, the large majority (97%) of cancers detected by MRI screening were early-stage tumors.<sup>324</sup> Among previously unaffected women diagnosed with invasive breast cancer during the study (n = 28), 1 patient died due to the cancer and 3 additional patients died due to other causes; the annual breast cancer-specific mortality rate was 0.5%. At a median follow-up of 8 years from diagnosis, none of the surviving patients (n = 24) has developed distant recurrence.<sup>324</sup> All of the studies discussed above evaluated a screening strategy that was conducted on an annual basis, and many of the studies included individuals without confirmed *BRCA1/2* mutation status. In a retrospective study, a different screening interval was evaluated, using alternating mammography and MRI screening every 6 months in women with confirmed *BRCA1/2* mutation (N = 73).<sup>325</sup> After a median follow-up of 2 years, 13 breast cancers were detected among 11 women; 12 of the tumors were detected by MRI screening but not by mammography obtained 6 months earlier. The sensitivity and specificity with MRI screening was 92% and 87%, respectively.<sup>325</sup>

The optimal surveillance approach in women at high risk for familial breast cancer remains uncertain, especially for women between the ages of 25 and 30 years. Although earlier studies have reported an

unlikely association between radiation exposure from mammography and increased risk for breast cancer in carriers of a *BRCA1/2* mutation,<sup>326,327</sup> a report from a large cohort study suggested an increased risk in women exposed to radiation at a young age.<sup>328</sup> A retrospective cohort study (from the GENE-RAD-RISK study) showed that exposure to diagnostic radiation (including mammography) prior to age 30 years was associated with increased risk for breast cancer in women with a *BRCA1/2* mutation (N = 1993).<sup>328</sup> Thus, one of the potential benefits of incorporating MRI modalities into surveillance strategies may include minimizing the radiation risks associated with mammography, in addition to the higher sensitivity of MRI screening in detecting tumors. The use of MRI, however, may potentially be associated with higher false-positive results and higher costs relative to mammography. The appropriate imaging modalities and surveillance intervals are still under investigation. In a report based on a computer simulation model that evaluated different annual screening strategies in *BRCA1/2* mutation carriers, a screening approach that included annual MRI starting at age 25 years combined with alternating digital mammography/MRI starting at age 30 years was shown to be the most effective strategy when radiation risks, life expectancy, and false-positive rates were considered.<sup>329</sup> Future prospective trials are needed to evaluate the different surveillance strategies in individuals at high risk for familial breast cancer. 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 guidelines from the ACS.<sup>269</sup>

Post-test counseling in women with a confirmed *BRCA1/2* mutation (or highly suspected of having the mutation based on presence of known deleterious mutation in the family) includes discussion of risk-reducing mastectomy and/or salpingo-oophorectomy. Counseling for these risk-



reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, reconstructive options, management of menopausal symptoms, and discussion of reproductive desires. It is important to address the psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures.

For women who have not elected ovarian cancer risk-reducing surgery, transvaginal ultrasound may be considered starting at age 30 to 35 years. Determining serum CA-125 levels may also be considered as a screening test. However, routine transvaginal ultrasound and determination of serum CA-125 levels are not endorsed, but may be done at the clinicians' discretion. These screening procedures have not been shown to be sufficiently sensitive or specific, and current research does not provide evidence that they are a reasonable substitute for a bilateral risk-reduction salpingo-oophorectomy in this population.<sup>330,331</sup>

Men testing positive for a *BRCA1/2* mutation should have an annual clinical breast examination, and undergo training in breast self-examination with regular monthly practice starting at age 35 years. Regularly scheduled mammography is not recommended by the panel, as there are only limited data to support breast imaging in men, since male breast cancer is rare. Screening for prostate cancer starting at age 40 years should be recommended for *BRCA2* carriers and considered for *BRCA1* carriers.

For both men and women testing positive for a *BRCA1/2* mutation, a full body skin and eye exam for melanoma screening and investigational protocols for pancreatic cancer screening should be considered. Although no specific screening guidelines exist for these tumor types, individualized screening approaches may be provided according to personal or family history of cancer.

### Risk Reduction Surgery

#### ***Bilateral Total Mastectomy***

Retrospective analyses with median follow-up periods of 13 to 14 years have indicated that bilateral risk-reduction mastectomy (RRM) decreased the risk of developing breast cancer by at least 90% in moderate- and high-risk women and in known *BRCA1/2* mutation carriers.<sup>332,333</sup> 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.<sup>334,335</sup>

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.<sup>336</sup> 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.<sup>337</sup>

#### ***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).<sup>83,84</sup> Although the risk for ovarian cancer is generally considered to be lower than the risk for breast cancer in a *BRCA1/2* mutation carrier,<sup>41,42,338</sup> 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 RRSO after completion of childbearing in these women. Rebbeck and colleagues found that the mean age of diagnosis of ovarian cancer was 50.8 years for *BRCA1/2* carriers.<sup>339</sup>

An observational prospective study of 5,783 women with a *BRCA1/2* mutation showed that ovarian cancer is more prevalent in individuals with *BRCA1* (4.2%) than *BRCA2* (0.6%) mutations.<sup>340</sup> In *BRCA1* mutation carriers, prevalence of ovarian, fallopian tube, and peritoneal cancers found during risk-reducing surgery was 1.5% for those younger than age 40 and 3.8% in those between the ages of 40 and 49.<sup>340</sup> The highest incidence rate for *BRCA1* mutation carriers was observed between the ages of 50 and 59 years (annual risk, 1.7%); for *BRCA2* mutation carriers, the highest incidence rate was observed between the ages of 60 and 69 years (annual risk, 0.6%). Therefore, the recommended age for RRSO could be younger for women with a *BRCA1* mutation than for women with a *BRCA2* mutation.

The effectiveness of RRSO in reducing the risk for 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 for ovarian or fallopian cancer following RRSO.<sup>341</sup> In a large prospective study of women who carried deleterious *BRCA1/2* mutations (N = 1079), RRSO significantly reduced the risk for *BRCA1*-associated gynecologic tumors (including ovarian, fallopian tube, or primary peritoneal cancers) by 85% compared with observation during a 3-year follow-up period (HR, 0.15; 95% CI, 0.04–0.56; *P* = .005).<sup>342</sup> An observational study of 5,783 women with a *BRCA1/2* mutation showed that risk-reducing oophorectomy reduces risk for ovarian, fallopian, or peritoneal cancer by 80% (HR, 0.20; 95% CI, 0.13–0.30) and all-cause mortality by 77% (HR, 0.23; 95% CI, 0.13–0.39).<sup>340</sup> RRSO reduces

mortality at all ages in *BRCA1* mutation carriers, but among *BRCA2* mutations carriers RRSO is only associated with reduced mortality in those between the ages of 41 and 60.<sup>340</sup> However, a 1% to 4.3% residual risk for a primary peritoneal carcinoma has been reported in some studies.<sup>114,339,341,343–345</sup> RRSO may provide an opportunity for gynecologic cancer detection in high-risk women. An analysis of 966 RRSO procedures showed that invasive or intraepithelial ovarian, tubal, or peritoneal neoplasms were detected in 4.6% of *BRCA1* carriers and 3.5% of *BRCA2* carriers.<sup>346</sup> Presence of a *BRCA1/2* mutation was associated with detection of clinically occult neoplasms during RRSO (*P* = .006).

RRSO is also reported to reduce the risk for breast cancer in carriers of a *BRCA1/2* mutation by approximately 50%.<sup>339,341,345,347</sup> In the case-control international study by Eisen et al, a 56% (OR, 0.44; 95% CI, 0.29–0.66; *P* < .001) and a 43% (OR, 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.<sup>347</sup> HRs of 0.47 (95% CI, 0.29–0.77)<sup>339</sup> and 0.30 (95% CI, 0.11–0.84; *P* = .022)<sup>344</sup> 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 meta-analysis that found similar reductions in breast cancer risk of approximately 50% for *BRCA1/2* mutation carriers following RRSO.<sup>341</sup> 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.<sup>342</sup> Another retrospective analysis including 676 women with stage I or II breast cancer and a *BRCA1/2* mutation showed that oophorectomy was associated with decreased risk of mortality from breast cancer in

*BRCA1* mutation carriers (HR, 0.38; 95% CI, 0.19–0.77,  $P = .007$ ), but not in carriers of a *BRCA2* mutation ( $P = .23$ ).<sup>348</sup> Mortality risk was also significantly impacted in *BRCA1/2* mutation carriers who had ER-negative breast cancer (HR, 0.07; 95% CI, 0.01–0.51,  $P = .009$ ).

A recent prospective cohort study from the Netherlands ( $N = 822$ ) did not find a statistically significant difference in breast cancer incidence between *BRCA1/2* mutation carriers who opted for an RRSO and women who did not, regardless of whether the mutation was for *BRCA1* or *BRCA2*.<sup>349</sup> Study investigators argued that previous study findings showing a 50% decrease in breast cancer risk may have been influenced by bias, specifically inclusion of patients with a history of breast or ovarian cancer in the comparison group and immortal person-time bias. One study that corrected for immortal person-time bias as a result of this analysis continued to find a protective effect of RRSO on breast cancer incidence in *BRCA1/2* mutation carriers (HR, 0.59; 95% CI, 0.42–0.82,  $P < .001$ ).<sup>350</sup>

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 an RRSO at age 40 years or younger (OR, 0.36; 95% CI, 0.20–0.64) relative to *BRCA1* carriers aged 41 to 50 years who had this procedure (OR, 0.50; 95% CI, 0.27–0.92).<sup>347</sup> A nonsignificant reduction in breast cancer risk was found for women aged 51 years or older, although only a small number of women were included in this group.<sup>347</sup> However, results from Rebbeck et al also suggest that RRSO after age 50 is not associated with a substantial decrease in breast cancer risk.<sup>345</sup> Due to the limited data, an optimal age for RRSO is difficult to specify.

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.<sup>351</sup> In addition, results of a case-control study of *BRCA1* mutation carriers showed no association between use of HRT and increased breast cancer risk in postmenopausal *BRCA1* mutation carriers.<sup>352</sup> However, caution should be used when considering use of HRT in mutation carriers following RRSO, given the limitations inherent in nonrandomized studies.<sup>353,354</sup>

Salpingectomy (surgical removal of the fallopian tube) completion rates are increasing, especially in women younger than age 50.<sup>355</sup> Despite some evidence regarding the safety and feasibility of this procedure,<sup>355,356</sup> more data are needed regarding its efficacy in reducing the risk for ovarian cancer.<sup>357</sup> Further, *BRCA1/2* carriers who undergo salpingectomy without oophorectomy may not get the 50% reduction in breast cancer risk that *BRCA1/2* carriers who undergo oophorectomy receive. Therefore, at this time, the panel does not recommend risk-reducing salpingectomy alone as the standard of care in *BRCA1/2* carriers.

The NCCN Guidelines Panel recommends RRSO for women with a known *BRCA1/2* mutation, typically between ages 35 and 40 years for women with a *BRCA1* mutation. For women with a *BRCA2* mutation who have undergone efforts to maximize their breast cancer prevention (ie, bilateral mastectomy), it is reasonable to delay RRSO until between ages 40 and 45 years since ovarian cancer onset tends to be later in women with a *BRCA2* mutation.<sup>340</sup> RRSO should only be considered upon completion of childbearing. Peritoneal washings should be performed at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.<sup>115,116</sup> The protocol published by the College of American Pathologists (2009) can be consulted for details on specimen evaluation.<sup>358</sup> See the NCCN



Guidelines for Ovarian Cancer for treatment of findings (available at [www.NCCN.org](http://www.NCCN.org)).

The decision to undergo RRSO is a complex one and should be made ideally in consultation with a gynecologic oncologist, especially when the patient wishes to undergo RRSO before the age at which it is typically recommended (ie, age 35). Topics that should be addressed include impact on reproduction, impact on breast and ovarian cancer risk, risks associated with premature menopause (eg, osteoporosis, cardiovascular disease, cognitive changes, changes to vasomotor symptoms, sexual concerns), and other medical issues. The panel recommends that a gynecologic oncologist help patients considering RRSO understand how it may impact quality of life.

### Chemoprevention

The use of selective estrogen receptor modulators (ie, tamoxifen, raloxifene) has been shown to reduce the risk for invasive breast cancer in postmenopausal women considered at high risk for developing breast cancer.<sup>359-364</sup> However, only limited data are available on the specific use of these agents in patients with *BRCA1/2* mutations. As previously discussed, patients with *BRCA1/2* mutations who are diagnosed with breast cancer have elevated risks for developing contralateral breast tumors. In one of the largest prospective series of *BRCA1/2* mutation carriers evaluated, the mean cumulative lifetime risks for contralateral breast cancer were estimated to be 83% for *BRCA1* carriers and 62% for *BRCA2* carriers.<sup>46</sup> Patients with *BRCA1/2* mutations who have intact contralateral breast tissue (and who do not undergo oophorectomy or receive chemoprevention) have an estimated 40% risk for contralateral breast cancer at 10 years.<sup>365</sup> Case-control studies from the Hereditary Breast Cancer Clinical Study Group reported that the use of tamoxifen protected against contralateral breast cancer with an OR of 0.38 (95%

CI, 0.19–0.74) to 0.50 (95% CI, 0.30–0.85) among *BRCA1* mutation carriers and 0.42 (95% CI, 0.17–1.02) to 0.63 (95% CI, 0.20–1.50) among *BRCA2* carriers.<sup>366,367</sup> This translates to an approximately 45% to 60% reduction in risk for contralateral tumors among *BRCA1/2* mutation carriers with breast cancer. The data were not consistent with regards to the protective effects of tamoxifen in the subset of *BRCA1/2* mutation carriers who also underwent oophorectomy. In addition, no data were available on the estrogen receptor status of the tumors. An evaluation of the subset of healthy individuals with a *BRCA1/2* mutation in the Breast Cancer Prevention Trial 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).<sup>368</sup> However, an analysis of 288 women who developed breast cancer during their participation in this trial showed that tamoxifen use was not associated with a reduction in breast cancer risk in those with a *BRCA1* mutation.<sup>368</sup> These findings may be related to the greater likelihood for development of estrogen receptor-negative tumors in *BRCA1* mutation carriers relative to *BRCA2* mutation carriers. However, this analysis was limited by the very small number of individuals with a *BRCA1/2* mutation (n = 19; 7% of participants diagnosed with breast cancer). Recently, common single-nucleotide polymorphisms were identified in genes (*ZNF423* and *CTSO*) that are involved in estrogen-dependent regulation of *BRCA1* expression.<sup>369</sup> These gene variants were associated with alterations in breast cancer risk during treatment with selective estrogen receptor modulators, and may eventually pave the way for predicting the likelihood of benefit with these chemopreventive approaches in individual patients.

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



risk for ovarian cancer by 45% to 50% in *BRCA1* mutation carriers and by 60% in *BRCA2* mutation carriers<sup>370,371</sup>; moreover, risks appeared to decrease with longer duration of oral contraceptive use.<sup>371</sup> In a 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 for 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).<sup>372</sup> A more recent meta-analysis including one cohort study (N = 3,181) and three case-control studies (1,096 cases and 2,878 controls) also showed an inverse association between ovarian cancer and having ever used oral contraceptives (OR, 0.58; 95% CI = 0.46–0.73).<sup>373</sup>

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 (OR, 1.20; 95% CI, 1.02–1.40), but not among *BRCA2* mutation carriers.<sup>374</sup> Among *BRCA1* mutation carriers, breast cancer risks with oral contraceptives were significantly associated with ≥5 years of oral contraceptive use (OR, 1.33; 95% CI, 1.11–1.60), breast cancer diagnosed before age 40 (OR, 1.38; 95% CI, 1.11–1.72), and use of oral contraceptives before 1975 (OR, 1.42; 95% CI, 1.17–1.75).<sup>374</sup> In another case-control study, oral contraceptive use for at least 1 year was not significantly associated with breast cancer risks in either *BRCA1/2* mutation carriers.<sup>375</sup> However, among *BRCA2* mutation carriers, use of oral contraceptives for at least 5 years was associated with a significantly increased risk for breast cancer (OR, 2.06; 95% CI, 1.08–3.94); results were similar when only the cases with oral contraceptive use on or after 1975 were considered.<sup>375</sup> Other case-

control studies have reported no significant associations with oral contraceptive use (especially with the use of low-dose formulations after 1975) and risks for breast cancer in *BRCA1/2* mutation carriers.<sup>376,377</sup> 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 (OR, 0.22; 95% CI, 0.10–0.49; *P* < .001), though not for *BRCA2* mutation carriers.<sup>377</sup> Differences in the study design employed by these case-control studies make it difficult to compare outcomes between studies, and likely account for the conflicting results. The study design might have differed with regard to factors such as the criteria for defining the “control” population for the study (eg, 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 (eg, nationality, ethnicity, geographic region, age groups), age of onset of breast cancer, and formulations or duration of oral contraceptives used. Two meta-analyses showed that oral contraceptive use is not significantly associated with breast cancer risk in *BRCA1/2* mutation carriers.<sup>372,373</sup>

### Reproductive Options

The outcomes of genetic testing can have a profound impact on family planning decisions for individuals of reproductive age who are found to be carriers of *BRCA1/2* mutations. 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 *BRCA1/2* 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.<sup>310,378</sup> 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 (ie, 6 to 8 cells) after in vitro fertilization (IVF). This procedure allows for the selection of unaffected embryos to be transferred to the uterus,<sup>310,378</sup> and may, therefore, offer the advantage of avoiding potential termination of pregnancy. The PGD process requires the use of IVF regardless of the fertility status of the couple (ie, 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 geographic 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.<sup>310,378</sup> For example, PGD may be considered in cases where both partners carry a *BRCA2* mutation, for which there may be a high risk for the offspring to develop Fanconi anemia, a rare autosomal recessive condition.<sup>309</sup> Although the use of prenatal diagnosis or PGD is relatively well established for severe hereditary disorders with very high penetrance and/or early onset, its use in conditions associated with lower penetrance and/or later onset (eg, 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, and social and economic factors. Based on results from surveys administered to women at high risk for hereditary breast or ovarian cancer, 50% to 75% of respondents felt that PGD was an acceptable option for high-risk individuals,<sup>379,380</sup> yet only about 14% to 33% would consider undergoing PGD themselves.<sup>379,381</sup> A survey in high-risk men (N = 228; carriers of a *BRCA* mutation; or having a partner or first-degree relative with a *BRCA* mutation) showed that 80% of these men were unaware of PGD; after being informed of the definition of PGD, 34% indicated that they would consider the option of using PGD.<sup>382</sup> Importantly, these surveys suggested that the majority of high-risk women and men have little or no knowledge of PGD,<sup>380,382,383</sup> 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,<sup>384,385</sup> 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 *BRCA1/2* 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 *Li-Fraumeni Syndrome Testing Criteria* in the algorithm). Cancers associated with LFS include but are not limited to premenopausal breast cancer, bone

and soft tissue sarcomas, CNS tumor, adrenocortical carcinoma, unusually early onset of other adenocarcinomas, or other childhood cancers.<sup>148,164,171</sup> 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. The NCCN Guidelines Panel also suggests consideration of *TP53* mutation testing in those with early-onset breast cancer ( $\leq 30$  years of age), given the association between early-onset breast cancer and *TP53* mutations.<sup>148,173,175,176</sup> This testing may be done alone, concurrently with *BRCA1/2* testing, or as a follow-up test if the *BRCA1/2* testing result is negative. 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.

An individual with a known deleterious *TP53* mutation in a close family member who does not undergo testing should be followed according to the same recommendations as a carrier of a *TP53* mutation (see *Li-Fraumeni Syndrome Management* in the algorithm). 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 *BRCA-Related Breast and/or Ovarian Cancer Syndrome Testing Criteria* and *Cowden Syndrome Testing Criteria* in the algorithm). Alternatively, testing another family member with the next highest likelihood of having a mutation may be considered. As previously discussed in the *BRCA1/2* testing section above, testing of unaffected individuals should only be considered when an appropriate affected family member is not available for testing.

Importantly, the significant limitations of interpreting testing results for an unaffected individual should be discussed prior to testing.

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 at the age of the earliest known breast cancer in the family, if below age 20 years) because of the very early age of breast cancer onset seen in these families. Recommendations for breast screening in LFS are similar to those for *BRCA*-related breast and ovarian cancer syndrome management, although screening is begun at an earlier age. They include annual breast MRI screening (preferred) or mammogram if MRI is not available for women ages 20 to 29; annual mammogram and breast MRI screening in women ages 30 to 75; and management on an individual basis for women older than 75 years. For women with a family history of breast cancer diagnosed earlier than age 20 years, breast MRI screening may begin at the earliest age of diagnosis. In women treated for breast cancer, mammography and breast MRI screening should be done on remaining breast tissue.

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. Counseling for risk-reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries, and reconstructive options. It is also important to address the psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures.



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, especially when there is a high index of suspicion for second malignancies in cancer survivors and rare cancers (see *Li-Fraumeni Syndrome Management* in the algorithm). Clinicians should address screening limitations for other cancers associated with LFS. Colonoscopy should be considered every 2 to 5 years, starting at age 25, or 5 years before the earliest known colon cancer diagnosis in family history. 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 dermatologic and neurologic examination should be done. Pediatricians should be made aware of the risk for childhood cancers in affected families.

Whole-body MRI for screening of cancers associated with LFS is being evaluated in multiple international trials. Other LFS screening components are being evaluated in protocols, including regular blood screening for hematologic malignancies, and biochemical screening. In a prospective observational study, a clinical surveillance protocol for asymptomatic *TP53* mutation carriers from eight families affected by LFS was incorporated.<sup>386</sup> 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 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 the 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 the abdomen and pelvis every 3 to 4 months, complete urinalysis every

3 to 4 months, and 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.<sup>386</sup> 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%;  $P = .016$ ).<sup>386</sup> 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. Annual whole-body MRI with rapid non-contrast exams may be considered. The brain may be examined as part of whole-body MRI or as a separate exam.

Only very limited data exist on the use of prenatal diagnostics/genetic testing for *TP53* mutations in families with LFS.<sup>387,388</sup> Counseling for reproductive options such as prenatal diagnosis, PGD, and assisted reproduction may be warranted for couples expressing concern over the mutation carrier status of their future offspring. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options. For general discussions on the topic of reproductive options and counseling considerations, see the Discussion section above on *Reproductive Options* under *Risk*



*Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome.*

### **Risk Assessment, Counseling, and Management: Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome**

The assessment of individuals suspected of having Cowden syndrome/PHTS 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 Cowden Syndrome/PHTS Testing Criteria in the algorithm). The NCCN Guidelines Panel has established a list of criteria to help indicate which individuals are candidates for *PTEN* gene mutation testing (see Cowden Syndrome/PHTS Testing Criteria in the algorithm). These criteria are used to assess the need for further risk assessment and genetic testing, but are not intended to serve as clinical diagnostic criteria.

#### **Testing Criteria**

Testing criteria for Cowden syndrome/PHTS 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 includes individuals meeting diagnostic criteria for Cowden syndrome<sup>389</sup>; or 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 it is unlikely that any of these conditions can stand alone as a definitive diagnostic criterion of Cowden syndrome/PHTS. Another criterion that can be considered to be sufficient to warrant *PTEN* gene mutation testing is a

family history that includes the presence of a known deleterious *PTEN* mutation.

The next category of criteria represents “major” features associated with Cowden syndrome/PHTS.<sup>180,184,192,389</sup> The major criteria include the presence of breast cancer, macrocephaly (ie, megalcephaly),<sup>211</sup> endometrial cancer, follicular thyroid cancer, multiple gastrointestinal hamartomas or ganglioneuromas, macular pigmentation of glans penis, and certain mucocutaneous lesions that are often observed in patients with Cowden syndrome (ie, one biopsy-proven trichilemmoma, multiple palmoplantar keratoses, multiple or extensive oral mucosal papillomatosis, multiple cutaneous facial papules). 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/PHTS, and clinical judgment is needed when evaluating such lesions. An individual exhibiting 2 or more major criteria where one criterion is macrocephaly meets the testing threshold. An individual with 3 or more major criteria (without macrocephaly) is also considered to meet the threshold for testing. In addition, individuals exhibiting 1 major criterion with 3 or more minor criteria (discussed below) also meet the testing threshold; if an individual exhibits 2 or more major criteria (eg, breast cancer, follicular thyroid cancer) but does not have macrocephaly, then one of the major criteria may be included as one of the 3 minor criteria to meet the testing threshold.

The final category of criteria represents features with a “minor” association with Cowden syndrome/PHTS.<sup>180,184,192,389</sup> These include autism spectrum disorder (without macrocephaly), colon cancer, esophageal glycogenic acanthosis (3 or more), lipomas, intellectual disability, papillary or follicular variant of papillary thyroid cancer, thyroid

structural lesions other than follicular thyroid cancer (eg, adenoma, nodules, goiter), renal cell carcinoma, a single gastrointestinal hamartoma or ganglioneuroma, testicular lipomatosis, or vascular anomalies (including multiple intracranial developmental venous anomalies). The panel felt that evidence from the literature was insufficient to include fibrocystic breast disease, fibromas, or uterine fibroids as part of the testing criteria. An individual would need to exhibit 4 or more minor criteria or, as discussed above, 3 or more minor and one major criterion to meet testing.

Lastly, an at-risk individual (first-degree relative of an affected individual) with one or more major criterion or 2 or more minor criteria, along with a relative diagnosed with Cowden syndrome/PHTS or BBRs (for whom testing has not been performed), would also meet the threshold for *PTEN* testing. Individuals not meeting testing criteria should be followed according to recommendations tailored to his/her personal cancer history and family history.

### Genetic Testing

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. A comprehensive clinical test should not include testing for succinate dehydrogenase (*SDH*), as there is no conclusive evidence that this gene is associated with PHTS.<sup>390</sup>

### Clinical Diagnostic Criteria

The *PTEN* mutation frequency in individuals meeting International Cowden Consortium diagnostic criteria for Cowden syndrome has previously been estimated at about 80%.<sup>188,213</sup> However, evaluation of data based on samples analyzed at a single academic pathology

laboratory (N = 802 evaluable) reported a much lower frequency (34%) of *PTEN* mutations among individuals meeting diagnostic criteria<sup>184</sup> for Cowden syndrome.<sup>180</sup> The authors concluded that the current Consortium diagnostic criteria are not as sensitive in identifying individuals with *PTEN* mutations as previously estimated. Since *PTEN* mutations are relatively rare, recommendations regarding Cowden syndrome diagnostic criteria may be based on studies with a small number of patients. Studies with larger samples have their flaws as well, as patients are selected for testing based on the number and magnitude of clinical features, which may lead to overestimation of the features of Cowden syndrome.<sup>188</sup> A review was conducted examining each consortium diagnostic criterion, and revised criteria were proposed that are more stringent and take into account clinical features that are often seen in PHTS.<sup>188</sup> The criteria were designed by focusing on clinical features associated with *PTEN* mutations. The panel recommends using these criteria for clinical diagnosis of PHTS.

Like the testing criteria, diagnostic criteria are categorized as major and minor. Major criteria are as follows: breast cancer, epithelial endometrial cancer, follicular thyroid cancer, 3 or more gastrointestinal hamartomas (including ganglioneuromas, excluding hyperplastic polyps), LDD, macrocephaly (regardless of stature, 58 cm for females, 60 cm for males), and macular pigmentation of the glans penis. A final major criterion is multiple mucocutaneous lesions (3 or more multiple trichilemmomas, 3 or more palmoplantar keratotic pits and/or acral hyperkeratotic papules, 3 or more mucocutaneous neuromas, or oral papillomas). Oral papillomas may be included if there are 3 or more, or if there is evidence from a biopsy or from a dermatologist diagnosis.

Minor criteria include the following: autism spectrum disorder, colon cancer, 3 or more esophageal glycogenic acanthosis, 3 or more lipomas, mental retardation (IQ ≤75), renal cell carcinoma, testicular

lipomatosis, thyroid cancer (papillary or follicular variant of papillary), thyroid structural lesions, and vascular anomalies (eg, multiple intracranial developmental venous anomalies).

A clinical diagnosis in an individual would include the following: exhibiting 3 or more major criteria where one is macrocephaly, LDD, or gastrointestinal hamartomas; or 2 major and 3 minor criteria. A clinical diagnosis in a family in which one individual meets these PHTS clinical diagnosis criteria or has a *PTEN* mutation would include the following: any 2 major criteria with or without any minor criteria; 1 major and 2 minor criteria; or 3 minor criteria.

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 *Cowden Syndrome/PHTS Management* in the algorithm). 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 Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria and *Li-Fraumeni Syndrome Testing Criteria* in the algorithm). Alternatively, testing another family member with the next highest likelihood of having a mutation may be considered. Multi-gene testing may also be considered.

If a *PTEN* mutation is not found, or a VUS was found and Cowden syndrome/PHTS diagnostic criteria are met, then individual management should proceed based on the recommended guidelines (see *Cowden Syndrome/PHTS Management* in the algorithm). If diagnostic criteria are not met, then research and individualized recommendations based on personal and family history should be offered.

## Screening Recommendations

Cancer is the major health risk associated with Cowden syndrome/PHTS. Therefore, the NCCN Panel had outlined guidelines for prevention and early detection screening of commonly associated cancers with Cowden syndrome/PHTS. Current medical management recommendations for individuals with Cowden syndrome/PHTS include annual physical examinations, starting at age 18 years (or 5 years before the youngest age of diagnosis of a component cancer in the family).

The recommendations for *women* with Cowden syndrome/PHTS focus on primary and secondary prevention options for breast cancer since this is the most commonly associated cancer in individuals with Cowden syndrome/PHTS based on the available literature. Women should begin regular monthly breast self-examinations at age 18 and have a semiannual clinical breast examination beginning at age 25 or 5 to 10 years earlier than the earliest known breast cancer in the family (whichever comes first). Women should also have an annual mammogram and breast MRI screening starting at ages 30 to 35 years, or 5 to 10 years earlier than the earliest known breast cancer in the family (whichever comes first). After age 75, management should be considered on an individual basis. In women treated for breast cancer, mammography and breast MRI screening should be done on remaining breast tissue.

Although there are no data regarding risk reduction surgery in women with Cowden syndrome, the option of RRM and hysterectomy should be discussed on a case-by-case basis. Oophorectomy is not indicated for Cowden syndrome alone, but may be indicated for other reasons. Counseling for risk-reducing surgeries may include discussion of extent of cancer risk reduction/protection, risks associated with surgeries,



reconstructive options, and reproductive desires. It is also important to address the psychosocial and quality-of-life aspects of undergoing risk-reducing surgical procedures.

The panel recommends patient education regarding the symptoms of endometrial cancer including the necessity of a prompt response to such symptoms. For endometrial cancer screening, women diagnosed with Cowden syndrome should consider annual random endometrial biopsies and/or ultrasound beginning at age 30 to 35.

Both men and women with Cowden syndrome/PHTS have approximately at least a 3% to 10% lifetime risk of developing thyroid cancer,<sup>17</sup> compared to about 1% in the general population.<sup>391</sup> An annual thyroid ultrasound should be performed, beginning at the time of PHTS diagnosis. In addition, colonoscopy is recommended starting at age 35 years, or earlier if symptomatic. If a close relative was diagnosed with colon cancer before age 40, then colonoscopy screening should begin 5 to 10 years before the age of the earliest known diagnosis. Colonoscopy should be performed every 5 years or more frequently in cases where the patient is symptomatic or polyps are found. To screen for renal cell carcinoma, renal ultrasound should be considered every 1 to 2 years beginning at age 40. Dermatologic management may be considered for some patients. If there are symptoms in children, then assessment of psychomotor abilities should be considered, as well as a brain MRI. 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.

No published data exist on the use of prenatal diagnostics/genetic testing for *PTEN* mutations in families with Cowden syndrome. However, for couples expressing the desire that their offspring not carry a familial *PTEN* mutation, options for prenatal diagnosis, PGD, and

assisted reproduction can be discussed. Such counseling should include a comprehensive discussion of the potential risks, benefits, and limitations of reproductive options. For general discussions on the topic of reproductive options and counseling considerations, see the Discussion section above on *Reproductive Options* under *Risk Assessment, Counseling, and Management: BRCA-Related Breast/Ovarian Cancer Syndrome*.



**Table 1. Glossary of Relevant Genetic Terms (from the National Cancer Institute [NCI])**

***Autosomal dominant***

Autosomal dominant inheritance refers to genetic conditions that occur when a mutation is present in one copy of a given gene (ie, 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 (ie, 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 (ie, 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 proband, and in females it is called a probanda.

***Sporadic cancer***

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



**Table 2. Genetic Test Results to Determine the Presence of a Cancer-Predisposing Gene**

<b>Result</b>	<b>Description</b>
<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.

### References

1. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759-767. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2188735>.
2. Vogelstein B, Kinzler KW. The multistep nature of cancer. *Trends Genet* 1993;9:138-141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8516849>.
3. Lynch HT, Watson P, Conway TA, Lynch JF. Clinical/genetic features in hereditary breast cancer. *Breast Cancer Res Treat* 1990;15:63-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2322650>.
4. Pharoah PD, Day NE, Duffy S, et al. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997;71:800-809. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9180149>.
5. Berliner JL, Fay AM. Risk assessment and genetic counseling for hereditary breast and ovarian cancer: recommendations of the National Society of Genetic Counselors. *J Genet Couns* 2007;16:241-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17508274>.
6. Foulkes WD. Inherited susceptibility to common cancers. *N Engl J Med* 2008;359:2143-2153. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19005198>.
7. Trepanier A, Ahrens M, McKinnon W, et al. Genetic cancer risk assessment and counseling: recommendations of the national society of genetic counselors. *J Genet Couns* 2004;13:83-114. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15604628>.
8. Pharoah PD, Antoniou A, Bobrow M, et al. Polygenic susceptibility to breast cancer and implications for prevention. *Nat Genet* 2002;31:33-36. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11984562>.
9. Lancaster JM, Powell CB, Chen LM, Richardson DL. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol* 2015;136:3-7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25238946>.
10. Shiovitz S, Korde LA. Genetics of breast cancer: a topic in evolution. *Ann Oncol* 2015;26:1291-1299. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25605744>.
11. Moyer VA. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:271-281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24366376>.
12. Weitzel JN, Blazer KR, MacDonald DJ, et al. Genetics, genomics, and cancer risk assessment: state of the art and future directions in the era of personalized medicine. *CA Cancer J Clin* 2011;61:327-359. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21858794>.
13. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: [http://www.nlm.nih.gov/bsd/bsd\\_key.html](http://www.nlm.nih.gov/bsd/bsd_key.html). Accessed July 24, 2014.
14. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25559415>.
15. Blackwood MA, Weber BL. BRCA1 and BRCA2: from molecular genetics to clinical medicine. *J Clin Oncol* 1998;16:1969-1977. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9586917>.
16. Venkitaraman AR. Cancer susceptibility and the functions of BRCA1 and BRCA2. *Cell* 2002;108:171-182. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11832208>.
17. Pilarski R. Cowden syndrome: a critical review of the clinical literature. *J Genet Couns* 2009;18:13-27. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18972196>.
18. Schneider KA, Garber J. Li-Fraumeni syndrome. *GeneReviews*; 2013. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1311/>.

19. Brooks-Wilson AR, Kaurah P, Suriano G, et al. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. *J Med Genet* 2004;41:508-517. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15235021>.
20. Kaurah P, MacMillan A, Boyd N, et al. Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. *JAMA* 2007;297:2360-2372. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17545690>.
21. Schrader KA, Masciari S, Boyd N, et al. Hereditary diffuse gastric cancer: association with lobular breast cancer. *Fam Cancer* 2008;7:73-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18046629>.
22. Masciari S, Larsson N, Senz J, et al. Germline E-cadherin mutations in familial lobular breast cancer. *J Med Genet* 2007;44:726-731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17660459>.
23. Oliveira C, Bordin MC, Grehan N, et al. Screening E-cadherin in gastric cancer families reveals germline mutations only in hereditary diffuse gastric cancer kindred. *Hum Mutat* 2002;19:510-517. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11968083>.
24. Simon R, Zhang X. On the dynamics of breast tumor development in women carrying germline BRCA1 and BRCA2 mutations. *Int J Cancer* 2008;122:1916-1917. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18098285>.
25. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. *Obstet Gynecol* 2009;113:957-966. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19305347>.
26. Whittemore AS. Risk of breast cancer in carriers of BRCA gene mutations. *N Engl J Med* 1997;337:788-789. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9289641>.
27. Metcalfe KA, Poll A, Royer R, et al. Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. *J Clin Oncol* 2010;28:387-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20008623>.
28. Bergman A, Einbeigi Z, Olofsson U, et al. The western Swedish BRCA1 founder mutation 3171ins5; a 3.7 cM conserved haplotype of today is a reminiscence of a 1500-year-old mutation. *Eur J Hum Genet* 2001;9:787-793. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11781691>.
29. Csokay B, Udvarhelyi N, Sulyok Z, et al. High frequency of germline BRCA2 mutations among Hungarian male breast cancer patients without family history. *Cancer Res* 1999;59:995-998. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10070953>.
30. Ji J, Hemminki K. Familial risk for histology-specific bone cancers: an updated study in Sweden. *Eur J Cancer* 2006;42:2343-2349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16859907>.
31. Mikaelssdottir EK, Valgeirsdottir S, Eyfjord JE, Rafnar T. The Icelandic founder mutation BRCA2 999del5: analysis of expression. *Breast Cancer Res* 2004;6:R284-290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15217494>.
32. Petrij-Bosch A, Peelen T, van Vliet M, et al. BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients. *Nat Genet* 1997;17:341-345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9354803>.
33. Tonin PN, Mes-Masson AM, Futreal PA, et al. Founder BRCA1 and BRCA2 mutations in French Canadian breast and ovarian cancer families. *Am J Hum Genet* 1998;63:1341-1351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9792861>.
34. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The Breast Cancer Linkage Consortium. *Am J Hum Genet*



1998;62:676-689. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9497246>.

35. Yun MH, Hiom K. Understanding the functions of BRCA1 in the DNA-damage response. Biochem Soc Trans 2009;37:597-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19442256>.

36. Cipak L, Watanabe N, Bessho T. The role of BRCA2 in replication-coupled DNA interstrand cross-link repair in vitro. Nat Struct Mol Biol 2006;13:729-733. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16845393>.

37. Wooster R, Neuhausen SL, Mangion J, et al. Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. Science 1994;265:2088-2090. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8091231>.

38. Abeliovich D, Kaduri L, Lerer I, et al. The founder mutations 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2 appear in 60% of ovarian cancer and 30% of early-onset breast cancer patients among Ashkenazi women. Am J Hum Genet 1997;60:505-514. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9042909>.

39. Levy-Lahad E, Catane R, Eisenberg S, et al. Founder BRCA1 and BRCA2 mutations in Ashkenazi Jews in Israel: frequency and differential penetrance in ovarian cancer and in breast-ovarian cancer families. Am J Hum Genet 1997;60:1059-1067. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9150153>.

40. Petrucelli N, Daly MB, Bars Culver JO, Feldman GL. BRCA1 and BRCA2 hereditary breast/ovarian cancer. GeneReviews; 2011. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1247/>.

41. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br J Cancer 2000;83:1301-1308. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/11044354>.

42. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-1130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12677558>.

43. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25:1329-1333. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17416853>.

44. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 1994;343:692-695. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/7907678>.

45. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science 2003;302:643-646. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/14576434>.

46. Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst 2013;105:812-822. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23628597>.

47. Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98:1694-1706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17148771>.

48. van den Broek AJ, van 't Veer LJ, Hoening MJ, et al. Impact of age at primary breast cancer on contralateral breast cancer risk in BRCA1/2 mutation carriers. J Clin Oncol 2016;34:409-418. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/26700119>.

49. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a

BRCA1 or BRCA2 Mutation. JAMA 2006;296:185-192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16835424>.

50. Risch HA, McLaughlin JR, Cole DE, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001;68:700-710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11179017>.

51. Rebbeck TR, Mitra N, Wan F, et al. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. Jama 2015;313:1347-1361. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25849179>.

52. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol 2008;26:4282-4288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18779615>.

53. Eerola H, Heikkila P, Tamminen A, et al. Relationship of patients' age to histopathological features of breast tumours in BRCA1 and BRCA2 and mutation-negative breast cancer families. Breast Cancer Res 2005;7:R465-469. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15987451>.

54. Lakhani SR, Reis-Filho JS, Fulford L, et al. Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 2005;11:5175-5180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16033833>.

55. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002;20:2310-2318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11981002>.

56. Lee E, McKean-Cowdin R, Ma H, et al. Characteristics of triple-negative breast cancer in patients with a BRCA1 mutation: results from a population-based study of young women. J Clin Oncol 2011;29:4373-4380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22010008>.

57. Young SR, Pilarski RT, Donenberg T, et al. The prevalence of BRCA1 mutations among young women with triple-negative breast cancer. BMC Cancer 2009;9:86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19298662>.

58. Evans DG, Howell A, Ward D, et al. Prevalence of BRCA1 and BRCA2 mutations in triple negative breast cancer. J Med Genet 2011;48:520-522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21653198>.

59. Fostira F, Tsilaidou M, Papadimitriou C, et al. Prevalence of BRCA1 mutations among 403 women with triple-negative breast cancer: implications for genetic screening selection criteria: a Hellenic Cooperative Oncology Group study. Breast Cancer Res Treat 2012;134:353-362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22434525>.

60. Gonzalez-Angulo AM, Timms KM, Liu S, et al. Incidence and Outcome of BRCA Mutations in Unselected Patients with Triple Receptor-Negative Breast Cancer. Clin Cancer Res 2011;17:1082-1089. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21233401>.

61. Rummel S, Varner E, Shriver CD, Ellsworth RE. Evaluation of BRCA1 mutations in an unselected patient population with triple-negative breast cancer. Breast Cancer Res Treat 2013;137:119-125. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23192404>.

62. Saura C, Saanez-Olle G, Bosch N, et al. High prevalence of BRCA1/2 germline mutations in female breast cancer patients with triple-negative phenotype (TNBC) and family history [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 1534. Available at: [http://meeting.ascopubs.org/cgi/content/abstract/28/15\\_suppl/1534](http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/1534).

63. Couch FJ, Hart SN, Sharma P, et al. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. *J Clin Oncol* 2015;33:304-311. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25452441>.

64. Tun NM, Villani G, Ong K, et al. Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: a meta-analysis. *Clin Genet* 2014;85:43-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24000781>.

65. Meyer P, Landgraf K, Hogel B, et al. BRCA2 mutations and triple-negative breast cancer. *PLoS One* 2012;7:e38361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22666503>.

66. Comen E, Davids M, Kirchhoff T, et al. Relative contributions of BRCA1 and BRCA2 mutations to "triple-negative" breast cancer in Ashkenazi Women. *Breast Cancer Res Treat* 2011;129:185-190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21394499>.

67. Lee LJ, Alexander B, Schnitt SJ, et al. Clinical outcome of triple negative breast cancer in BRCA1 mutation carriers and noncarriers. *Cancer* 2011;117:3093-3100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21264845>.

68. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. *J Clin Oncol* 2004;22:735-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14966099>.

69. Basham VM, Lipscombe JM, Ward JM, et al. BRCA1 and BRCA2 mutations in a population-based study of male breast cancer. *Breast Cancer Res* 2002;4:R2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11879560>.

70. Couch FJ, Farid LM, DeShano ML, et al. BRCA2 germline mutations in male breast cancer cases and breast cancer families. *Nat Genet*

1996;13:123-125. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8673091>.

71. Ding YC, Steele L, Kuan CJ, et al. Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. *Breast Cancer Res Treat* 2011;126:771-778. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20927582>.

72. Friedman LS, Gayther SA, Kurosaki T, et al. Mutation analysis of BRCA1 and BRCA2 in a male breast cancer population. *Am J Hum Genet* 1997;60:313-319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9012404>.

73. Evans DG, Susnerwala I, Dawson J, et al. Risk of breast cancer in male BRCA2 carriers. *J Med Genet* 2010;47:710-711. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20587410>.

74. Tai YC, Domchek S, Parmigiani G, Chen S. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. *J Natl Cancer Inst* 2007;99:1811-1814. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18042939>.

75. What are the key statistics about breast cancer in men? 2015. Available at: <http://www.cancer.org/cancer/breastcancerinmen/detailedguide/breast-cancer-in-men-key-statistics>. Accessed May 28, 2015.

76. Pal T, Bonner D, Cragun D, et al. A high frequency of BRCA mutations in young black women with breast cancer residing in Florida. *Cancer* 2015;121:4173-4180. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26287763>.

77. Bordeleau L, Panchal S, Goodwin P. Prognosis of BRCA-associated breast cancer: a summary of evidence. *Breast Cancer Res Treat* 2010;119:13-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19789974>.



78. Verhoog LC, Berns EM, Brekelmans CT, et al. Prognostic significance of germline BRCA2 mutations in hereditary breast cancer patients. *J Clin Oncol* 2000;18:119s-124s. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11060339>.
79. Zhong Q, Peng HL, Zhao X, et al. Effects of BRCA1- and BRCA2-related mutations on ovarian and breast cancer survival: a meta-analysis. *Clin Cancer Res* 2015;21:211-220. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25348513>.
80. van den Broek AJ, Schmidt MK, van 't Veer LJ, et al. Worse breast cancer prognosis of BRCA1/BRCA2 mutation carriers: what's the evidence? A systematic review with meta-analysis. *PLoS One* 2015;10:e0120189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25816289>.
81. Nilsson MP, Hartman L, Idvall I, et al. Long-term prognosis of early-onset breast cancer in a population-based cohort with a known BRCA1/2 mutation status. *Breast Cancer Res Treat* 2014;144:133-142. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24477976>.
82. Noori SF, Gangi A, Nelson ME, et al. Comparison of nodal metastasis between BRCA mutation carriers and non-BRCA mutation carriers with breast cancer. *Ann Surg Oncol* 2014;21:3324-3329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25047471>.
83. Levine DA, Argenta PA, Yee CJ, et al. Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. *J Clin Oncol* 2003;21:4222-4227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14615451>.
84. Piver MS, Jishi MF, Tsukada Y, Nava G. Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. A report of the Gilda Radner Familial Ovarian Cancer Registry. *Cancer* 1993;71:2751-2755. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8467455>.
85. Jazaeri AA, Lu K, Schmandt R, et al. Molecular determinants of tumor differentiation in papillary serous ovarian carcinoma. *Mol Carcinog* 2003;36:53-59. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12557260>.
86. Norquist BM, Harrell MI, Brady MF, et al. Inherited mutations in women with ovarian carcinoma. *JAMA Oncol* 2015;1-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26720728>.
87. Song H, Cicek MS, Dicks E, et al. The contribution of deleterious germline mutations in BRCA1, BRCA2 and the mismatch repair genes to ovarian cancer in the population. *Hum Mol Genet* 2014;23:4703-4709. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24728189>.
88. Pal T, Permuth-Wey J, Betts JA, et al. BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. *Cancer* 2005;104:2807-2816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16284991>.
89. Schrader KA, Hurlburt J, Kalloger SE, et al. Germline BRCA1 and BRCA2 mutations in ovarian cancer: utility of a histology-based referral strategy. *Obstet Gynecol* 2012;120:235-240. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22776961>.
90. Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecol Oncol* 2011;121:353-357. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21324516>.
91. Gayther SA, Russell P, Harrington P, et al. The contribution of germline BRCA1 and BRCA2 mutations to familial ovarian cancer: no evidence for other ovarian cancer-susceptibility genes. *Am J Hum Genet* 1999;65:1021-1029. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10486320>.
92. Sekine M, Nagata H, Tsuji S, et al. Localization of a novel susceptibility gene for familial ovarian cancer to chromosome 3p22-p25.



Hum Mol Genet 2001;10:1421-1429. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/11440995>.

93. Lynch HT, Casey MJ, Snyder CL, et al. Hereditary ovarian carcinoma: heterogeneity, molecular genetics, pathology, and management. Mol Oncol 2009;3:97-137. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19383374>.

94. Kauff ND, Mitra N, Robson ME, et al. Risk of ovarian cancer in BRCA1 and BRCA2 mutation-negative hereditary breast cancer families. J Natl Cancer Inst 2005;97:1382-1384. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16174860>.

95. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol 2012;30:2654-2663. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22711857>.

96. Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012;307:382-390. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22274685>.

97. Cass I, Baldwin RL, Varkey T, et al. Improved survival in women with BRCA-associated ovarian carcinoma. Cancer 2003;97:2187-2195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12712470>.

98. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, et al. Effect of BRCA1/2 mutations on long-term survival of patients with invasive ovarian cancer: the national Israeli study of ovarian cancer. J Clin Oncol 2008;26:20-25. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18165636>.

99. Tan DS, Rothermundt C, Thomas K, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol 2008;26:5530-5536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18955455>.

100. Yang D, Khan S, Sun Y, et al. Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer. JAMA 2011;306:1557-1565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21990299>.

101. Berchuck A, Heron KA, Carney ME, et al. Frequency of germline and somatic BRCA1 mutations in ovarian cancer. Clin Cancer Res 1998;4:2433-2437. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9796975>.

102. Bjorge T, Lie AK, Hovig E, et al. BRCA1 mutations in ovarian cancer and borderline tumours in Norway: a nested case-control study. Br J Cancer 2004;91:1829-1834. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15477862>.

103. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res 2004;10:2473-2481. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15073127>.

104. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/18208621>.

105. Rechsteiner M, Zimmermann AK, Wild PJ, et al. TP53 mutations are common in all subtypes of epithelial ovarian cancer and occur concomitantly with KRAS mutations in the mucinous type. Exp Mol Pathol 2013;95:235-241. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23965232>.

106. Werness BA, Ramus SJ, DiCioccio RA, et al. Histopathology, FIGO stage, and BRCA mutation status of ovarian cancers from the Gilda Radner Familial Ovarian Cancer Registry. Int J Gynecol Pathol 2004;23:29-34. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/14668547>.

107. Ayadi-Kaddour A, Bouraoui S, Bellil K, et al. Colonic adenocarcinoma and bilateral malignant ovarian sex cord tumor with

annular tubules in Peutz-Jeghers syndrome. *Pathologica* 2004;96:117-120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15524052>.

108. Clements A, Robison K, Granai C, et al. A case of Peutz-Jeghers syndrome with breast cancer, bilateral sex cord tumor with annular tubules, and adenoma malignum caused by STK11 gene mutation. *Int J Gynecol Cancer* 2009;19:1591-1594. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19955943>.

109. Kondi-Pafiti A, Bakalianou K, Iavazzo C, et al. Endometrial carcinoma and ovarian sex cord tumor with annular tubules in a patient with history of Peutz-Jeghers syndrome and multiple malignancies. *Eur J Gynaecol Oncol* 2011;32:452-454. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21941977>.

110. Lele SM, Sawh RN, Zaharopoulos P, et al. Malignant ovarian sex cord tumor with annular tubules in a patient with Peutz-Jeghers syndrome: a case report. *Mod Pathol* 2000;13:466-470. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10786816>.

111. Young RH. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. *Mod Pathol* 2005;18 Suppl 2:S81-98. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15502809>.

112. Goulvent T, Ray-Coquard I, Borel S, et al. DICER1 and FOXL2 mutations in ovarian sex cord-stromal tumours: a GINECO Group study. *Histopathology* 2016;68:279-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26033501>.

113. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol* 2007;25:3985-3990. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17761984>.

114. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2

carriers. *Gynecol Oncol* 2006;100:58-64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16137750>.

115. Powell CB, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *Int J Gynecol Cancer* 2011;21:846-851. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21670699>.

116. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *J Clin Oncol* 2005;23:127-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15625367>.

117. Shaw PA, Rouzbahman M, Pizer ES, et al. Candidate serous cancer precursors in fallopian tube epithelium of BRCA1/2 mutation carriers. *Mod Pathol* 2009;22:1133-1138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19543244>.

118. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol* 2006;30:230-236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16434898>.

119. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. *Am J Surg Pathol* 2007;31:161-169. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17255760>.

120. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. *J Natl Cancer Inst* 1999;91:1310-1316. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10433620>.

121. Agalliu I, Gern R, Leanza S, Burk RD. Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. *Clin Cancer Res* 2009;15:1112-1120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19188187>.

122. Gallagher DJ, Gaudet MM, Pal P, et al. Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 2010;16:2115-2121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20215531>.
123. Kirchhoff T, Kauff ND, Mitra N, et al. BRCA mutations and risk of prostate cancer in Ashkenazi Jews. Clin Cancer Res 2004;10:2918-2921. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15131025>.
124. Leongamornlert D, Mahmud N, Tymrakiewicz M, et al. Germline BRCA1 mutations increase prostate cancer risk. Br J Cancer 2012;106:1697-1701. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22516946>.
125. Tulinius H, Olafsdottir GH, Sigvaldason H, et al. The effect of a single BRCA2 mutation on cancer in Iceland. J Med Genet 2002;39:457-462. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12114473>.
126. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711-719. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16141007>.
127. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 2012;11:235-242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22187320>.
128. Mersch J, Jackson MA, Park M, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer 2015;121:269-275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25224030>.
129. Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. Eur Urol 2014;66:489-499. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24484606>.
130. Castro E, Goh C, Olmos D, et al. Germline BRCA mutations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. J Clin Oncol 2013;31:1748-1757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23569316>.
131. Mitra A, Fisher C, Foster CS, et al. Prostate cancer in male BRCA1 and BRCA2 mutation carriers has a more aggressive phenotype. Br J Cancer 2008;98:502-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18182994>.
132. Narod SA, Neuhausen S, Vichodez G, et al. Rapid progression of prostate cancer in men with a BRCA2 mutation. Br J Cancer 2008;99:371-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18577985>.
133. Thorne H, Willems AJ, Niedermayr E, et al. Decreased prostate cancer-specific survival of men with BRCA2 mutations from multiple breast cancer families. Cancer Prev Res (Phila) 2011;4:1002-1010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21733824>.
134. Tryggvadottir L, Vidarsdottir L, Thorgeirsson T, et al. Prostate cancer progression and survival in BRCA2 mutation carriers. J Natl Cancer Inst 2007;99:929-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17565157>.
135. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol 2009;27:433-438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19064968>.
136. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12569143>.
137. Kim DH, Crawford B, Ziegler J, Beattie MS. Prevalence and characteristics of pancreatic cancer in families with BRCA1 and BRCA2



mutations. *Fam Cancer* 2009;8:153-158. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/18855126>.

138. Lynch HT, Deters CA, Snyder CL, et al. BRCA1 and pancreatic cancer: pedigree findings and their causal relationships. *Cancer Genet Cytogenet* 2005;158:119-125. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15796958>.

139. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. *Cancer Res* 2002;62:3789-3793. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/12097290>.

140. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. *Cancer* 2015;121:4382-4388. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/26440929>.

141. Holter S, Borgida A, Dodd A, et al. Germline BRCA mutations in a large clinic-based cohort of patients with pancreatic adenocarcinoma. *J Clin Oncol* 2015;33:3124-3129. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/25940717>.

142. Zhen DB, Rabe KG, Gallinger S, et al. BRCA1, BRCA2, PALB2, and CDKN2A mutations in familial pancreatic cancer: a PACGENE study. *Genet Med* 2015;17:569-577. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/25356972>.

143. Lucas AL, Shakya R, Lipsyc MD, et al. High prevalence of BRCA1 and BRCA2 germline mutations with loss of heterozygosity in a series of resected pancreatic adenocarcinoma and other neoplastic lesions. *Clin Cancer Res* 2013;19:3396-3403. Available at:  
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3959126/>.

144. Stadler ZK, Salo-Mullen E, Patil SM, et al. Prevalence of BRCA1 and BRCA2 mutations in Ashkenazi Jewish families with breast and

pancreatic cancer. *Cancer* 2012;118:493-499. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/21598239>.

145. Lorenzo Bermejo J, Hemminki K. Risk of cancer at sites other than the breast in Swedish families eligible for BRCA1 or BRCA2 mutation testing. *Ann Oncol* 2004;15:1834-1841. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15550590>.

146. Beiner ME, Finch A, Rosen B, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. *Gynecol Oncol* 2007;104:7-10. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16962648>.

147. Sidransky D, Tokino T, Helzlsouer K, et al. Inherited p53 gene mutations in breast cancer. *Cancer Res* 1992;52:2984-2986. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/1581912>.

148. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *J Clin Oncol* 2009;27:1250-1256. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19204208>.

149. Lalloo F, Varley J, Ellis D, et al. Prediction of pathogenic mutations in patients with early-onset breast cancer by family history. *Lancet* 2003;361:1101-1102. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/12672316>.

150. Masciari S, Dewanwala A, Stoffel EM, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. *Genet Med* 2011;13:651-657. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/21552135/>.

151. Lane DP. Cancer. p53, guardian of the genome. *Nature* 1992;358:15-16. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/1614522>.

152. Levine AJ. p53, the cellular gatekeeper for growth and division. *Cell* 1997;88:323-331. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/9039259>.



153. Garber JE, Goldstein AM, Kantor AF, et al. Follow-up study of twenty-four families with Li-Fraumeni syndrome. *Cancer Res* 1991;51:6094-6097. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1933872>.

154. Nichols KE, Malkin D, Garber JE, et al. Germ-line p53 mutations predispose to a wide spectrum of early-onset cancers. *Cancer Epidemiol Biomarkers Prev* 2001;10:83-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11219776>.

155. Siddiqui R, Onel K, Facio F, et al. The TP53 mutational spectrum and frequency of CHEK2\*1100delC in Li-Fraumeni-like kindreds. *Fam Cancer* 2005;4:177-181. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15951970>.

156. Birch JM, Hartley AL, Tricker KJ, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. *Cancer Res* 1994;54:1298-1304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8118819>.

157. Krutikova V, Trkova M, Fleitz J, et al. Identification of five new families strengthens the link between childhood choroid plexus carcinoma and germline TP53 mutations. *Eur J Cancer* 2005;41:1597-1603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15925506>.

158. Li FP, Fraumeni JF, Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? *Ann Intern Med* 1969;71:747-752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/5360287>.

159. Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res* 1988;48:5358-5362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3409256>.

160. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science* 1990;250:1233-1238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1978757>.

161. Varley JM, Evans DG, Birch JM. Li-Fraumeni syndrome--a molecular and clinical review. *Br J Cancer* 1997;76:1-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9218725>.

162. Melhem-Bertrandt A, Bojadzieva J, Ready KJ, et al. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. *Cancer* 2011;118:908-913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21761402>.

163. Wilson JR, Bateman AC, Hanson H, et al. A novel HER2-positive breast cancer phenotype arising from germline TP53 mutations. *J Med Genet* 2010;47:771-774. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20805372>.

164. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. *J Natl Cancer Inst* 1998;90:606-611. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9554443>.

165. Lustbader ED, Williams WR, Bondy ML, et al. Segregation analysis of cancer in families of childhood soft-tissue-sarcoma patients. *Am J Hum Genet* 1992;51:344-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1642235>.

166. Birch JM, Blair V, Kelsey AM, et al. Cancer phenotype correlates with constitutional TP53 genotype in families with the Li-Fraumeni syndrome. *Oncogene* 1998;17:1061-1068. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9764816>.

167. Chompret A. The Li-Fraumeni syndrome. *Biochimie* 2002;84:75-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11900879>.

168. Chompret 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11332399>.

169. Eeles RA. Germline mutations in the TP53 gene. *Cancer Surv* 1995;25:101-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8718514>.

170. Bougeard G, Sesboue R, Baert-Desurmont S, et al. Molecular basis of the Li-Fraumeni syndrome: an update from the French LFS families. *J Med Genet* 2008;45:535-538. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18511570>.

171. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J Clin Oncol* 2015;33:2345-2352. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26014290>.

172. Tinat J, Bougeard G, Baert-Desurmont S, et al. 2009 version of the Chompret criteria for Li Fraumeni syndrome. *J Clin Oncol* 2009;27:e108-109; author reply e110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19652052>.

173. Ginsburg OM, Akbari MR, Aziz Z, et al. The prevalence of germline TP53 mutations in women diagnosed with breast cancer before age 30. *Fam Cancer* 2009;8:563-567. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19714488>.

174. Lalloo F, Varley J, Moran A, et al. BRCA1, BRCA2 and TP53 mutations in very early-onset breast cancer with associated risks to relatives. *Eur J Cancer* 2006;42:1143-1150. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16644204>.

175. Lee DS, Yoon SY, Looi LM, et al. Comparable frequency of BRCA1, BRCA2 and TP53 germline mutations in a multi-ethnic Asian cohort suggests TP53 screening should be offered together with BRCA1/2 screening to early-onset breast cancer patients. *Breast Cancer Res* 2012;14:R66. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22507745>.

176. Mouchawar J, Korch C, Byers T, et al. Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast

cancer: Australian Breast Cancer Family Study. *Cancer Res* 2010;70:4795-4800. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20501846>.

177. McCuaig JM, Armel SR, Novokmet A, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? *Fam Cancer* 2012;11:607-613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22851211>.

178. Orloff MS, Eng C. Genetic and phenotypic heterogeneity in the PTEN hamartoma tumour syndrome. *Oncogene* 2008;27:5387-5397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18794875>.

179. Eng C. PTEN hamartoma tumor syndrome (PTHS). *GeneReviews*; 2009. Available at: Available at: <http://www.ncbi.nlm.nih.gov/books/NBK1488/>.

180. Pilarski R, Stephens JA, Noss R, et al. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. *J Med Genet* 2011;48:505-512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21659347>.

181. Varga EA, Pastore M, Prior T, et al. The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. *Genet Med* 2009;11:111-117. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19265751>.

182. Hobert JA, Eng C. PTEN hamartoma tumor syndrome: an overview. *Genet Med* 2009;11:687-694. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19668082>.

183. Nelen MR, Kremer H, Konings IB, et al. Novel PTEN mutations in patients with Cowden disease: absence of clear genotype-phenotype correlations. *Eur J Hum Genet* 1999;7:267-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10234502>.

184. Pilarski R, Eng C. Will the real Cowden syndrome please stand up (again)? Expanding mutational and clinical spectra of the PTEN

hamartoma tumour syndrome. J Med Genet 2004;41:323-326. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15121767>.

185. Bennett KL, Mester J, Eng C. Germline epigenetic regulation of KILLIN in Cowden and Cowden-like syndrome. Jama 2010;304:2724-2731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21177507>.

186. Starink TM, van der Veen JP, Arwert F, et al. The Cowden syndrome: a clinical and genetic study in 21 patients. Clin Genet 1986;29:222-233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3698331>.

187. Brownstein MH, Wolf M, Bikowski JB. Cowden's disease: a cutaneous marker of breast cancer. Cancer 1978;41:2393-2398. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/657103>.

188. Pilarski R, Burt R, Kohlman W, et al. Cowden syndrome and the PTEN hamartoma tumor syndrome: systematic review and revised diagnostic criteria. J Natl Cancer Inst 2013;105:1607-1616. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24136893>.

189. Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet 2013;50:255-263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23335809>.

190. Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract 2010;8:6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20565722>.

191. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18:400-407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22252256>.

192. Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis

of a prospective study of 3042 probands. Am J Hum Genet 2011;88:42-56. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21194675>.

193. Zbuk KM, Eng C. Hamartomatous polyposis syndromes. Nat Clin Pract Gastroenterol Hepatol 2007;4:492-502. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17768394>.

194. Black D, Bogomolny F, Robson ME, et al. Evaluation of germline PTEN mutations in endometrial cancer patients. Gynecol Oncol 2005;96:21-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15589575>.

195. Nelen MR, Padberg GW, Peeters EA, et al. Localization of the gene for Cowden disease to chromosome 10q22-23. Nat Genet 1996;13:114-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8673088>.

196. Schaffer JV, Kamino H, Witkiewicz A, et al. Mucocutaneous neuromas: an underrecognized manifestation of PTEN hamartoma-tumor syndrome. Arch Dermatol 2006;142:625-632. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16702501>.

197. Brownstein MH, Mehregan AH, Bikowski JB, et al. The dermatopathology of Cowden's syndrome. Br J Dermatol 1979;100:667-673. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/465314>.

198. Brownstein MH, Mehregan AH, Bilowski JB. Trichilemmomas in Cowden's disease. JAMA 1977;238:26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/577252>.

199. Heald B, Mester J, Rybicki L, et al. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology 2010;139:1927-1933. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20600018>.

200. Stanich PP, Owens VL, Sweetser S, et al. Colonic polyposis and neoplasia in Cowden syndrome. Mayo Clin Proc 2011;86:489-492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21628613>.



201. Stanich PP, Pilarski R, Rock J, et al. Colonic manifestations of PTEN hamartoma tumor syndrome: case series and systematic review. *World J Gastroenterol* 2014;20:1833-1838. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24587660>.
202. Al-Thihli K, Palma L, Marcus V, et al. A case of Cowden's syndrome presenting with gastric carcinomas and gastrointestinal polyposis. *Nat Clin Pract Gastroenterol Hepatol* 2009;6:184-189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19190598>.
203. Nieuwenhuis MH, Kets CM, Murphy-Ryan M, et al. Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. *Fam Cancer* 2014;13:57-63. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23934601>.
204. Zhou XP, Waite KA, Pilarski R, et al. Germline PTEN promoter mutations and deletions in Cowden/Bannayan-Riley-Ruvalcaba syndrome result in aberrant PTEN protein and dysregulation of the phosphoinositol-3-kinase/Akt pathway. *Am J Hum Genet* 2003;73:404-411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12844284>.
205. Zhou XP, Marsh DJ, Morrison CD, et al. Germline inactivation of PTEN and dysregulation of the phosphoinositol-3-kinase/Akt pathway cause human Lhermitte-Duclos disease in adults. *Am J Hum Genet* 2003;73:1191-1198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14566704>.
206. Andres RH, Guzman R, Weis J, et al. Lhermitte-Duclos disease with atypical vascularization--case report and review of the literature. *Clin Neuropathol* 2009;28:83-90. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19353838>.
207. Butler MG, Dasouki MJ, Zhou XP, et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet* 2005;42:318-321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15805158>.
208. Herman GE, Butter E, Enrile B, et al. Increasing knowledge of PTEN germline mutations: Two additional patients with autism and macrocephaly. *Am J Med Genet A* 2007;143:589-593. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17286265>.
209. Herman GE, Henninger N, Ratliff-Schaub K, et al. Genetic testing in autism: how much is enough? *Genet Med* 2007;9:268-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17505203>.
210. Orrico A, Galli L, Buoni S, et al. Novel PTEN mutations in neurodevelopmental disorders and macrocephaly. *Clin Genet* 2009;75:195-198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18759867>.
211. Roche AF, Mukherjee D, Guo SM, Moore WM. Head circumference reference data: birth to 18 years. *Pediatrics* 1987;79:706-712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3575026>.
212. Gorlin RJ, Cohen MM, Jr., Condon LM, Burke BA. Bannayan-Riley-Ruvalcaba syndrome. *Am J Med Genet* 1992;44:307-314. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1336932>.
213. Marsh DJ, Coulon V, Lunetta KL, et al. Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutation. *Hum Mol Genet* 1998;7:507-515. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9467011>.
214. Kapoor NS, Curcio LD, Blakemore CA, et al. Multigene panel testing detects equal rates of pathogenic BRCA1/2 mutations and has a higher diagnostic yield compared to limited BRCA1/2 analysis alone in patients at risk for hereditary breast cancer. *Ann Surg Oncol* 2015;22:3282-3288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26219241>.
215. Pharoah PD, Guilford P, Caldas C. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary



diffuse gastric cancer families. *Gastroenterology* 2001;121:1348-1353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11729114>.

216. Hearle N, Schumacher V, Menko FH, et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 2006;12:3209-3215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16707622>.

217. Walsh T, Casadei S, Coats KH, et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *JAMA* 2006;295:1379-1388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16551709>.

218. Apostolou P, Fostira F. Hereditary breast cancer: the era of new susceptibility genes. *Biomed Res Int* 2013;2013:747318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23586058>.

219. Friedrichsen DM, Malone KE, Doody DR, et al. Frequency of CHEK2 mutations in a population based, case-control study of breast cancer in young women. *Breast Cancer Res* 2004;6:R629-635. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15535844>.

220. Iniesta MD, Gorin MA, Chien LC, et al. Absence of CHEK2\*1100delC mutation in families with hereditary breast cancer in North America. *Cancer Genet Cytogenet* 2010;202:136-140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20875877>.

221. Kuusisto KM, Bebel A, Vihinen M, et al. Screening for BRCA1, BRCA2, CHEK2, PALB2, BRIP1, RAD50, and CDH1 mutations in high-risk Finnish BRCA1/2-founder mutation-negative breast and/or ovarian cancer individuals. *Breast Cancer Res* 2011;13:R20. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21356067>.

222. Cybulski C, Wokolorczyk D, Jakubowska A, et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. *J Clin Oncol* 2011;29:3747-3752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21876083>.

223. Weischer M, Bojesen SE, Ellervik C, et al. CHEK2\*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 patient cases and 27,000 controls. *J Clin Oncol* 2008;26:542-548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18172190>.

224. Thompson ER, Rowley SM, Li N, et al. Panel testing for familial breast cancer: calibrating the tension between research and clinical care. *J Clin Oncol* 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26786923>.

225. Casadei S, Norquist BM, Walsh T, et al. Contribution of inherited mutations in the BRCA2-interacting protein PALB2 to familial breast cancer. *Cancer Res* 2011;71:2222-2229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21285249>.

226. Cybulski C, Kluzniak W, Huzarski T, et al. Clinical outcomes in women with breast cancer and a PALB2 mutation: a prospective cohort analysis. *Lancet Oncol* 2015;16:638-644. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25959805>.

227. Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014;371:497-506. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25099575>.

228. Kanchi KL, Johnson KJ, Lu C, et al. Integrated analysis of germline and somatic variants in ovarian cancer. *Nat Commun* 2014;5:3156. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24448499>.

229. Broeks A, Urbanus JH, Floore AN, et al. ATM-heterozygous germline mutations contribute to breast cancer-susceptibility. *Am J Hum Genet* 2000;66:494-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10677309>.

230. Brunet J, Gutierrez-Enriquez S, Torres A, et al. ATM germline mutations in Spanish early-onset breast cancer patients negative for BRCA1/BRCA2 mutations. *Clin Genet* 2008;73:465-473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18384426>.

231. Heikkinen K, Rapakko K, Karppinen SM, et al. Association of common ATM polymorphism with bilateral breast cancer. *Int J Cancer* 2005;116:69-72. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15756685>.

232. Thompson D, Antoniou AC, Jenkins M, et al. Two ATM variants and breast cancer risk. *Hum Mutat* 2005;25:594-595. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15880680>.

233. Tommiska J, Jansen L, Kilpivaara O, et al. ATM variants and cancer risk in breast cancer patients from Southern Finland. *BMC Cancer* 2006;6:209. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16914028>.

234. Goldgar DE, Healey S, Dowty JG, et al. Rare variants in the ATM gene and risk of breast cancer. *Breast Cancer Res* 2011;13:R73.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21787400>.

235. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. *Lancet Oncol* 2011;12:49-55. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21145788>.

236. Rumilla K, Schowalter KV, Lindor NM, et al. Frequency of deletions of EPCAM (TACSTD1) in MSH2-associated Lynch syndrome cases. *J Mol Diagn* 2011;13:93-99. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21227399>.

237. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011;305:2304-2310. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21642682>.

238. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. *JAMA* 2006;296:1507-1517. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17003399>.

239. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *Int J Cancer* 2008;123:444-449. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18398828>.

240. Kohlmann W, Gruber S. Lynch Syndrome. *GeneReviews at GeneTests: Medical Genetics Information Resource* 2011. Available at:

<http://www.ncbi.nlm.nih.gov/books/NBK1211/>.

241. Goodfellow PJ, Billingsley CC, Lankes HA, et al. Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for Lynch syndrome screening in endometrial cancers from GOG210: an NRG Oncology and Gynecologic Oncology Group study. *J Clin Oncol* 2015;33:4301-4308. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26552419>.

242. Lu KH, Daniels M. Endometrial and ovarian cancer in women with Lynch syndrome: update in screening and prevention. *Fam Cancer* 2013;12:273-277. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23765559>.

243. Chen LM, Yang KY, Little SE, et al. Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. *Obstet Gynecol* 2007;110:18-25. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17601891>.

244. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N Engl J Med* 2006;354:261-269. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16421367>.

245. Stuckless S, Green J, Dawson L, et al. Impact of gynecological screening in Lynch syndrome carriers with an MSH2 mutation. *Clin Genet* 2013;83:359-364. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22775459>.

246. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis

colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand 2011;90:437-444. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/21306348>.

247. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 2009;27:4793-4797. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/19720893>.

248. Renkonen-Sinisalo L, Butzow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007;120:821-824. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17096354>.

249. Harkness EF, Barrow E, Newton K, et al. Lynch syndrome caused by MLH1 mutations is associated with an increased risk of breast cancer: a cohort study. J Med Genet 2015;52:553-556. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/26101330>.

250. Ramus SJ, Song H, Dicks E, et al. Germline mutations in the BRIP1, BARD1, PALB2, and NBN genes in women with ovarian cancer. J Natl Cancer Inst 2015;107. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/26315354>.

251. Rafnar T, Gudbjartsson DF, Sulem P, et al. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet 2011;43:1104-1107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21964575>.

252. Loveday C, Turnbull C, Ruark E, et al. Germline RAD51C mutations confer susceptibility to ovarian cancer. Nat Genet 2012;44:475-476; author reply 476. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22538716>.

253. Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet 2011;43:879-882. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/21822267>.

254. Pelttari LM, Heikkinen T, Thompson D, et al. RAD51C is a susceptibility gene for ovarian cancer. Hum Mol Genet 2011;20:3278-3288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21616938>.

255. Pelttari LM, Kiiski J, Nurminen R, et al. A Finnish founder mutation in RAD51D: analysis in breast, ovarian, prostate, and colorectal cancer. J Med Genet 2012;49:429-432. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/22652533>.

256. Song H, Dicks E, Ramus SJ, et al. Contribution of germline mutations in the RAD51B, RAD51C, and RAD51D genes to ovarian cancer in the population. J Clin Oncol 2015;33:2901-2907. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/26261251>.

257. Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. Am J Prev Med 2004;27:239-245. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15450637>.

258. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 2004;292:1480-1489. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/15383520>.

259. Colditz GA, Willett WC, Hunter DJ, et al. Family history, age, and risk of breast cancer. Prospective data from the Nurses' Health Study. JAMA 1993;270:338-343. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8123079>.

260. Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk. The Utah Population Database. JAMA 1993;270:1563-1568. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8371466>.

261. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer 1994;73:643-651. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/8299086>.



262. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879-1886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2593165>.

263. Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst 1999;91:1541-1548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10491430>.

264. Gail MH, Costantino JP. Validating and improving models for projecting the absolute risk of breast cancer. J Natl Cancer Inst 2001;93:334-335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11238688>.

265. Rockhill B, Spiegelman D, Byrne C, et al. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst 2001;93:358-366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11238697>.

266. Euhus DM, Leitch AM, Huth JF, Peters GN. Limitations of the Gail model in the specialized breast cancer risk assessment clinic. Breast J 2002;8:23-27. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11856157>.

267. Antoniou AC, Hardy R, Walker L, et al. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK genetics clinics. J Med Genet 2008;45:425-431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18413374>.

268. Parmigiani G, Chen S, Iversen ES, Jr., et al. Validity of models for predicting BRCA1 and BRCA2 mutations. Ann Intern Med 2007;147:441-450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17909205>.

269. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to

mammography. CA Cancer J Clin 2007;57:75-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17392385>.

270. Murphy CD, Lee JM, Drohan B, et al. The American Cancer Society guidelines for breast screening with magnetic resonance imaging: an argument for genetic testing. Cancer 2008;113:3116-3120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18932252>.

271. Bluman LG, Rimer BK, Berry DA, et al. Attitudes, knowledge, and risk perceptions of women with breast and/or ovarian cancer considering testing for BRCA1 and BRCA2. J Clin Oncol 1999;17:1040-1046. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10071299>.

272. Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns 2008;17:424-433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18792771>.

273. Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. Am J Hum Genet 1995;56:745-752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7887430>.

274. Calzone KA, Soballe PW. Genetic testing for cancer susceptibility. Surg Clin North Am 2008;88:705-721. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18672137>.

275. Weitzel JN, Lagos VI, Cullinane CA, et al. Limited family structure and BRCA gene mutation status in single cases of breast cancer. JAMA 2007;297:2587-2595. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17579227>.

276. Bodian CA, Perzin KH, Lattes R. Lobular neoplasia. Long term risk of breast cancer and relation to other factors. Cancer 1996;78:1024-1034. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8780540>.



277. Osborne MP, Hoda SA. Current management of lobular carcinoma in situ of the breast. *Oncology (Williston Park)* 1994;8:45-49; discussion 49, 53-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8167087>.

278. Beral V, Doll R, Hermon C, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 2008;371:303-314. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18294997>.

279. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289:3243-3253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12824205>.

280. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12117397>.

281. Weiss LK, Burkman RT, Cushing-Haugen KL, et al. Hormone replacement therapy regimens and breast cancer risk(1). *Obstet Gynecol* 2002;100:1148-1158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12468157>.

282. Armstrong J, Toscano M, Kotchko N, et al. Utilization and outcomes of BRCA genetic testing and counseling in a national commercially insured population: the ABOUT study. *JAMA Oncol* 2015;1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26426480>.

283. Genetic Information Non-Discrimination Act of 2008 (GINA). Vol. Public Law No. 110-233.

284. Berliner JL, Fay AM, Cummings SA, et al. NSGC practice guideline: risk assessment and genetic counseling for hereditary breast

and ovarian cancer. *J Genet Couns* 2013;22:155-163. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23188549>.

285. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. *J Clin Oncol* 2003;21:2397-2406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12692171>.

286. Robson ME, Storm CD, Weitzel J, et al. American society of clinical oncology policy statement update: genetic and genomic testing for cancer susceptibility. *J Clin Oncol* 2010;28:893-901. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20065170>.

287. Hong YC, Liu HM, Chen PS, et al. Hair follicle: a reliable source of recipient origin after allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2007;40:871-874. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17704789>.

288. Tran SD, Pillemer SR, Dutra A, et al. Differentiation of human bone marrow-derived cells into buccal epithelial cells in vivo: a molecular analytical study. *Lancet* 2003;361:1084-1088. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12672312>.

289. Eccles DM, Mitchell G, Monteiro AN, et al. BRCA1 and BRCA2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance. *Ann Oncol* 2015;26:2057-2065. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26153499>.

290. Bougeard G, Baert-Desurmont S, Tournier I, et al. Impact of the MDM2 SNP309 and p53 Arg72Pro polymorphism on age of tumour onset in Li-Fraumeni syndrome. *J Med Genet* 2006;43:531-533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16258005>.

291. Chibon F, Primois C, Bressieux JM, et al. Contribution of PTEN large rearrangements in Cowden disease: a multiplex amplifiable probe hybridisation (MAPH) screening approach. *J Med Genet* 2008;45:657-665. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18456716>.

292. Palma MD, Domchek SM, Stopfer J, et al. The relative contribution of point mutations and genomic rearrangements in BRCA1 and BRCA2 in high-risk breast cancer families. *Cancer Res* 2008;68:7006-7014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18703817>.
293. Weitzel JN, Lagos VI, Herzog JS, et al. Evidence for common ancestral origin of a recurring BRCA1 genomic rearrangement identified in high-risk Hispanic families. *Cancer Epidemiol Biomarkers Prev* 2007;16:1615-1620. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17646271>.
294. Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. *J Clin Oncol* 2014;32:2001-2009. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24733792>.
295. Desmond A, Kurian AW, Gabree M, et al. Clinical actionability of multigene panel testing for hereditary breast and ovarian cancer risk assessment. *JAMA Oncol* 2015;1:943-951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26270727>.
296. Hall MJ, Forman AD, Pilarski R, et al. Gene panel testing for inherited cancer risk. *J Natl Compr Canc Netw* 2014;12:1339-1346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25190699>.
297. Walsh T, Casadei S, Lee MK, et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A* 2011;108:18032-18037. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22006311>.
298. Castera L, Krieger S, Rousselin A, et al. Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet* 2014;22:1305-1313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24549055>.
299. Rainville IR, Rana HQ. Next-generation sequencing for inherited breast cancer risk: counseling through the complexity. *Curr Oncol Rep* 2014;16:371. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24488544>.
300. Tung N, Battelli C, Allen B, et al. Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel. *Cancer* 2015;121:25-33. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25186627>.
301. Walsh T, Lee MK, Casadei S, et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci U S A* 2010;107:12629-12633. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20616022>.
302. Bombard Y, Bach PB, Offit K. Translating genomics in cancer care. *J Natl Compr Canc Netw* 2013;11:1343-1353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24225968>.
303. Cragun D, Radford C, Dolinsky JS, et al. Panel-based testing for inherited colorectal cancer: a descriptive study of clinical testing performed by a US laboratory. *Clin Genet* 2014;86:510-520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24506336>.
304. LaDuca H, Stuenkel AJ, Dolinsky JS, et al. Utilization of multigene panels in hereditary cancer predisposition testing: analysis of more than 2,000 patients. *Genet Med* 2014;16:830-837. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24763289>.
305. Mauer CB, Pirzadeh-Miller SM, Robinson LD, Euhus DM. The integration of next-generation sequencing panels in the clinical cancer genetics practice: an institutional experience. *Genet Med* 2014;16:407-412. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24113346>.
306. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing



for cancer susceptibility. J Clin Oncol 2015;33:3660-3667. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26324357>.

307. Ethical and policy issues in genetic testing and screening of children. Pediatrics 2013;131:620-622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23428972>.

308. Mohamad HB, Apffelstaedt JP. Counseling for male BRCA mutation carriers: a review. Breast 2008;17:441-450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18657973>.

309. Offit K, Levran O, Mullaney B, et al. Shared genetic susceptibility to breast cancer, brain tumors, and Fanconi anemia. J Natl Cancer Inst 2003;95:1548-1551. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14559878>.

310. Offit K, Sagi M, Hurley K. Preimplantation genetic diagnosis for cancer syndromes: a new challenge for preventive medicine. JAMA 2006;296:2727-2730. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17164459>.

311. Warner E, Plewes DB, Hill KA, et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004;292:1317-1325. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15367553>.

312. Kriege M, Brekelmans CT, Boetes C, et al. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 2004;351:427-437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15282350>.

313. Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769-1778. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15910949>.

314. Stoutjesdijk MJ, Boetes C, Jager GJ, et al. Magnetic resonance imaging and mammography in women with a hereditary risk of breast cancer. J Natl Cancer Inst 2001;93:1095-1102. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11459871>.

315. Berg WA. How well does supplemental screening magnetic resonance imaging work in high-risk women? J Clin Oncol 2014;32:2193-2196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24934782>.

316. Buist DS, Porter PL, Lehman C, et al. Factors contributing to mammography failure in women aged 40-49 years. J Natl Cancer Inst 2004;96:1432-1440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15467032>.

317. Mandelson MT, Oestreicher N, Porter PL, et al. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst 2000;92:1081-1087. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10880551>.

318. Tilanus-Linthorst M, Verhoog L, Obdeijn IM, et al. A BRCA1/2 mutation, high breast density and prominent pushing margins of a tumor independently contribute to a frequent false-negative mammography. Int J Cancer 2002;102:91-95. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12353239>.

319. van Gils CH, Otten JD, Verbeek AL, et al. Effect of mammographic breast density on breast cancer screening performance: a study in Nijmegen, The Netherlands. J Epidemiol Community Health 1998;52:267-271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9616416>.

320. Gilliland FD, Joste N, Stauber PM, et al. Biologic characteristics of interval and screen-detected breast cancers. J Natl Cancer Inst 2000;92:743-749. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10793111>.



321. Kuhl CK, Schrading S, Leutner CC, et al. Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J Clin Oncol* 2005;23:8469-8476. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16293877>.

322. Riedl CC, Ponhold L, Flory D, et al. Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high risk for breast cancer. *Clin Cancer Res* 2007;13:6144-6152. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17947480>.

323. Sardanelli F, Podo F, D'Agnolo G, et al. Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): interim results. *Radiology* 2007;242:698-715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17244718>.

324. Passaperuma K, Warner E, Causer PA, et al. Long-term results of screening with magnetic resonance imaging in women with BRCA mutations. *Br J Cancer* 2012;107:24-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22588560>.

325. Le-Petross HT, Whitman GJ, Atchley DP, et al. Effectiveness of alternating mammography and magnetic resonance imaging for screening women with deleterious BRCA mutations at high risk of breast cancer. *Cancer* 2011;117:3900-3907. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21365619>.

326. Goldfrank D, Chuai S, Bernstein JL, et al. Effect of mammography on breast cancer risk in women with mutations in BRCA1 or BRCA2. *Cancer Epidemiol Biomarkers Prev* 2006;15:2311-2313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17119064>.

327. Narod SA, Lubinski J, Ghadirian P, et al. Screening mammography and risk of breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. *Lancet Oncol* 2006;7:402-406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16648044>.

328. Pijpe A, Andrieu N, Easton DF, et al. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK). *BMJ* 2012;345:e5660. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22956590>.

329. Lowry KP, Lee JM, Kong CY, et al. Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: a comparative effectiveness analysis. *Cancer* 2012;118:2021-2030. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21935911>.

330. Evans DG, Gaarenstroom KN, Stirling D, et al. Screening for familial ovarian cancer: poor survival of BRCA1/2 related cancers. *J Med Genet* 2009;46:593-597. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18413372>.

331. Woodward ER, Sleightholme HV, Considine AM, et al. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. *BJOG* 2007;114:1500-1509. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17903229>.

332. Hartmann LC, Schaid DJ, Woods JE, et al. Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med* 1999;340:77-84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9887158>.

333. Hartmann LC, Sellers TA, Schaid DJ, et al. Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst* 2001;93:1633-1637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11698567>.

334. Meijers-Heijboer H, van Geel B, van Putten WL, et al. Breast cancer after prophylactic bilateral mastectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2001;345:159-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11463009>.



335. Rebbeck TR, Friebel T, Lynch HT, et al. Bilateral prophylactic mastectomy reduces breast cancer risk in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2004;22:1055-1062. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14981104>.

336. van Dijk S, van Roosmalen MS, Otten W, Stalmeier PF. Decision making regarding prophylactic mastectomy: stability of preferences and the impact of anticipated feelings of regret. J Clin Oncol 2008;26:2358-2363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18467728>.

337. Morrow M, Mehrara B. Prophylactic mastectomy and the timing of breast reconstruction. Br J Surg 2009;96:1-2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19109821>.

338. Satagopan JM, Boyd J, Kauff ND, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. Clin Cancer Res 2002;8:3776-3781. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12473589>.

339. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346:1616-1622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12023993>.

340. Finch AP, Lubinski J, Moller P, et al. Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. J Clin Oncol 2014;32:1547-1553. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24567435>.

341. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101:80-87. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19141781>.

342. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin

Oncol 2008;26:1331-1337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18268356>.

343. Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609-1615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12023992>.

344. Kemel Y, Kauff ND, Robson ME, et al. Four-year follow-up of outcomes following risk-reducing salpingo-oophorectomy in BRCA mutation carriers [abstract]. J Clin Oncol (Meeting Abstracts) 2005;23(Supple 16):Abstract 1013. Available at: [http://meeting.ascopubs.org/cgi/content/abstract/23/16\\_suppl/1013](http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/1013).

345. Rebbeck TR, Levin AM, Eisen A, et al. Breast cancer risk after bilateral prophylactic oophorectomy in BRCA1 mutation carriers. J Natl Cancer Inst 1999;91:1475-1479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10469748>.

346. Sherman ME, Piedmonte M, Mai PL, et al. Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. J Clin Oncol 2014;32:3275-3283. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25199754>.

347. Eisen A, Lubinski J, Klijn J, et al. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. J Clin Oncol 2005;23:7491-7496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16234515>.

348. Metcalfe K, Lynch HT, Foulkes WD, et al. Effect of oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. JAMA Oncol 2015;1:306-313. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26181175>.

349. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, et al. Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl

Cancer Inst 2015;107. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25788320>.

350. Chai X, Domchek S, Kauff N, et al. RE: Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. J Natl Cancer Inst 2015;107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26264690>.

351. Rebbeck TR, Friebel T, Wagner T, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol 2005;23:7804-7810. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16219936>.

352. Eisen A, Lubinski J, Gronwald J, et al. Hormone therapy and the risk of breast cancer in BRCA1 mutation carriers. J Natl Cancer Inst 2008;100:1361-1367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18812548>.

353. Chlebowski RT, Prentice RL. Menopausal hormone therapy in BRCA1 mutation carriers: uncertainty and caution. J Natl Cancer Inst 2008;100:1341-1343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18812547>.

354. Garber JE, Hartman AR. Prophylactic oophorectomy and hormone replacement therapy: protection at what price? J Clin Oncol 2004;22:978-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14981100>.

355. McAlpine JN, Hanley GE, Woo MM, et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. Am J Obstet Gynecol 2014;210:471.e471-411. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24412119>.

356. Findley AD, Siedhoff MT, Hobbs KA, et al. Short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve: a

pilot randomized controlled trial. Fertil Steril 2013;100:1704-1708.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23993887>.

357. Daly MB, Drescher CW, Yates MS, et al. Salpingectomy as a means to reduce ovarian cancer risk. Cancer Prev Res (Phila) 2015;8:342-348. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25586903>.

358. College of American Pathologists (CAP). Protocol for the Examination of Specimens From Patients With Carcinoma of the Ovary. 2009. Available at: [http://www.cap.org/apps/docs/committees/cancer/cancer\\_protocols/2009/Ovary\\_09protocol.pdf](http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2009/Ovary_09protocol.pdf). Accessed March 2011.

359. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple outcomes of raloxifene evaluation. JAMA 1999;281:2189-2197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10376571>.

360. Cuzick J, Sestak I, Bonanni B, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet 2013;381:1827-1834. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23639488>.

361. Lippman ME, Cummings SR, Disch DP, et al. Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk. Clin Cancer Res 2006;12:5242-5247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16951244>.

362. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. J Natl Cancer Inst 2004;96:1751-1761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15572757>.

363. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 2006;295:2727-2741. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16754727>.

364. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing breast cancer. Cancer Prev Res (Phila) 2010;3:696-706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20404000>.

365. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328-2335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15197194>.

366. Gronwald J, Tung N, Foulkes WD, et al. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. Int J Cancer 2006;118:2281-2284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16331614>.

367. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. Lancet 2000;356:1876-1881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11130383>.

368. King MC, Wieand S, Hale K, et al. Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 2001;286:2251-2256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11710890>.

369. Ingle JN, Liu M, Wickerham DL, et al. Selective estrogen receptor modulators and pharmacogenomic variation in ZNF423 regulation of BRCA1 expression: individualized breast cancer prevention. Cancer

Discov 2013;3:812-825. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23764426>.

370. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet Oncol 2007;8:26-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17196508>.

371. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998;339:424-428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9700175>.

372. Iodice S, Barile M, Rotmensz N, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 2010;46:2275-2284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20537530>.

373. Moorman PG, Havrilesky LJ, Gierisch JM, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. J Clin Oncol 2013;31:4188-4198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24145348>.

374. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94:1773-1779. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12464649>.

375. Haile RW, Thomas DC, McGuire V, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863-1870. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17021353>.

376. Lee E, Ma H, McKean-Cowdin R, et al. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based



study. Cancer Epidemiol Biomarkers Prev 2008;17:3170-3178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18990759>.

377. Milne RL, Knight JA, John EM, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005;14:350-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15734957>.

378. Offit K, Kohut K, Clagett B, et al. Cancer genetic testing and assisted reproduction. J Clin Oncol 2006;24:4775-4782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16840542>.

379. Menon U, Harper J, Sharma A, et al. Views of BRCA gene mutation carriers on preimplantation genetic diagnosis as a reproductive option for hereditary breast and ovarian cancer. Hum Reprod 2007;22:1573-1577. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17428877>.

380. Quinn G, Vadaparampil S, Wilson C, et al. Attitudes of high-risk women toward preimplantation genetic diagnosis. Fertil Steril 2009;91:2361-2368. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18440521>.

381. Vadaparampil ST, Quinn GP, Knapp C, et al. Factors associated with preimplantation genetic diagnosis acceptance among women concerned about hereditary breast and ovarian cancer. Genet Med 2009;11:757-765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19710615>.

382. Quinn GP, Vadaparampil ST, Miree CA, et al. High risk men's perceptions of pre-implantation genetic diagnosis for hereditary breast and ovarian cancer. Hum Reprod 2010;25:2543-2550. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20713415>.

383. Quinn GP, Vadaparampil ST, King LM, et al. Conflict between values and technology: perceptions of preimplantation genetic diagnosis among women at increased risk for hereditary breast and

ovarian cancer. Fam Cancer 2009;8:441-449. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19554475>.

384. Jasper MJ, Liebelt J, Hussey ND. Preimplantation genetic diagnosis for BRCA1 exon 13 duplication mutation using linked polymorphic markers resulting in a live birth. Prenat Diagn 2008;28:292-298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18302307>.

385. Sagi M, Weinberg N, Eilat A, et al. Preimplantation genetic diagnosis for BRCA1/2--a novel clinical experience. Prenat Diagn 2009;29:508-513. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19248143>.

386. 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21601526>.

387. Avigad S, Peleg D, Barel D, et al. Prenatal diagnosis in Li-Fraumeni syndrome. J Pediatr Hematol Oncol 2004;26:541-545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15342977>.

388. Prochazkova K, Foretova L, Sedlacek Z. A rare tumor and an ethical dilemma in a family with a germline TP53 mutation. Cancer Genet Cytogenet 2008;180:65-69. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18068537>.

389. Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000;37:828-830. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11073535>.

390. Bayley JP. Succinate dehydrogenase gene variants and their role in Cowden syndrome. Am J Hum Genet 2011;88:674-675; author reply 676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21565294>.





391. SEER Stat Fact Sheets: Thyroid Cancer. 2015. Available at:  
<http://seer.cancer.gov/statfacts/html/thyro.html>. Accessed May 28,  
2015.

