HEREDITARY CANCER: IDENTIFYING THOSE AT RISK AND MANAGING CARE FOR PREVIVORS AND SURVIVORS

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GOALS OF THIS EXPERIENCE ARE TO INCREASE PROVIDER:

- knowledge of hereditary breast and ovarian cancer risk, family history “red flags” and genetic testing options
- confidence in obtaining and evaluating family histories and providing appropriate medical follow up
- awareness of current evidence-based guidelines
SPECIFIC LEARNING OBJECTIVES:

1. Recognize the significance of family history in cancer risk
2. Demonstrate the ability to recall key “red flags” and identify those at risk
3. Provide appropriate referrals and follow up for patients at increased risk

CHAPTER INDEX

Family History Background and Pre-Test
The Case of the Frantic Cousin
The Case of the Hidden Cancer
The Case of the Anxious Grandmother
The Average Case of Colon Cancer
The Case of the Single Generation Cancer
The Case of the Family History Afterthought
Resources and References
“Family history is still the cheapest, most accessible, most time-tested way to get a rough estimate of the genetic component of disease risk.”

W. Gregory Feero, M.D., Ph.D.
Senior Advisor to the Director
for Genomic Medicine
NHGRI, NIH

- 853 charts reviewed of Michigan residents with cancer
- 82% documented presence or absence of family history of cancer. Of those:
  - 30% had positive family history of cancer
  - Over 80% documented relationship to patient and gender of affected family member
  - Over 94% missing age of onset/diagnosis of affected family member’s cancer

Health Plan Chart Review (2005-2007)

- 668 charts (60% from Family Practice, 25% from Internal Medicine, 15% from Pediatrics)
- Providers are collecting family history information.
- 92% of charts documented family history
  - 42% documented family history of cancer
  - 93% documented relationship of affected
  - Over 98% of charts never documented age of onset of affected
WHAT IS THE ADDED VALUE OF FAMILY HISTORY?

- Discussion of family history may enhance interaction with providers
- Awareness of familial risk may be a motivating factor for behavior change and screening uptake
- Earlier or more frequent screening based on familial risk may be cost-effective
- Family-centered approaches to risk reduction may be more effective and have longer impact

NATIONAL COALITION FOR HEALTH PROFESSIONAL EDUCATION IN GENETICS (NCHPEG)

National Coalition for Health Professional Education in Genetics® (NCHPEG)

NCHPEG’s Core Competencies in Genetics – September 2007

BASELINE COMPETENCIES:

- At a minimum, each health-care professional should be able to:
  1. Examine one’s competence of practice on a regular basis, identifying areas of strength and areas where professional development related to genetics and genomics would be beneficial.
  2. Understand that health-related genetic information can have important social and psychological implications for individuals and families.
  3. Know how and when to initiate a referral to a genetics professional.

SKILLS:

- All health professionals should be able to:
  1. Gather genetic family history information, including at minimum a three-generation history.
  2. Identify and refer clients who might benefit from genetic services or from consultation with other professionals for management of issues related to a genetic diagnosis.
  3. Explain effectively the reasons for and benefits of genetic services.
  4. Use information technology to obtain reliable, current information about genetics.
  5. Explain that the informed-consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question.
Healthy People 2020 Summary of Objectives

Genomics

<table>
<thead>
<tr>
<th>Number</th>
<th>Objective Short Title</th>
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<tbody>
<tr>
<td>G–1</td>
<td>Genetic counseling for women with a family history of breast and/or ovarian</td>
</tr>
<tr>
<td>G–2</td>
<td>Genetic testing for persons with colorectal cancer to detect Lynch syndrome</td>
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FOR EXISTING PATIENTS, HOW OFTEN DO YOU UPDATE A PATIENT’S FAMILY HISTORY?

A. At every visit
B. At most visits
C. At half of visits
D. At a few visits
E. Never

WHAT IS YOUR CURRENT KNOWLEDGE LEVEL OF CANCER GENETICS AND RELATED ISSUES? WOULD YOU SAY:

1. Very High
2. High
3. Average
4. Low
5. Very low
WHAT IS YOUR CURRENT CONFIDENCE LEVEL IN YOUR ABILITY TO IDENTIFY PATIENTS AT RISK FOR HEREDITARY CANCER? WOULD YOU SAY:

1. Very High
2. High
3. Average
4. Low
5. Very Low

WHICH OF THE FOLLOWING EVIDENCE-BASED GUIDELINES REGARDING GENETIC TESTING FOR HEREDITARY CANCER HAVE YOU HEARD OF?

2. NCCN (National Comprehensive Cancer Network) guidelines on Genetic/Familial High-Risk Assessment: Breast and Ovarian (2011)
3. Both
4. Neither
You are a trusted healthcare provider with the lives of patients in your hands. Each and every day you make medical decisions that may influence, not only the health of those patients in your office, but the health of hundreds of at-risk family members.

It is your mission and responsibility to assess and discuss the risk of hereditary disease in your patient. Any variation in your course of action could change the outcome for the patient sitting before you. Choose wisely and their risk may diminish. Choose poorly and your patient, or their loved ones, may perish.

Chapter Index

Chapter 2: The Case of the Frantic Cousin

A 27-year-old patient is referred to your office for increased breast screening and management. She has a family history of breast cancer and urged her family practice provider to send her for a mammogram. The provider preferred to send her to a high risk breast clinic for evaluation.
She says, ‘I’m so stressed about my cousin’s breast cancer diagnosis because she’s about my age. ’ I need a mammogram now – I can’t sleep, I can’t eat. I’m so worried.

FAMILY HISTORY:

- Paternal cousin - breast cancer at age 28
- Paternal uncle (that cousin’s father) - prostate cancer in his 40s
- Your patient’s father is cancer free and
- Paternal grandmother - breast cancer at 55 and ovarian cancer in her 70s.
1. Tell her she is not at increased risk because the cancer is on her father’s side and stress that breast cancer is only passed on through the mother.

2. Discuss that her family history is concerning and refer her for a baseline mammogram and genetic counseling to discuss her risk and possible testing.

3. Besides ordering her mammogram, you draw her blood for genetic testing of the breast cancer genes (BRCA1/2).
#1. Tell her she is not at increased risk because the cancer is on her father's side.

- The patient is relieved to hear this information as this has been weighing heavily on her for the past few weeks.
- You discuss general population screening recommendations for breast cancer (NCCN 2011).
  ~ Clinical breast exam every 1-3 years beginning at age 20
  ~ Mammograms and clinical exam annually beginning at age 40

But wait….there’s more

Two years later, your patient notices a lump in her breast at age 29. A biopsy is performed and she is found to have invasive ductal carcinoma.
The Best Choice!

#2: SHE GOES FOR GENETIC COUNSELING...

- It is recommended that the patient’s cousin undergo genetic testing for BRCA1/2.
- Your patient discusses this testing with her cousin and family and discovers that the cousin already had genetic testing.

#2: SHE GOES FOR GENETIC COUNSELING...

- The counselor obtains medical records and confirms a BRCA2 mutation in the cousin.
- Your patient’s father would be the next best candidate for testing, as his results would provide information about all of this children. He declines to be tested.
- Site-specific testing is ordered for your patient ($475).
She is positive for the familial BRCA2 mutation

#2: SHE GOES FOR GENETIC COUNSELING...

Based on her age, it is recommended that your patient have both a mammogram and breast MRI, as young women often have more dense breast tissue that may be better imaged through MRI.
#2: SHE GOES FOR GENETIC COUNSELING...

• Your patient’s site-specific BRCA2 testing for the familial mutation and is positive. View more information on Hereditary Breast and Ovarian Cancer Syndrome (HBOC).

• It is recommended that the patient have both a mammogram and breast MRI, as young women often have dense breast tissue that is better imaged through MRI. (Click here for HBOC management)

• Mammogram is normal. MRI discovers a small abnormality. A biopsy is performed which is confirmed as ductal carcinoma in situ (DCIS). It is small and was caught early. She has a lumpectomy and will continue with high risk breast screening.

#3: YOU ORDER GENETIC TESTING...

Not the best choice

• Like any lab test, you draw the patient’s blood and send it off for BRCA1/2 testing.

• 3 weeks later, the results arrive
She is found to have a BRCA 2 gene mutation.

**You disclose her test results and...**

- She relays this information to her family members
- She finds that her cousin already underwent BRCA testing and the familial mutation was known – your patient was so anxious to start her mammograms that she did not thoroughly explore the family history.
- **Full sequencing costs $3340 versus site specific testing for a known family mutation which costs ~$475.**

A difference of $2865 healthcare dollars that could have been saved!!
What did we learn?

- Early age at diagnosis is important to note (28 years old in a cousin).
- Paternal family history counts!! These genes can be passed from either side, typically with autosomal dominant inheritance.
- Breast MRI alternating with mammogram is recommended for younger women (NCCN/ACS / ACOG) – both Previvors and those with greater than a 20% lifetime risk.

Chapter Index

View the USPSTF Family History Criteria

Chapter 3: The Case of the Hidden Cancer

Your patient is an African American woman diagnosed 2 years ago with breast cancer at age 29. She was treated with a lumpectomy and radiation and is currently followed with annual mammogram and clinical breast exam. She is seen today for her routine follow up. She is currently healthy and reports no change in her medical history. Today, her breast exam is negative.
The patient’s mother had breast cancer at age 58 and she has a sister (age 28) who is healthy and cancer free. You recently ordered BRCA testing on your patient which revealed a variant in the BRCA2 gene.

HOW DO YOU PROCEED?

1. **Recommend she share her BRCA test results with her sister, so she too can be tested for the familial variant in BRCA2.**
2. **Reiterate that based on her BRCA results, her cancer is likely hereditary. You recommend MRI in addition to her current surveillance.**
3. **Strongly encourage that she go for genetic counseling to discuss the family history and BRCA results in more detail.**
# 1: RECOMMEND BRCA TESTING...

• You know all about BRCA1/2 testing because the testing laboratory recently gave a lunchtime learning session and supplied you with pre-packaged test kits.

• Based on your patients prior BRCA results, you recommend she talk with her sister about getting tested.

• Her sister follows up and testing is ordered through her PCP.

Chapter 6

The Sisters Results Are In...

She is found to have the same variant in the BRCA 2 gene as your patient.

More on variants of uncertain significance
#1: RECOMMEND BRCA TESTING FOR FAMILY:

Your patient’s sister never develops breast cancer. At age 38 your patient is diagnosed with endometrial cancer – a cancer that is not associated with the BRCA1 and BRCA2 genes.

Return to choices

#2: INCREASED HEREDITARY RISK – ADD MRI SURVEILLANCE

- You tell the patient that her cancer is likely hereditary, based on her BRCA results.
- You recommend MRI surveillance in addition to her mammograms.

Not the best choice
• She continues to have normal mammograms.

• At age 34 she reports painful, heavy menstruation and pain with intercourse. After physical exam she is told she likely has uterine fibroids. On ultrasound her ovaries look normal and her scan is consistent with uterine fibroids.

But wait, there’s more...

Chapter #2: INCREASED RISK – BEGIN MRI SURVEILLANCE

• By age 38, she has continued to have irregular, heavy bleeding over the last 3 years and has recently developed pain with urination, increased pain during intercourse, and general malaise.

• An ultrasound is ordered to assess her uterine fibroids. A biopsy is recommended.

• She is found to have endometrial cancer and a hysterectomy is performed to remove the tumor.

• While the cancer is confined to the endometrium, the patient is devastated by the diagnosis.
Referral form statement:
• Personal history of breast cancer at age 29
• Mother with breast cancer at 58

#3: REFER FOR GENETIC COUNSELING

• She was strongly encouraged to bring her mother with her to the appointment
• The counselor notes that the mother has a scar on her neck and a slight rasp in her voice.
• She inquires about the scar and discovers that she had non-medullary thyroid cancer at age 38
• Your patient was not aware of this history
• A limited physical examination is performed which reveals the mother (as well as your patient) are both macrocephalic (98th %ile).
While it is important to discuss and rule out BRCA1/2 (HBOC syndrome).

It is much more likely that this family has Cowden syndrome – caused by changes in the PTEN gene.

PTEN testing was recommended and ordered.

HAVE YOU HEARD OF COWDEN SYNDROME?

1. Yes
2. No
3. Don’t Know

View more information on Cowden Syndrome
#3: REFER FOR GENETIC COUNSELING

- PTEN testing - mutation identified in mother
- Your patient’s mother tests positive as does a brother
- Her sister tests negative

- Although the risk for endometrial cancer is ~10%, your patient and her husband talk with doctors about having children right away (at age 30). They discuss her options as a breast cancer survivor.
- At age 35 she begins annual suction biopsies which are recommended for women with Cowden syndrome.
- Suspicious cells are found and confirmed to be cancer on follow up D & C. She has a hysterectomy; the cancer appears to be confined to the endometrium.

WHAT DID WE LEARN?

- Written Informed Consent is the law in Michigan for presymptomatic or predictive genetic testing.
- Test an affected individual first if possible – this gives you more information
- Up to 20% of African Americans will have a variant of uncertain significance in the BRCA genes. (View screening recommendations for those with a BRCA variant)
- There are other syndromes associated with hereditary breast cancer (PTEN or Cowden, Li-Fraumeni, etc.) For a list of other syndromes, view the MCGA position paper on genetic counseling.
Your patient is a 58-year-old female with a family history of breast cancer in her mother at age 72. There are no other diagnoses of breast or ovarian cancer in the family. Her mother still has her ovaries in tact. In addition, her mother had a genetic test for breast cancer and was found to be “low risk” (called Oncotype Dx).

She is concerned for the well-being of her children and grandchildren and wonders if they are at increased risk for cancer. She wonders if she should pursue genetic testing for the sake of her family.
WHAT DO YOU DISCUSS?

1. *Her mother’s breast cancer was late onset and unlikely to be hereditary. She and her children are not at increased risk.*

2. *Consult with a geneticist regarding possible genetic testing.*

3. *Discuss that her mother already had a “low risk” test result for breast cancer called Oncotype Dx.*

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Now what if?

• Indeed, her risk to have a gene mutation in BRCA1/2 is < 1%.

• Based on family history her children are not at increased risk. General population screening guidelines should be followed (Mammograms beginning at age 40, every 1-2 years).

• This patient goes on to live a long and cancer-free life.
When in doubt, a referral is always appropriate.

However, given her mother’s age at diagnosis, the patient’s risk for breast cancer is not increased over the general population. And neither she, nor her mother, meet Medicare criteria for testing or the USPSTF guidelines.

Genetic testing is not indicated and the screening recommendations you have been following are appropriate: annual mammograms and clinical breast exams.

Not the best choice

#2: CONSULT WITH THE EXPERTS

This “low risk” gene assay has no bearing on hereditary cancer risk.

It looks at tumor characteristics to estimate risk of cancer recurrence and response to chemotherapy.
REVIEW OF THE PATIENT’S HISTORY:

58-year-old female

Mother with breast cancer at age 72.

No other diagnoses of breast or ovarian cancer in the family and her mother still has her ovaries in tact.

Now we learn she is Ashkenazi Jewish.

DOES THIS CHANGE WHAT YOU WOULD TELL HER?

1. *Her mother’s breast cancer was late onset and is unlikely to be related to a hereditary cancer syndrome. Her children are not at increased risk.*

2. *Consult with a geneticist regarding possible genetic testing.*

3. *Or decide, based on ancestry, that the patient should have comprehensive BRCA1/2 testing.*
#1: LATE ONSET/ LOW RISK

- You tell the patient that the risk for her cancer to be caused by a hereditary gene mutation is low. And that her children are not at increased risk. General population screening should be followed.

- However, this patient does not go on to live a happy and cancer-free life...

- 10 years later the patient presents with bloating and abdominal discomfort.

Chapter LATE ONSET / LOW RISK?

The patient is diagnosed with stage IV ovarian cancer with peritoneal disease.

Radical radiation and chemotherapy treatments fail to reduce the spread. After a difficult fight, she dies in hospice care.
#2: Consult with the experts

- Ashkenazi Jewish ancestry with any family history of breast/ovarian cancer, is enough to recommend BRCA1/2 testing for the patient or her mother (AND for her mother to meet Medicare criteria).
- You refer her to Genetics and suggest she take her mother with her to the appointment.
- Testing is ordered and your patient has a BRCA1 mutation detected on the 3-site Jewish panel. Her children are at a 50% risk.
- A test that costs about $575.

#3: DECIDE TO ORDER BRCA TESTING

- You order gene sequencing for BRCA1/2
- Written informed consent is obtained and the patient’s blood sample is sent to the lab.
- 4 weeks later, the test comes back positive.

However... This result came from a test that costs over $3340. The mutation identified is one of the Ashkenazi Jewish founder mutations and could have been identified through the Jewish 3-site panel for $575.
WHAT DID WE LEARN?

• A single diagnosis at an older age is most likely sporadic (or non-hereditary).

• Ashkenazi Jewish ancestry is important! Documenting ancestry can make the difference between identifying a family at risk and letting them slip through the cracks. View the USPSTF referral criteria for those with Ashkenazi Jewish ancestry.

• Tumor gene assays on breast tissue (such as Oncotype Dx, MammaPrint, and H:1 Ratio testing) do not assess hereditary causes of breast cancer. View the EGAPP recommendation statement.

• Population based screening guidelines should always be reinforced. (Mammograms beginning at age 40, every 1-2 years, ACS and ACOG).

• Due to inadequate screening techniques for ovarian cancer, prophylactic oophorectomy is currently recommended for women with a BRCA1/2 gene change (once women are done having children and/or are age 40.)

• View the Medicare Criteria for BRCA testing.

CHAPTER 5 The Average Case of Colorectal Cancer

Your patient is a 72-year-old man who was recently found to have colorectal cancer on colonoscopy. Surgery was performed and the tumor was removed. He has been diligent about his colon screening and has had colonoscopies every 10 years as is appropriate in the general population.

Mr. Richards is now concerned about his children and their risk for colon cancer. He has a cousin with ovarian cancer in her 70s and two daughters with endometrial cancer, in their 50s.
WHAT DO YOU DISCUSS?

1. Consult with the GI surgeon regarding possible genetic tumor analysis.

2. His colon cancer was late onset and is unlikely to be related to a hereditary cancer syndrome. His children are not at increased risk.

3. Recommend that his children begin colorectal screening 10 years earlier than the general population (at age 40).
#1: CONSULT WITH THE EXPERTS

- The GI surgeon agrees to order MSI / IHC testing on the tumor tissue (which is retained in Pathology).
- The results show loss of expression of MSH2 (one of the Lynch related genes).
- You refer the patient for genetic counseling, informed consent, and genetic testing.
- Mr. Richards is found to have an MSH2 mutation as are two of his children and five of his grandchildren.
- There is a 50% risk to immediate family members when mutations are identified.

#2: LATE ONSET / LOW RISK

- You tell the patient that the risk for his cancer to be caused by a hereditary gene mutation is low.
- Based on family history his children are not at increased risk. General population screening should be followed.

However…. 
• Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch Syndrome is the underlying cause in 2-3% of all colorectal cases.

• All colorectal tumors should undergo either MSI or IHC testing to determine if the tumor is likely to be hereditary. Subsequent genetic testing should be performed when a tumor is found to be high risk (EGAPP Recommendation Statement 2009).

• Mr. Richards youngest son, age 48, undergoes colonoscopy and is found to have a small mass in the proximal colon.
• He goes on to have genetic testing because of his young age and is found to have an MSH2 mutation.
• Lynch syndrome is an appropriate diagnosis for his family, as two of Mr. Richards’ daughters have had uterine cancer.
• Endometrial cancer is the primary diagnosis in 50% of women with Lynch syndrome.

#3: INCREASE SCREENING FOR FAMILY
An “ok” choice
WHAT DID WE LEARN?

- Approximately 2-3% of all individuals diagnosed with colorectal cancer have Lynch syndrome.
- MSI or IHC should be carried out on all colorectal tumors to determine if they are likely to be hereditary. View the ECAPP Recommendations on Colorectal Cancer Genetic Testing.
- Endometrial cancer is the primary diagnosis in 50% of women with Lynch syndrome and ovarian cancer is also noted in these families.
- Most hereditary cancer syndromes are autosomal dominant – meaning there is a 50% risk to first degree relatives.

View more information on Lynch Syndrome

Chapter 6 The Case of the Single Generation Cancer

Personal history:
- 50 colon polyps
- colorectal cancer at age 27

Parents:
- Both in their 50s
- No history of cancer
- Recent colonoscopies were negative for adenomatous polyps

Two brothers:
- 29 and 31
- Neither have had a colonoscopy

** No one has discussed hereditary cancer with him.**
CHAPTER 6: WHAT DO YOU TELL THIS PATIENT?

1. Carry out genetic testing for Familial Adenomatous Polyposis (FAP), given the patient’s polyp history.
2. With no cancer in his parents or extended family, this is most likely sporadic.
3. Ask if he would like to learn more about hereditary cancer risk and suggest genetic counseling.

Not the best choice

#1: ORDER TESTING FOR FAMILIAL ADENOMATOUS POLYPSIS (FAP)

- Based on the patient’s history of polyps and cancer at a young age, you order testing for FAP.
- Testing is negative for mutations in the APC gene.
- What do you tell the patient now?
#1: WHAT DO YOU TELL THIS PATIENT?

1. You are uncertain why he has so many polyps and recommend his family be screened just in case
2. Further investigate other syndromes in case something was missed
3. Tell him his polyps and cancer are likely sporadic

#2: NO FAMILY HISTORY = SPORADIC CANCER

- You tell him his cancer was most likely sporadic, especially since his parents have no history of polyps.
- Unfortunately, one of his brothers is diagnosed with colon cancer 2 years later.
- That makes two diagnoses in the same generation, with no additional family history.
- Is there another condition that should be discussed? (shout it out)
#3: HE WOULD LIKE MORE INFORMATION AND GOES FOR GENETIC COUNSELING...

Both Familial Adenomatous Polyposis (FAP) and MYH-Associated Polyposis (MAP) are discussed. Individuals with no family history can have a new mutation in the FAP gene (APC) or can have MAP which is an unusual recessive cancer condition.

Your patient is tested for FAP which is negative and for the two most common MAP mutations. MAP testing is positive for two mutations (Y165C and G382D). His 31-year-old brother tests positive and begins screening colonoscopies with polypectomy. His 29-year-old brother tests negative, and returns to population risk (he does not require special cancer screening).

#3: HAVE YOU HEARD OF MYH-ASSOCIATED POLYPOPOSIS?

1. Yes
2. No
3. Don’t Know

View more information on MYH-Associated Polyposis.
WHAT DID WE LEARN?

- **Multiple hereditary colon cancer syndromes exist.** While, it is important to rule out the most likely conditions first, testing does not always stop there.

- **Getting the family members screened is important!** If others have similar features, this can point to a specific hereditary condition. In this family, autosomal recessive inheritance (only one generation) was the key.

- **Testing negative for a familial mutation puts you back to general population risk.** His other brother is therefore saved from years of excessive cancer screening.

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CHAPTER The Case of the Family History

A 39-year-old woman arrives in your office with her son, who is in need of a routine checkup. After addressing her concerns and vaccinating her son, you wish her well and on her way.

As you grab the doorknob to leave the exam room, she says “by the way, Kent’s uncle (my brother) was diagnosed with breast cancer last week (at age 42)... should I be worried?”
WHAT DO YOU DO NEXT?

1. *Tell her that there is simply no time to discuss this today, as this is a pediatric clinic.*
2. *Ask more about her family history and tell her you're not sure about male breast cancer – she should see her regular doctor.*
3. *Provide the number for genetic counseling services and encourage her to schedule her first screening mammogram.*

Not the best choice

#1: YOU DO NOT ADDRESS HER CONCERNS AT THIS APPOINTMENT...

- Since you did not express any great concern at today’s visit, the patient is not concerned by her risk.
- She has regular mammograms, which are normal.
- At age 47 she develops abdominal discomfort and bloating.
- Imaging reveals stranding around the ovaries and suspicious lesions in the liver. *She is diagnosed with stage IV ovarian cancer with positive lymph nodes and liver metastasis.*
She died at age 49.

The Best Choice!

#2: ASK MORE ABOUT HER FAMILY HISTORY AND TELL HER YOU'RE NOT SURE...

- Her mother was diagnosed at 68 years old.
- She reports no other family history until you specifically ask about paternal history.
- You review the importance of mammography and clinical breast exams beginning at age 40.
- You do not order genetic testing at this time, but you strongly encourage her to see her primary care physician to discuss this family history.

She follows up with her physician who refers her to Genetics Clinic.
#3: GENETIC COUNSELING

"An OK Choice"

- She is focused on her mother’s history, but the paternal history is much more concerning.
- It is recommended that her brother have BRCA1/2 testing.

SHE GOES FOR GENETIC COUNSELING

- The patient has a mammogram, which reveals a small suspicious lesion. It is removed and found to be DCIS. She will continue to be followed by a breast surgeon at a high risk breast clinic.
- Her brother undergoes testing and is found to carry a BRCA2 mutation.
- Your patient has site-specific BRCA2 testing for the familial mutation and is positive. She would like to discuss having her ovaries removed in the future to reduce her risk.
WHAT DID WE LEARN?

- **Male breast cancer is a big red flag!** The risk of male breast cancer in the general population is < 1%. Men who carry a BRCA1/2 mutation have up to a 6-10% risk for breast cancer.

- **Appropriate management is crucial for high risk families and potentially save lives.** Prophylactic oophorectomy reduces the risk of breast cancer by 50% and the risk of ovarian cancer by nearly 90-96%. Prophylactic mastectomy reduces the risk of breast cancer by 90%.

REVIEW OF WHAT WE LEARNED

- Test the affected individual first when possible
- Paternal history counts!!
- Beware of early ages at diagnosis (under age 50)
- Screening, screening, screening!
- A single diagnosis at a later age is most likely sporadic (or non-hereditary)
- Tumor gene assays on breast tissue do not assess hereditary risk – only recurrence risk and receptivity to chemotherapy.
- Approximately 2-3% of all individuals diagnosed with colorectal cancer have Lynch syndrome
- MSI or IHC should be carried out on all colorectal tumors to determine if they are likely to be hereditary.
Review of what we learned

- Ancestry is important – Ashkenazi Jewish ancestry conveys an increased risk for hereditary breast and ovarian cancer.
- Always document the type of cancer, age and diagnosis and which family members are affected.
- Endometrial cancer is the primary diagnosis in 50% of women with Lynch syndrome and ovarian cancer is also noted in these families.
- Most hereditary cancer syndromes are autosomal dominant – meaning there is a 50% risk to first degree relatives.
- Finally, refer to the US Preventive Services Task Force recommendations for the most comprehensive evidence-based information on hereditary cancer screening.

MOST IMPORTANT FAMILY HISTORY FACTORS TO DOCUMENT!

1. Type of cancer
2. Who is affected / how are they related to your patient
3. At what age were they diagnosed
4. Ancestry
WHAT IS YOUR CURRENT KNOWLEDGE LEVEL OF CANCER GENETICS AND RELATED ISSUES? WOULD YOU SAY:

1. Very High
2. High
3. Average
4. Low
5. Very low

WHAT IS YOUR CURRENT CONFIDENCE LEVEL IN YOUR ABILITY TO IDENTIFY PATIENTS AT RISK FOR HEREDITARY CANCER? WOULD YOU SAY:

1. Very High
2. High
3. Average
4. Low
5. Very Low
WHICH OF THE FOLLOWING EVIDENCE-BASED GUIDELINES REGARDING GENETIC TESTING FOR HEREDITARY CANCER HAVE YOU HEARD OF?

2. NCCN (National Comprehensive Cancer Network) guidelines on Genetic/Familial High-Risk Assessment: Breast and Ovarian (2011)
3. Both
4. Neither

DID THIS TRAINING PROVIDE INFORMATION THAT WAS APPROPRIATE AND APPLICABLE IN YOUR CURRENT WORK?

A. Yes, very appropriate and applicable
B. Yes, somewhat appropriate and applicable
C. No, not at all appropriate or applicable
WILL THE CONTENT OF THIS TRAINING CHANGE YOUR CLINICAL PRACTICE IN ANY WAY?

A. Yes, I will make several changes
B. Yes, I will make a few changes
C. No, this web-based training will not change the way I practice

RESOURCES AND INFORMATION

http://www.cdc.gov/genomics/

http://www.nchpeg.org/

http://www.michigancancer.org/WhatWeDo/MCCUpdateArchive.cfm

http://www.aafp.org/online/en/home/clinical/exam/a-e.html
MDCH RESOURCES FOR PRACTICE

It’s time... know your family’s health history.

Unlock your past for a healthier future.

- talk about it
- write it down
- pass it on

Contact:

- 1-866-852-1247
- genetics@michigan.gov

- MI Cancer Genetics Alliance (MCGA)
  - www.MIGRC.org/cancer
  - To become a member email mcloskyj@michigan.gov

- MI Department of Community Health (MDCH)
  - www.michigan.gov/genomics

- MI Cancer Consortium (MCC)
  - www.michigancancer.org
• NCHPEG, Core Genetic Competencies for all Health Care professionals, 2007
• http://www.ahrq.gov/CLINIC/uspstfix.htm
• http://www.egappreviews.org/
• www.geneclinics.com
• www.cancer.org
• www.ccalliance.org

QUESTIONS AND DISCUSSION
HEREDITARY BREAST AND OVARIAN CANCER (HBOC) SYNDROME

• Caused by mutations in the BRCA1 or BRCA2 genes

• Accounts for 5-10% of all breast cancers. And 20% in Ashkenazi Jewish women diagnosed under age 45 (those of Eastern European descent).

• Approximately 1 in 200 people are carriers in the general population. Penetrance is estimated at 45 – 84%.

* Prostate and pancreatic cancer risk is not specifically addressed by the USPSTF evidence based guidelines, but is commonly seen in families with BRCA mutations.

Chapter

National Comprehensive Cancer Network (NCCN)

• The BRCA genes are autosomal dominant – they are not located on the sex chromosomes.

• Both men and women can pass on mutations in these genes to their children. Paternal history counts!
• General population risk for breast cancer is 1 in 8 or ~12%.

• **Age Cumulative Breast Cancer Risks Female BRCA carriers**

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 yrs</td>
<td>3.2%</td>
</tr>
<tr>
<td>40 yrs</td>
<td>19.1%</td>
</tr>
<tr>
<td>50 yrs</td>
<td>50.8%</td>
</tr>
<tr>
<td>60 yrs</td>
<td>54.2%</td>
</tr>
<tr>
<td>70 yrs</td>
<td>85%</td>
</tr>
</tbody>
</table>

• Men with BRCA1 or BRCA2 mutations have a 1.8% or 8% lifetime risk of breast cancer respectively (by age 80). NCCN guidelines quote a 6.9% lifetime risk.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Lifetime Cancer risk</th>
<th>Lifetime Cancer risk</th>
<th>2nd Cancer Risk within 5 yrs</th>
<th>2nd Cancer Risk within 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General Population</td>
<td>BRCA1/2 mutation carrier</td>
<td>General Population</td>
<td>BRCA1/2 mutation carrier</td>
</tr>
<tr>
<td>Breast</td>
<td>12%</td>
<td>36-85%</td>
<td>5%</td>
<td>12-20%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>20-45% (62%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>Slightly increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>Slightly increased</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Up to 20% of African American or Black women who undergo BRCA1/2 testing will carry a variant of uncertain significance.
• These variants may or may not be related to hereditary cancer risk.
• Therefore, it is best to test all affected individuals in the family first, to see if the variant tracks with the cancer.
• And informed consent is critical to ensure the patient is aware of this possible vague result.
• Your patient’s sister called her in tears stating, “I thought this test would give me a straight answer and now I’m more confused! So they don’t know if I need screening or not?”

Obtaining proper informed consent is the law in Michigan.

VARIANT of uncertain significance

This scenario leaves us with lots of questions:
• Is this variant truly related to cancer? Now you see it in one person with cancer and one person who is cancer free?
• What if her affected mother tests negative for the same BRCA variant? Would we still think it is related to cancer?
• Is there something else that we’re missing?
Management of risk in Previvors

**Surveillance**
- Clinical breast exam every 6 months beginning at age 25.
- Annual mammogram and breast MRI starting age 25 or 10 yrs younger than the earliest age of onset in the family.
- Concurrent transvaginal ultrasound and CA-125 every 6 months beginning at age 35. Current best practice, however, there is insufficient evidence of the efficacy in decreasing mortality.

**Chemoprevention**

**Prophylactic Surgery**
- Bilateral total mastectomy – decreases the breast cancer risk by 90%. Patient should be informed of this option.
- Bilateral oophorectomy after child bearing – decreases the ovarian cancer risk by 90-96% and decreases the breast cancer risk by 50%. Patient should be informed of this option.
1. Dutch Ancestry: deletions in exon 13 and exon 22
2. European (primarily British) ancestry: duplication of exon 13
3. European ancestry: deletion of exons 8 and 9
4. Deletion of exons 14-20

Single Site BRACAnalysis®
For Individuals with a Known Familial Mutation in BRCA1 or BRCA2
$475.00
Management of Risk

VARIANT OF UNCERTAIN SIGNIFICANCE TEST RESULTS

Surveillance

- Alternate mammogram and breast MRI starting age 25-35 or 10 yrs younger than the earliest age of onset within the family.

- Could consider annual transvaginal ultrasound and CA-125 for ovarian cancer screen. Best practice, however there is no evidence of efficacy in decreasing mortality.

USPSTF FAMILY HISTORY PATTERNS

- 2 first degree relatives with breast cancer (one of whom was diagnosed under age 50)
- 3 or more first/second degree relatives with breast cancer (regardless of age)
- A combination of both breast and ovarian cancer among related first/second degree relatives
- A first degree relative with bilateral breast cancer
- 2 or more first/second degree relatives with ovarian cancer (regardless of age)
- A first/second degree relative with breast AND ovarian cancer (at any age)
- A male relative with breast cancer (at any age)

http://www.ahrq.gov/CLINIC/uspsfix.htm
For women of Ashkenazi Jewish ancestry:

- A first degree relative with breast or ovarian cancer at any age
- 2 second degree relatives (on the same side of the family) with breast or ovarian cancer at any age
Chapter 2: Risk Assessment and Genetic Counseling

Cancer risk assessment, genetic counseling, and testing services are provided to patients either on-site or by referral, by a qualified genetics professional.

Michigan law states that a physician shall not order “a presymptomatic or predictive genetic test without first obtaining the written, informed consent.”

- Nature and purpose of the test
- Effectiveness and limitations
- Implications of taking the test, including, but not limited to, the medical risks and benefits.
- The future uses of the sample taken and the information gained from the test.
- The meaning of the test results and how results will be disclosed.
- Who will have access to the patient’s sample and result and the right to confidentiality.
COWDEN SYNDROME

PTEN

- Increased risk for cancers – breast, endometrial, and thyroid (non-medullary). Breast cancer risk 30-50%. Renal cell carcinoma risk increased to a lesser degree.
- Multiple lipomas (benign fatty tumors), hemangiomas.

- Macrocephaly (large head circumference).
- Higher incidence fibrocystic breast disease, fibroadenomas.
- Thyroid gland nodules (benign).

COWDEN SYNDROME

- Major criteria – breast and thyroid cancer, macrocephaly, endometrial cancer, and Lhermitte-Duclos disease (a benign cerebellar tumor).
Trichilemmomas, papillomatous papules, and mucosal papules

COWDEN SYNDROME SURVEILLANCE

- Annual breast cancer screening: mammography and MRI beginning at age 30-35 or 5-10 years before the earliest breast cancer in the family.
- For endometrial cancer (premenopausal women): annual blind suction biopsies beginning at age 35-40 or 5 years before the youngest endometrial cancer in the family.
- For endometrial cancer (postmenopausal women): annual transvaginal ultrasound with biopsy of suspicious areas.
COWDEN SYNDROME SURVEILLANCE

- Annual thyroid palpation. Baseline thyroid ultrasound at age 18. Consider annual thyroid ultrasound.
- Annual urine analysis. Urine cytology and renal ultrasound if FHx for renal cell carcinoma.

MEDICARE CRITERIA FOR BRCA1/2 TESTING

Personal history of breast cancer + one or more of the following:
- Diagnosed 45 yrs or younger with or without family history
- Diagnosed 50 yrs or younger or history of two primaries
  - with 1 or more close blood relatives with breast cancer OR
  - 1 or more close blood relatives with ovarian cancer**.
- Two breast primaries when first diagnosis was prior to age 50
- Diagnosed at any age with 2 or more relatives with breast and/or ovarian (at any age)
- Close male blood relative with breast cancer
- Personal history of ovarian cancer
- Is of certain ethnic ancestry (Ashkenazi Jewish, Icelandic, Swedish, Hungarian)
- A close relative with a known BRCA1/2 mutation

** Ovarian cancer includes fallopian, and primary peritoneal cancers as well.
Table 1: Hereditary Cancer Syndromes with an Increased Risk of Other Cancers

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Increased Risk of Cancers</th>
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<tbody>
<tr>
<td>Bloom Syndrome</td>
<td>Wiscott-Aldrich syndrome</td>
<td>4-5% of all cancers</td>
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Table 2: Non-Hereditary Cancer Syndromes

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</tr>
<tr>
<td>Neurofibromatosis</td>
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<td>1% of all cancers</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>Cowden syndrome</td>
<td>1% of all cancers</td>
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Appendix 1

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**EVALUATION OF GENOMIC APPLICATIONS IN PRACTICE AND PREVENTION (EGAPP) RECOMMENDATION STATEMENT: TUMOR GENE EXPRESSION PROFILING**

“For Oncotype Dx, the EWG found adequate evidence from one higher quality study, to support the association between recurrence score (RS) and rates of 10-year metastasis, and adequate evidence to support the association between RS and chemotherapy benefit.” Insufficient evidence was found for Mammaprint and H:I ratio testing.

---

**MYH-ASSOCIATED POLYPOSIS (MAP)**

- Multiple adenomatous polyps over the lifetime (10 to hundreds)
- Affected individuals may develop polyps or cancer early (20s to 50s).
- Recessive cancer syndrome: meaning it is common for an affected individual to have no family history – often affects only a single generation
- Approximately 1 in 100 individuals is a carrier for a gene change in the MYH gene.
- Risk of polyps and cancer is increased in carriers over the general population but not as high as those with two mutations.
MYH-ASSOCIATED POLYPOSIS (MAP)

• Typically Familial Adenomatous Polyposis (FAP) or Attenuated FAP must be ruled out first through APC-gene testing.
• Management (no set guidelines exist as of yet)
  – Sigmoidoscopy or colonoscopy every one to two years, beginning at age 18 years
  – Colonoscopy annually once polyps are detected
  – Consider colectomy if polyps cannot be adequately managed through colonoscopy and polypectomy.
• The risk for extra-colonic tumors or disease manifestations has not yet been clarified.

EVALUATION OF GENOMIC APPLICATIONS IN PRACTICE AND PREVENTION (EGAPP) RECOMMENDATION STATEMENT: TUMOR GENE EXPRESSION PROFILING

“For Oncotype Dx, the EWG found adequate evidence from one higher quality study, to support the association between recurrence score (RS) and rates of 10-year metastasis, and adequate evidence to support the association between RS and chemotherapy benefit.” Insufficient evidence was found for Mammaprint and H:I ratio testing.
LYNCH SYNDROME

- Also called Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC)
- Accounts for ~2-3% of all CRC diagnoses
- Caused by mutations in one of several DNA mismatch repair genes (MMR genes)
- Diagnosis can be at a younger age (<60)
- Autosomal Dominant
- Highly penetrant (70-80%)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>Lynch Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20%-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11%-19%</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9%-12%</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2%-7%</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4%-5%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1%-4%</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
</tr>
</tbody>
</table>

Mean Age of Onset

- Colon: 44 years
- Endometrium: 46 years
- Stomach: 56 years
- Ovary: 42.5 years
- Hepatobiliary tract: Not reported
- Urinary tract: ~55 years
- Small bowel: 49 years
- Brain/central nervous system: ~50 years

References:
LYNCH SYNDROME

• Colorectal CA
  – 2/3 occur in proximal colon
  – Newer literature reports an average age of onset of 61 years (Hampel et al. 2005)
  – Reported associated histologies: poorly differentiated, tumor-infiltrating lymphocytes, mucinous, signet ring, and cribiform

• Endometrial CA –
  – Second most common cancer in HNPCC
  – Survival advantage over sporadic cases
  – This is the initial presenting cancer in 50% of women with Lynch Syndrome

LYNCH SYNDROME TESTING

Microsatellite Instability (MSI)

• Short repeats scattered throughout genome
• Can be repeated 10 to 100s of times
• Increased rate of mutation within these regions
• Mutations in MMR genes lead to unstable microsatellites indicating a high likelihood of Lynch Syndrome
• 95% of Lynch colon tumors will be MSI high (unstable)
• 90% of the families meeting Amsterdam criteria have MSI high tumors
• 15% of sporadic colon tumors will be MSI high
LYNCH SYNDROME TESTING

Immunohistochemistry (IHC)
- Tumor samples are stained to identify which MMR proteins are present and which, if any, are missing.

Gene Sequencing for Lynch syndrome
- The missing protein represents the MMR gene that is not functioning in the tumor.
- That MMR gene is then sequenced.
- IHC is potentially diagnostic and patients should be fully informed about genetic testing prior to initiating IHC.
- Missing protein for MSH6 is pathognomonic for a genetic mutation in MSH6.
LYNCH SYNDROME SURVEILLANCE

• Colon cancer screen: begins 20-25 yo or 10 years before the age of the earliest colorectal cancer diagnosed in the family, every 1-2 years.
  – Colonoscopy reduces CRC by 62% in high risk families – strong evidence.

• Endometrial and ovarian cancer screen: Annual transvaginal ultrasound (TVU) and endometrial sampling begins at age 30-35. TVU measures endometrial thickness and evaluates the ovaries. Lack of evidence for effectiveness.

• Urinary tract cancer screen:
  – Urine analysis with cytology once 1-2 years, begins at 25-35 yo.
  – Insufficient evidence to assess the efficacy.

• Gastric Cancer screen: no recommended guideline how to screen.
  – Risk has marked variation between different populations. In Finland, the cumulative risk is 13%. In Netherlands, the risk is 2.1 – 4.3%.
Genetic Risk Assessment and \textit{BRCA} Mutation Testing for Breast and Ovarian Cancer Susceptibility: Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on genetic risk assessment and \textit{BRCA} mutation testing for breast and ovarian cancer susceptibility, along with the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, is included in the evidence synthesis available through the USPSTF Web site (www.preventiveservices.ahrq.gov). The recommendation is also posted on the Web site of the National Guideline Clearinghouse (www.guideline.gov).

**SUMMARY OF RECOMMENDATIONS**

The U.S. Preventive Services Task Force (USPSTF) recommends against routine referral for genetic counseling or routine breast cancer susceptibility gene (\textit{BRCA}) testing for women whose family history is not associated with an increased risk for deleterious mutations in breast cancer susceptibility gene 1 (\textit{BRCA1}) or breast cancer susceptibility gene 2 (\textit{BRCA2}).

This is a grade D recommendation. (See Appendix Table 1 for a description of the USPSTF classification of recommendations.)

The USPSTF found fair evidence that women without certain specific family history patterns, termed here “increased-risk family history” (see Clinical Considerations for a definition), have a low risk for developing breast or ovarian cancer associated with \textit{BRCA1} or \textit{BRCA2} mutations. Thus, any benefit to routine screening of these women for \textit{BRCA1} or \textit{BRCA2} mutations, or routine referral for genetic counseling, would be small or zero.

The USPSTF found fair evidence regarding important adverse ethical, legal, and social consequences that could result from routine referral and testing of these women. Interventions such as prophylactic surgery, chemoprevention, or intensive screening have known harms. The USPSTF estimated that the magnitude of these potential harms is small or greater.

The USPSTF concluded that the potential harms of routine referral for genetic counseling or \textit{BRCA} testing in these women outweigh the benefits. (See Appendix Table 2 for a description of the USPSTF classification of levels of evidence.)

The USPSTF recommends that women whose family history is associated with an increased risk for deleterious mutations in \textit{BRCA1} or \textit{BRCA2} genes be referred for genetic counseling and evaluation for \textit{BRCA} testing.

This is a grade B recommendation.

The USPSTF found fair evidence that women with certain specific family history patterns (increased-risk family history) have an increased risk for developing breast or ovarian cancer associated with \textit{BRCA1} or \textit{BRCA2} mutations. The USPSTF determined that these women would benefit from genetic counseling that allows informed decision making about testing and further prophylactic treatment. This counseling should be done by suitably trained health care providers. There is insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving health outcomes in these women if they test positive for deleterious \textit{BRCA1} or \textit{BRCA2} mutations. However, there is fair evidence that prophylactic surgery for these women significantly decreases breast and ovarian cancer incidence. Thus, the potential benefits of referral and discussion of testing and prophylactic treatment for these women may be substantial.

The USPSTF also found insufficient evidence regarding important adverse ethical, legal, and social consequences that could result from referral and testing of high-risk women.

See also:

- **Print**
  - Editorial comment: 388
  - Related article: 362
  - Summary for Patients: 1-47

- **Web-Only**
  - Conversion of tables into slides
Prophylactic surgery is associated with known harms. The USPSTF estimated that the magnitude of these potential harms is small.

The USPSTF concluded that the benefits of referring women with an increased-risk family history to suitably trained health care providers outweigh the harms.

**Clinical Considerations**

These recommendations apply to women who have not received a diagnosis of breast or ovarian cancer. They do not apply to women with a family history of breast or ovarian cancer that includes a relative with a known deleterious mutation in *BRCA1* or *BRCA2* genes; these women should be referred for genetic counseling. These recommendations do not apply to men.

Although there are no standardized referral criteria, women with an increased-risk family history should be considered for genetic counseling to further evaluate their potential risks.

Certain specific family history patterns are associated with an increased risk for deleterious mutations in the *BRCA1* or *BRCA2* gene. Both maternal and paternal family histories are important. For non–Ashkenazi Jewish women, these patterns include 2 first-degree relatives with breast cancer, 1 of whom received the diagnosis at age 50 years or younger; a combination of 3 or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancer among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; a combination of 2 or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancer at any age; and a history of breast cancer in a male relative.

For women of Ashkenazi Jewish heritage, an increased-risk family history includes any first-degree relative or 2 second-degree relatives on the same side of the family with breast or ovarian cancer.

About 2% of adult women in the general population have an increased-risk family history as defined here. Women with none of these family history patterns have a low probability of having a deleterious mutation in *BRCA1* or *BRCA2* genes.

Computational tools are available to predict the risk for clinically important *BRCA* mutations (that is, *BRCA* mutations associated with the presence of breast cancer, ovarian cancer, or both), but these tools have not been verified in the general population. There is no empirical evidence concerning the level of risk for a *BRCA* mutation that merits referral for genetic counseling.

Not all women with a potentially deleterious *BRCA* mutation will develop breast or ovarian cancer. In a woman who has a clinically important *BRCA* mutation, the probability of developing breast or ovarian cancer by age 70 years is estimated to be 35% to 84% for breast cancer and 10% to 50% for ovarian cancer.

Appropriate genetic counseling helps women make informed decisions, can improve their knowledge and perception of absolute risk for breast and ovarian cancer, and can often reduce anxiety. Genetic counseling includes elements of counseling: risk assessment; pedigree analysis; and, in some cases, recommendations for testing for *BRCA* mutations in affected family members, the presenting patient, or both. It is best delivered by a suitably trained health care provider.

A *BRCA* test is typically ordered by a physician. When done in concert with genetic counseling, the test assures the linkage of testing with appropriate management decisions. Genetic testing may lead to potential adverse ethical, legal, and social consequences, such as insurance and employment discrimination; these issues should be discussed in the context of genetic counseling and evaluation for testing.

Among women with *BRCA1* or *BRCA2* mutations, prophylactic mastectomy or oophorectomy decreases the incidence of breast and ovarian cancer; there is inadequate evidence for mortality benefits. Chemoprevention with selective estrogen receptor modulators may decrease incidence of estrogen receptor–positive breast cancer; however, it is also associated with adverse effects, such as pulmonary embolism, deep venous thrombosis, and endometrial cancer. Most breast cancer associated with *BRCA1* mutations is estrogen receptor–negative and thus is not prevented by tamoxifen. Intensive screening with mammography has poor sensitivity, and there is no evidence of benefit of intensive screening for women with *BRCA1* or *BRCA2* gene mutations. Magnetic resonance imaging (MRI) may detect more cases of cancer, but the effect on mortality is not clear.

Women with an increased-risk family history are at risk not only for deleterious *BRCA1* or *BRCA2* mutations but potentially for other unknown mutations as well. Women with an increased-risk family history who have negative results on tests for *BRCA1* and *BRCA2* mutations may also benefit from surgical prophylaxis.

The USPSTF has made recommendations on mammography screening for breast cancer, screening for ovarian cancer, and chemoprevention of breast cancer, which can be accessed at www.preventiveservices.ahrq.gov.

**Discussion**

Breast and ovarian cancer are associated with a family history of these conditions. Approximately 5% to 10% of women with breast cancer have a mother or sister with breast cancer, and up to 20% have a first-degree or a second-degree relative with breast cancer (1–6). Germline mutations in 2 genes, *BRCA1* and *BRCA2*, have been associated with an increased risk for breast cancer and ovarian cancer (7, 8). Specific *BRCA* mutations (founder mu-
tations) are clustered among certain ethnic groups, such as Ashkenazi Jews, and among families in the Netherlands, Iceland, and Sweden (1).

Several characteristics are associated with an increased likelihood of BRCA1 and BRCA2 mutations (1, 9–12). These include breast cancer diagnosed at an early age, bilateral breast cancer, history of both breast and ovarian cancer, presence of breast cancer in 1 or more male family members, multiple cases of breast cancer in the family, both breast and ovarian cancer in the family, 1 or more family members with 2 primary cases of cancer, and Ashkenazi Jewish background. No direct measures of the prevalence of clinically important BRCA1 or BRCA2 mutations in the general, non-Jewish U.S. population have been published; however, models have estimated it to be about 1 in 300 to 500 (13–16). Prevalence estimates in a large study of individuals from referral populations with various levels of family history ranged from 3.9% (no breast cancer diagnosed in relatives <50 years of age and no ovarian cancer) to 16.4% (breast cancer diagnosed in a relative <50 years of age and ovarian cancer diagnosed at any age) (17).

Penetrance is the probability of developing breast or ovarian cancer in women who have a BRCA1 or BRCA2 mutation. Published reports of penetrance describe estimates of BRCA1 and BRCA2 mutations ranging from 35% to 84% for breast cancer and 10% to 50% for ovarian cancer, calculated to age 70 years, for non–Ashkenazi Jewish women or those unselected for ethnicity (1, 13, 14, 18–22). Among Ashkenazi Jewish women, penetrance estimates range from 26% to 81% for breast cancer and 10% to 46% for ovarian cancer (1, 23–29). Estimates are higher for relatives of women with cancer diagnosed at younger ages, for women from families with greater numbers of affected relatives (when based on data from families selected for breast and ovarian cancer), and when certain methods of analysis are used.

A systematic review of the evidence found no population-based randomized, controlled trials of risk assessment and BRCA mutation testing using the outcomes of incidence of breast and ovarian cancer or cause-specific mortality (1). The USPSTF therefore examined the chain of evidence for accuracy of risk assessment tools, efficacy of preventive interventions, and the harms of screening and interventions.

Although several tools to predict risk for deleterious BRCA mutations have been developed from data on previously tested women, no studies of their effectiveness in a primary care screening population are available (30). These risk tools include the Myriad Genetic Laboratories model, the Couch model, BRCAPRO, and the Tyrer model (1). Much of the data used to develop the models are from women with existing cancer, and their applicability to asymptomatic, cancer-free women in the general population is unknown. Three tools have been developed to guide primary care clinicians in assessing risk and guiding referral: the Family History Risk Assessment Tool (FHAT), the Manchester scoring system, and the Risk Assessment in Genetics (RAGs) tool (31). The sensitivity and specificity of FHAT for a clinically important BRCA1 or BRCA2 mutation were 94% and 51%, respectively. The Manchester scoring system was developed in the United Kingdom to predict deleterious BRCA1 or BRCA2 mutations at the 10% likelihood level and had an 87% sensitivity and a 66% specificity (32). The RAGs tool, a computer program designed to support assessment and management of family breast and ovarian cancer in primary care settings (33), is used to assign patients to categories of low risk (<10%), moderate risk (10% to 25%), and high risk (>25%). Primary care clinicians can then manage recommendations of reassurance, referral to a breast clinic, or referral to a geneticist on the basis of the patient’s respective risk categories (34).

The interventions that can be offered to a woman with a deleterious BRCA1 or BRCA2 mutation or other increased risk for hereditary breast cancer include intensive screening, chemoprevention, prophylactic mastectomy or oophorectomy, or a combination. Overall, evidence on the efficacy of intensive surveillance of BRCA1 and BRCA2 carriers to reduce morbidity or mortality is insufficient. Recent descriptive studies report increased risk for interval cancer (cancer occurring between mammograms) in BRCA1-positive patients with and without previous cancer who were receiving annual mammographic screening. This indicates that annual mammography may miss aggressive cancer in carriers of the BRCA mutation (1).

Good evidence shows that MRI has higher sensitivity for detecting breast cancer among women with a BRCA1 or BRCA2 mutation than does mammography, clinical breast examination, or ultrasonography. One study compared these screening methods in 236 Canadian women 25 to 65 years of age who had BRCA1 or BRCA2 mutations (35). The women underwent 1 to 3 annual screening examinations, including MRI, mammography, and ultrasonography, and received clinical breast examinations every 6 months. The researchers found that MRI was more sensitive for detecting breast cancer (sensitivity, 77%; specificity, 95.4%) than mammography (sensitivity, 36%; specificity, 99.8%), ultrasonography (sensitivity, 33%; specificity, 96%), or clinical breast examination alone (sensitivity, 9%; specificity, 99.3%). However, use of MRI, ultrasonography, and mammography in combination had the highest sensitivity, 95%. The effect of this increased detection on morbidity and mortality remains unclear. Expert groups recommend intensive screening for breast cancer in patients with the BRCA mutation (36).

The evidence is also insufficient to determine the morbidity and mortality effects of intensive screening for ovarian cancer among women with BRCA1 or BRCA2 mutations. One study in which 1610 women with a family history of ovarian cancer were screened with transvaginal ultrasonography showed a high rate of false-positive results.
Good-quality evidence from 4 randomized, controlled trials shows that prophylactic tamoxifen reduces the risk for estrogen receptor–positive breast cancer in women without previous breast cancer (38, 39). A meta-analysis of these trials showed a relative risk for total breast cancer of 0.62 (95% CI, 0.46 to 0.83) (1). Further analysis of the largest of these trials showed a possible reduction in breast cancer incidence for women with BRCA2 mutations but not those with BRCA1 mutations, possibly because women with BRCA1 mutations had predominantly estrogen receptor–negative tumors. Conclusions are difficult to draw because of the small number of breast cancer cases in this analysis (40).

Fair-quality evidence is available on the effectiveness of prophylactic surgery to prevent breast and ovarian cancer. Cohort studies of prophylactic surgery have several methodologic limitations that should be considered when interpreting and generalizing their results, such as selection bias, retrospective study design, lack of a control group for estimation of benefit-attributable outcome in the untreated group, and inability to define risk reduction attributable to mastectomy in patients electing to have both mastectomy and oophorectomy (41). Four published studies (2 of fair quality and 2 that did not meet USPSTF quality criteria) of prophylactic bilateral mastectomy in high-risk women show a consistent 85% to 100% reduction in risk for breast cancer despite differences in study designs and comparison groups (for example, sisters [42], matched controls [43], a surveillance group [44], and penetrance models [45]). Four studies of prophylactic oophorectomy reported reduced risks for ovarian and breast cancer (46–49), although the number of cases was small and the confidence intervals for the only prospective study crossed 1.0 for both outcomes (50). Overall, oophorectomy reduced ovarian cancer risk by 85% to 100% and reduced breast cancer risk by 53% to 68%.

No studies have described cancer incidence or mortality outcomes associated with genetic counseling, although 10 fair- to good-quality randomized, controlled trials reported psychological and behavioral outcomes (1). These studies examined the impact of genetic counseling on worrying about breast cancer, anxiety, depression, perception of cancer risk, and intention to participate in genetic testing. Studies were conducted in highly selected samples of women, and results may not be generalizable to a screening population. Five of 7 trials showed that breast cancer worry decreased after genetic counseling, and 2 studies showed no significant effect (1). Three studies reported decreased anxiety after genetic counseling, and 3 reported no significant effect. One study reported decreased depression after genetic counseling, and 4 found no significant effect (1). Results of a meta-analysis showed that genetic counseling significantly decreased generalized anxiety, although the reduction in psychological distress was not significant (51).

There is poor evidence (conflicting studies) regarding whether genetic counseling increases or decreases the accuracy of patients’ risk perception.

The USPSTF examined the available evidence on harms of screening and intervention. Approximately 12% of high-risk families without a BRCA1 or BRCA2 coding-region mutation may have other clinically important genomic rearrangements (52). Approximately 13% of tests report mutations of unknown significance; however, the harms associated with such test results are not known (53).

Routine referral for genetic counseling and consideration of BRCA1 and BRCA2 testing clearly has important psychological, ethical, legal, and social implications, although they are not well quantified in the literature. Among these are the potential for burdening patients with the knowledge of mutations of unknown importance and the potential for affecting family members other than the individual patient. The potential harms of intensive screening include overdiagnosis and overtreatment. There is good-quality evidence on the harms of prophylactic tamoxifen (1), including thromboembolic events, endometrial cancer, and hot flashes. Fair-quality evidence shows that prophylactic mastectomy can cause hematoma, infection, contracture, or implant rupture (with reconstruction) and that prophylactic oophorectomy can cause infection, bleeding, urinary tract or bowel injury, and premature menopause. Overall, the USPSTF estimates that the magnitude of these potential harms is at least small.

**Research Gaps**

Population studies are needed to determine the prevalence and penetrance of various mutations in the BRCA gene and the factors that influence penetrance for women with these mutations. Research has focused on highly selected women in referral centers and has generally reported short-term outcomes. Issues requiring additional study include the effectiveness of risk stratification and genetic counseling when delivered in different settings and by different types of providers, appropriate training for counselors, use of system supports, and patient acceptance of educational strategies. The impact of BRCA testing on ethical, legal, and social issues needs to be better clarified. We also need to understand the effect of genetic counseling on the emotions and behavior of the patient and her first-degree female relatives.

Enhanced screening with such methods as MRI needs to be better studied in high-risk women. Future studies should examine the impact of intensive MRI screening on breast cancer mortality and on possible overtreatment. Studies specifically designed to examine the potential benefit of chemoprophylaxis in women with known deleterious BRCA mutations are essential to establish whether there are any effective alternatives to prophylactic surgery. There is a paucity of data on BRCA-associated ovarian cancer; further research in screening and management of
women at high risk for ovarian cancer is needed. It would be helpful to develop and validate tools feasible for use in primary care practice that would help clinicians make appropriate referrals for genetic counseling.

Recommendations of Other Groups

A few organizations have made recommendations on genetic susceptibility testing. The American College of Medical Genetics (ACMG) recommends risk assessment and genetic counseling before testing for BRCA1/BRCA2 mutations in individuals at increased risk, based on a personal or family history of breast cancer, ovarian cancer, or both (54). In a previous guideline published in 1996, the ACMG recommended testing for BRCA1 mutations in high-risk families and population screening of Ashkenazi Jewish individuals after discussion of test limitations and appropriate informed consent (55). The National Comprehensive Cancer Network recommends offering genetic susceptibility testing (after risk assessment and counseling) to individuals who meet the criteria for hereditary breast or ovarian cancer or both (56). The American Society of Clinical Oncology recommends that genetic testing be offered when 1) an individual has a personal or family history that suggests a genetic cancer susceptibility and 2) the test can be adequately interpreted and its results will influence diagnosis or management of the patient or family members at risk for hereditary cancer (57). The American College of Obstetricians and Gynecologists Committee Opinion on breast and ovarian cancer screening, written in 2000, recommends offering BRCA1 mutation testing to families in which multiple family members have had breast or ovarian cancer or in which a BRCA1 mutation has been found (58).

AppenDIX

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Appendix Table 1. U.S. Preventive Services Task Force Recommendations and Ratings*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends that clinicians provide [the service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.</td>
</tr>
<tr>
<td>I</td>
<td>The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
</tr>
</tbody>
</table>

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. U.S. Preventive Services Task Force Grades for Strength of Overall Evidence*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes</td>
</tr>
<tr>
<td>Fair</td>
<td>Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes</td>
</tr>
<tr>
<td>Poor</td>
<td>Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes</td>
</tr>
</tbody>
</table>

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

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This list includes members of the Task Force at the time these recommendations were finalized. For a list of current Task Force members, go to www.ahrq.gov/clinic/uspstfab.htm.

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Disclaimer: Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.
Requests for Single Reprints: Reprints are available from the US Preventive Services Task Force Web site (www.preventiveservices.ahrq.gov) and in print through the Agency for Healthcare Research and Quality Publications Clearinghouse (800-358-9295).

References


NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version.1.2012

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BR/OV-1

Discussion

BR/OV-2

See Assessment

Assessment

BR/OV-3

See Discussion for details.

Discussion

BR/OV-4

For no known familial PTEN mutation, the genetic testing recommendation was modified as: "Consider genetic testing in the absence of a family history of diffuse gastric cancer, including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies" with a corresponding footnote, "See Discussion for details.

Footnote: "Some centers are evaluating novel imaging technologies as investigational tools" was removed.

Cowden Syndrome

COWD-A

A bullet regarding reproductive options was added: "For couples expressing the desire that their offspring not carry a familial TP53 mutation, discussion should include known risks, limitations, and benefits of these technologies" with a corresponding footnote, "See Discussion for details.

Footnote: "Consider genetic testing for Li-Fraumeni syndrome testing criteria, and/or Cowden syndrome."
**NCCN Guidelines Version 1.2012**

**Breast and/or Ovarian Cancer Genetic Assessment**

**Patient needs and concerns:**
- Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
- Goals for cancer family risk assessment

**Detailed family history:**
- Expanded pedigree to include first-, second-, and third-degree relatives (parents, siblings, children, grandparents, aunts, uncles, nieces, nephews, grandchildren, half-siblings, great-grandparents, great-aunts, great-uncles, great-grandchildren, first cousins)
  (See BR/OV-1)
- Types of cancer
- Bilaterality
- Age at diagnosis
- History of chemoprevention and/or risk-reducing surgery
- Medical record documentation as needed, particularly pathology reports of primary cancers

**Detailed medical and surgical history:**
- Any personal cancer history
- Carcinogen exposure (eg, history of radiation therapy)
- Reproductive history
- Hormone use
- Previous breast biopsies
- History of salpingo-oophorectomy

**Focused physical exam (refer to specific syndrome):**
- Breast/ovarian
- Dermatologic, including oral mucosa
- Head circumference
- Thyroid

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

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

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**Discussion**

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**NCCN Guidelines Index**

**Genetics Table of Contents**

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**BR/OV-2**

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**BR/OV-3**

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**PEDIGREE: FIRST-, SECOND-, AND THIRD-DEGREE RELATIVES OF PROBAND**

- 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.

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**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA\textsuperscript{a,b,c}

- Individual from a family with a known deleterious BRCA1/BRCA2 mutation
- Personal history of breast cancer\textsuperscript{d} = one or more of the following:
  - Diagnosed age < 45 y
  - Diagnosed age = 50 y with \geq 1 close blood relative\textsuperscript{e} with breast cancer < 50 y and/or \geq 1 close blood relative\textsuperscript{e} with epithelial ovarian\textsuperscript{f} cancer at any age
  - Two breast primaries\textsuperscript{g} when first breast cancer diagnosis occurred: age 50 y
  - Diagnosed age = 60 y with a triple negative breast cancer
- Diagnosed age: 50 y with limited family history\textsuperscript{h}
- Diagnosed at any age, with \geq 2 close blood relatives\textsuperscript{i} with breast and/or epithelial ovarian\textsuperscript{j} cancer at any age
- Close male blood relative\textsuperscript{k} with breast cancer
- For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish) no additional family history may be required\textsuperscript{l}

\textsuperscript{a}One or more of these criteria is suggestive of hereditary breast/ovarian cancer syndrome that warrants further personalized risk assessment, genetic counseling and management. The maternal and paternal sides should be considered independently. Other malignancies reported in some HBOC families include prostate and melanoma.

\textsuperscript{b}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. If available, DNA should be extracted from a fibroblast culture. If the source of DNA is not possible, buccal samples can be considered, subject to the risk of donor DNA contamination.

\textsuperscript{c}Patients with limited family history, such as fewer than 2 first- or second-degree female relatives or female relatives surviving beyond 45 years in either lineage, may have an underestimated probability of a familial mutation.

\textsuperscript{d}For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included.

\textsuperscript{e}Close blood relatives include first-, second-, and third-degree relatives.

\textsuperscript{f}BRCA1/BRCA2

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

\textsuperscript{h}Two breast primaries include bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors at any age.

\textsuperscript{i}Testing for Ashkenazi Jewish founder-specific mutation(s), should be performed first.

\textsuperscript{j}Comprehensive genetic testing includes full sequencing of BRCA1/BRCA2 and detection of large genomic rearrangements.

\textsuperscript{k}Genetic testing for familial BRCA1/2 in children < 18 y is generally not recommended.

\textsuperscript{l}If Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.

\textsuperscript{m}Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

\textsuperscript{n}If more than one affected, first consider: youngest age at diagnosis, bilateral disease, multiple primaries, early ovarian cancer, most closely related to the proband/patient/consultant. If no living family member with breast or ovarian cancer, consider testing of second affected family members affected with cancers thought to be related to BRCA1/BRCA2 eg, prostate, pancreas, melanoma.

\textsuperscript{o}Variant of unknown significance found (uninformative)\textsuperscript{p}

\textsuperscript{p}For both affected and unaffected individuals of Ashkenazi Jewish descent with no known familial mutation, full test for the three common mutations. Then, if negative for the three mutations, consider full sequence testing if ancestry also includes non-Ashkenazi Jewish relatives or other HBOC criteria is met. If all affected family members are deceased, consider testing of paraffin-derived DNA from deceased relatives, if DNA is obtainable. For both affected and unaffected individuals who are non-Ashkenazi Jewish and who have no known familial mutation, full sequence testing is the approach, if testing is done.

\textsuperscript{q}If no mutation is found, consider other hereditary breast cancer syndromes such as Li-Fraumeni and/or Cowden syndrome.

\textsuperscript{r}Testing for variant of unknown significance should not be used for clinical purposes. Consider referral to research studies that aim to define functional impact of variant.

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

- Breast self-exam training and education starting at age 18 y.
- Clinical breast exam, every 6-12 mo,1 starting at age 25 y.
- Annual mammogram and breast MRI,2 screening starting at age 25 y, or individualized based on earliest age of onset in family.3
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks.
- Recommend risk-reducing salpingo-oophorectomy,4 ideally between 35 and 40 y, and upon completion of child bearing, or individualized based on earliest age of onset of ovarian cancer in the family. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short term hormone replacement therapy (HRT) to a recommended maximum age of natural menopause, and related medical issues.
- For those patients who have not elected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound (preferably day 1-10 of menstrual cycle in premenopausal women) + CA-125 (preferably after day 5 of menstrual cycle in premenopausal women),5 every 6 mo starting at age 30 y or 5-10 y before the earliest age of first diagnosis of ovarian cancer in the family.
- Consider chemoprevention options for breast and ovarian cancer, including discussing risks and benefits 6 (See NCCN Breast Cancer Risk Reduction Guidelines).
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies and more frequent screening intervals) in the context of a clinical trial.

Continued on next page

1 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.
2 High-quality breast MRI limitations include having: a need for a dedicated breast coil, the ability to perform biopsy under MRI guidance, experienced radiologists in breast MRI, and regional availability. Breast MRI is performed preferably day 7-15 of menstrual cycle for premenopausal women.
3 The appropriateness of imaging scheduling is still under study.
4 Given the high rate of occult disease, special attention should be given to sampling and pathologic review of the ovaries and fallopian tubes. (See Discussion for details.) See the College of American Pathologists. Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary.
5 There are data that annual transvaginal ultrasound and CA-125 are not effective strategies for screening for ovarian cancer in high risk women. There are limited data regarding the effectiveness of a six month screening interval, thus until such data are available it is reasonable to consider this approach in high risk women, especially in the context of a clinical research setting.
6 Data suggest that oral contraceptives (OC) reduce ovarian cancer risk in BRCA mutation carriers. The risk/benefit ratio is uncertain because of contradictory evidence about OC increasing breast cancer risk; however, OC use for contraception is acceptable. (See Discussion for details.)

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

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

MEN

- Breast self-exam training and education starting at age 35 y.
- Clinical breast exam, every 6-12 mo, starting at age 35 y.
- Consider baseline mammogram at age 40 y; annual mammogram if gynecomastia or parenchymal/glandular breast density on baseline study.
- Adhere to screening guidelines for prostate cancer (See NCCN Prostate Cancer Early Detection Guidelines).

MEN and WOMEN

- Education regarding signs and symptoms of cancer(s), especially those associated with BRCA gene mutations.
- Refer to appropriate NCCN guidelines for other cancer screening.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

REPRODUCTIVE OPTIONS

- For couples expressing the desire that their offspring not carry a familial BRCA mutation, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies. 7
- For BRCA2 mutations carriers, risk of a rare (recessive) Fanconi anemia/brain tumor phenotype in offspring if both partners carry a BRCA2 mutation should be discussed. 9

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

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