CHAPTER INDEX

1. Family History Background and Pre-Test
2. The Case of the Frantic Cousin
3. The Case of the Hidden Cancer
4. The Case of the Anxious Grandmother
5. The Case of the Family History Afterthought
6. Review and Post-Test
7. Resources and References
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. Describe features and risks of common hereditary cancer syndromes related to breast and ovarian cancer risk

4. Provide appropriate referrals and follow up for patients at increased risk

5. Recognize the difference between germline testing for inherited mutations and somatic testing through gene assay
Chapter 1: Family History and Cancer

Genes, environment, and behaviors interact with each other to cause disease.
“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
66.4% of Michigan adults thought family health history was very important to personal health.

37% of Michigan adults actively collect health information for the purpose of creating a family health history.
50.7%
- 66.4% of Michigan adults thought family health history was very important to personal health

29.1%
- 37% of Michigan adults have actively collected health information for the purpose of creating a family health history
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:**

<table>
<thead>
<tr>
<th>At a minimum, each health-care professional should be able to:</th>
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<tbody>
<tr>
<td>a. 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.</td>
</tr>
<tr>
<td>b. Understand that health-related genetic information can have important social and psychological implications for individuals and families.</td>
</tr>
<tr>
<td>c. Know how and when to make a referral to a genetics professional.</td>
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</table>

**SKILLS:**

<table>
<thead>
<tr>
<th>All health professionals should be able to:</th>
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<tbody>
<tr>
<td>2.1 Gather genetic family history information, including at minimum a three-generation history.</td>
</tr>
<tr>
<td>2.2 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.</td>
</tr>
<tr>
<td>2.3 Explain effectively the reasons for and benefits of genetic services.</td>
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<tr>
<td>2.4 Use information technology to obtain credible, current information about genetics.</td>
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<tr>
<td>2.5 Assure that the informed-consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question.</td>
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Genomics

Overview
Objectives
Interventions & Resources

Download all Genomics Objectives [PDF – 10 KB]

G-1 Increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling

G-2 Developmental) increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome (or familial colorectal cancer syndromes)

Download all Genomics Objectives [PDF – 10 KB]

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200 Independence Avenue, S.W., Washington, DC 20201
Page last updated: Monday, July 18, 2011

Chapter 1
Genomics

G-1 Increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling

<table>
<thead>
<tr>
<th>Baseline</th>
<th>23.3 percent of women with a family history of breast and/or ovarian cancer received genetic counseling in 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>25.6 percent</td>
</tr>
<tr>
<td>Target-Setting Method</td>
<td>10 percent improvement</td>
</tr>
<tr>
<td>Data Source</td>
<td>National Health Interview Survey (NHIS), CDC, NCHS</td>
</tr>
</tbody>
</table>

More Information: [Data from the HHS Health Indicators Warehouse]

G-2 (Developmental) Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome (or familial colorectal cancer syndromes)
# 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>
</tr>
</tbody>
</table>
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
PRETEST
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
WHICH OF THE PATIENTS BELOW IS AT GREATER RISK FOR HEREDITARY CANCER?

- Patient A whose mother and maternal aunt had ovarian cancer (age 55 and 60)
- Patient B whose mother had breast cancer at age 60
- Do not know
FILL IN THE BLANK: APPROXIMATELY ____% OF BREAST CANCERS ARE THOUGHT TO BE CAUSED BY AN INHERITED GENE CHANGE (PREDISPOSITION TO CANCER).

A. ≤1%
B. 5-10%
C. 20-30%
D. 50% or greater
TRUE OR FALSE: BREAST CANCER IS ONLY INHERITED FROM THE MOTHER’S SIDE OF THE FAMILY.

A. True
B. False
C. Do not know
ALL OF THE FOLLOWING INCREASE A PATIENT’S RISK FOR HEREDITARY BREAST AND OVARIAN CANCER SYNDROME, EXCEPT:

A. Ashkenazi Jewish Ancestry
B. A known BRCA mutation in the family
C. Young ages at diagnosis in the family (< age 50)
D. A significant paternal family history of breast and ovarian cancer
E. Late age at menarche
F. Do Not Know
TRUE OR FALSE: MICHIGAN LAW REQUIRES WRITTEN INFORMED CONSENT TO BE OBTAINED PRIOR TO PREDICTIVE OR PRESYMPTOMATOMIC GENETIC TESTING.

1. True
2. False
3. Do Not Know
THE FOLLOWING TYPES OF CANCER ARE SEEN IN FAMILIES WITH BRCA1/2, HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOC), EXCEPT:

A. Breast cancer
B. Ovarian cancer
C. Colorectal cancer
D. Prostate cancer
E. Pancreatic cancer
F. Do not know
TRUE OR FALSE: TUMOR ANALYSIS TESTS SUCH AS ONCOTYPE DX OR MAMMAPRINT CAN TELL YOU ABOUT A WOMAN’S RISK FOR INHERITED CANCER.

1. True
2. False
3. Do Not Know
A 40 YEAR OLD BRCA1 MUTATION CARRIER IS VERY WORRIED ABOUT HER RISK FOR CANCER. COST AND OTHER CONSIDERATIONS ASIDE, WHAT IS THE SINGLE MOST RISK-REDUCING OPTION LISTED BELOW?

A. CA 125 and transvaginal ultrasound
B. Use birth control pills
C. MRI screening
D. prophylactic removal of the ovaries/tubes
E. all of the above are equally effective at her age
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.
Your 27-year-old patient comes to your office for her annual check up. Toward the end of the visit she begs you to send her for a mammogram. You are somewhat confused as to her urgency and explain the general population screening guidelines (mammograms beginning at age 40).
She says, “I’m so stressed about my cousin’s breast cancer diagnosis because she’s about my age.” Even though you’re running late, you decide to discuss her family history.
HERE IS WHAT YOU FIND:

- 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.
WHAT DO YOU DECIDE TO DO?

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 with her that her family history is concerning and refer her for genetic counseling to discuss her risk and possible testing.**

3. **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.
#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
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...

- 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 (ACS / ACOG)
Chapter 3: The Case of the Hidden Cancer

Your patient is a 28-year-old, African American female seen in clinic for her annual check up. She is currently healthy and reports no change in her medical history. Today, her breast exam is negative.
Upon reviewing her intake, you discover that her mother had breast cancer at age 58 and her sister recently had breast cancer at age 34. She reports that her sister had BRCA testing and has a variant in the BRCA 2 gene. You obtain her sisters records and confirm a variant in the BRCA 2 gene.
1. Order site-specific BRCA testing on your patient for the familial variant in BRCA2

2. Her risk for hereditary cancer is increased. You refer her for an early mammogram

3. Strongly encourage that she go for genetic counseling to discuss the family history
# 1: ORDER 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.

- After discussing her sister’s test result, you draw your patient’s blood for testing and send everything off to the lab.

- 2 weeks later the results arrive
The Results Are In...

She is found to have the same variant in the BRCA2 gene as her sister.

More on variants of uncertain significance
#1: ORDER BRCA TESTING:

Your patient never develops breast cancer, but she does develop endometrial cancer – a cancer that is not associated with the BRCA1 and BRCA2 genes.
#2: INCREASED RISK - BEGIN SURVEILLANCE

- You tell the patient that her risk is increased based on her family history.

- You know that she should begin mammography screening 10 years earlier than the youngest diagnosis in the family.

- So, you refer her for a mammogram and recommend that she continue with mammograms annually.
• She continues to have normal mammograms.

• At age 30 she reports painful, heavy menstruation and pain with intercourse. After physical exam she is told she likely has uterine fibroids. An ultrasound confirms this diagnosis.

But wait, there’s more...
• By age 32, she has continued to have irregular, heavy bleeding over the last 5 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 and the need for a hysterectomy. She has not yet had children.
# 3: SHE SEES A QUALIFIED HEALTHCARE PROFESSIONAL FOR GENETIC COUNSELING AND RISK ASSESSMENT

Need to find genetic services?
Visit: [www.migeneticsconnection.org/cancer](http://www.migeneticsconnection.org/cancer)
Or view the directory here

Referral form statement:
• Mother with breast cancer at 58
• Sister with breast cancer at 34
She was strongly encouraged to bring her mother and sister 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.

Her daughters were 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 for your patient’s mother.
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 and sister test positive
- One other sister and brother test negative
- Although the risk for endometrial cancer is ~10%, your patient and her husband decide to have children right away (at age 30).
- After having two healthy children by 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.**
The Best Choice!

#1: YOU TELL THE PATIENT THAT THE RISK FOR A HEREDITARY GENE MUTATION IS LOW.

- 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.
#3: YOU TELL THE PATIENT THAT SHE IS AT LOW RISK BASED ON HER MOTHER’S “LOW RISK” GENETIC TEST RESULT.

- 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.
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:I 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.
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, Dylan’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 very limited time in clinic to discuss this with her, as this is a pediatric clinic, and recommend she see her own doctor*

2. *Ask more about the family history and tell her you’re not sure about male breast cancer but provide what resources you can*

3. *Provide the number for genetic counseling services and encourage her to schedule her first screening mammogram.*
#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.

And…
She dies at age 49.
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.
• 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.
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.

She goes for genetic counseling...
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.
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.
• 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

Take the Post-Test
Chapter 6 Post-Test
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
WHICH OF THE PATIENTS BELOW IS AT GREATER RISK FOR HEREDITARY CANCER?

- Patient A whose mother and maternal aunt had ovarian cancer (age 55 and 60)
- Patient B whose mother had breast cancer at age 60
- Do not know
FILL IN THE BLANK: APPROXIMATELY ____% OF BREAST CANCERS ARE THOUGHT TO BE CAUSED BY AN INHERITED GENE CHANGE (PREDISPOSITION TO CANCER).

A. ≤1%
B. 5-10%
C. 20-30%
D. 50% or greater
TRUE OR FALSE: BREAST CANCER IS ONLY INHERITED FROM THE MOTHER’S SIDE OF THE FAMILY.

A. True
B. False
C. Do not know
ALL OF THE FOLLOWING INCREASE A PATIENT’S RISK FOR HEREDITARY BREAST AND OVARIAN CANCER SYNDROME, EXCEPT:

A. Ashkenazi Jewish Ancestry
B. A known BRCA mutation in the family
C. Young ages at diagnosis in the family (< age 50)
D. A significant paternal family history of breast and ovarian cancer
E. Late age at menarche
F. Do Not Know
TRUE OR FALSE: MICHIGAN LAW REQUIRES WRITTEN INFORMED CONSENT TO BE OBTAINED PRIOR TO PREDICTIVE OR PRESYMPTOMATIC GENETIC TESTING.

1. True
2. False
3. Do Not Know
THE FOLLOWING TYPES OF CANCER ARE SEEN IN FAMILIES WITH BRCA1/2, HEREDITARY BREAST AND OVARIAN CANCER SYNDROME (HBOC), EXCEPT:

A. Breast cancer
B. Ovarian cancer
C. Colorectal cancer
D. Prostate cancer
E. Pancreatic cancer
F. Do not know
TRUE OR FALSE: TUMOR ANALYSIS TESTS SUCH AS ONCOTYPE DX OR MAMMAPRINT CAN TELL YOU ABOUT A WOMAN’S RISK FOR INHERITED CANCER.

1. True
2. False
3. Do Not Know
A 40 year old BRCA1 mutation carrier is very worried about her risk for cancer. Cost and other considerations aside, what is the single most risk-reducing option listed below?

A. CA 125 and transvaginal ultrasound
B. Use birth control pills
C. MRI screening
D. Prophylactic removal of the ovaries/tubes
E. All of the above are equally effective at her age
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

Informed Consent for Genetic Testing

Family History and Your Health

September through October 2009

Michigan Department of Community Health

Cancer Family History Guide

Cancer Genetics Program Resources

Order Form

Family History and Your Health - MDCH Fact card

Family History and Your Health - MDCH Fact sheet

Family History Guide: A pocket tool for providers, patients, and families
Contact:

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

• MI Cancer Genetics Alliance (MCGA)
  – www.migeneticsconnection.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.
• 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></th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 yrs</td>
<td>3.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>40 yrs</td>
<td>19.1%</td>
<td>12%</td>
</tr>
<tr>
<td>50 yrs</td>
<td>50.8%</td>
<td>46%</td>
</tr>
<tr>
<td>60 yrs</td>
<td>54.2%</td>
<td>61%</td>
</tr>
<tr>
<td>70 yrs</td>
<td>85%</td>
<td>86%</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>2(^{nd}) Cancer Risk within 5 yrs General Population</th>
<th>2(^{nd}) Cancer Risk within 5 yrs BRCA1/2 mutation carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>12%</td>
<td>36-85%</td>
<td>5%</td>
<td>12-20%</td>
</tr>
<tr>
<td>Breast</td>
<td>1.6%</td>
<td>20-45% (62%)(^*)</td>
<td>Slightly increased</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Ovary</td>
<td>Slightly increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></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 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 is furious stating, “I thought this test would give us some answers and now I’m more confused! So do I need screening or what?”

Obtaining proper informed consent is the law in Michigan!
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 do you tell your patient for screening?
- Do you send her to a high risk breast clinic to alternate MRI with mammogram every 6 months?
- What if her affected mother tests negative for the same BRCA variant? Would we still think it is related to cancer?
Management of HBOC

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.
Management of HBOC

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.
BRCA1

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

Used with permission from Nancie Petrucelli, Karmanos Cancer Institute, Detroit, MI
Management of HBOC

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.

VARIANT OF UNCERTAIN SIGNIFICANCE TEST RESULTS
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/uspstfix.htm
NCCN Guidelines™ Version 1.2011
Breast and/or Ovarian Cancer Genetic Assessment

CRITERIA FOR FURTHER RISK EVALUATION

An affected individual with one or more of the following:

- Early-age-onset breast cancer
- Triple negative (ER-, PR-, HER2-) breast cancer
- Two breast cancer primaries in a single individual
- Breast cancer at any age, with
  - ≥ 1 close blood relative with breast cancer ≤ 50 y, or
  - ≥ 1 close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, or
  - ≥ 2 close blood relatives with breast cancer and/or pancreatic cancer at any age
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations or leukemia/lymphoma on the same side of family
- Ovarian/fallopian tube/primary peritoneal cancer
- Male breast cancer

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

- ≥ 2 breast primaries from the same side of family (maternal or paternal)
- ≥ 1 ovarian primary from the same side of family (maternal or paternal)
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations or leukemia/lymphoma on the same side of family
- A known mutation in a breast cancer susceptibility gene
- From a population at risk
- Male breast cancer

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

a Clinically use age ≤ 50 y because studies define early onset as either ≤ 40 or ≤ 50 y. 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.

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

c Close blood relatives include first-, second-, and third-degree relatives.

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.

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

For dermatologic manifestations, see COVID-1.

For populations at risk, requirements for inclusion may be modified (e.g., women of Ashkenazi Jewish descent with breast or ovarian cancer at any age).

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

BR/OV-1
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

http://www.ahrq.gov/CLINIC/uspstfix.htm
MCGA CANCER GENETICS DIRECTORY
Standard 2.3: 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.

Genetics professionals include people with the following:

- An American Board of Genetic Counseling (ABGC) or American Board of Medical Genetics (ABMG) board-certified/board-eligible or (in some states) a licensed genetic counselor
- An American College of Medical Genetics physician board certified in medical genetics
- A Genetics Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APNG), credentialed through the Genetics Nursing Credentialing Commission (GNCC). Credentialing is obtained through successful completion of a professional portfolio review process.
- An advanced practice oncology nurse who is prepared at the graduate level (master or doctorate) with specialized education in cancer genetics and hereditary cancer predisposition syndromes*; certification by the Oncology Nursing Certification Corporation is preferred.
- A board-certified physician with experience in cancer genetics (defined as providing cancer risk assessment on a regular basis).

*Please note, specialized training in cancer genetics should be ongoing; educational seminars offered by commercial laboratories about how to perform genetic testing are not considered adequate training for cancer risk assessment and genetic counseling.
• 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

• 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).
- **Minor criteria** -- learning difficulties, GI hamartomas, fibrocystic disease of the breast, lipomas, fibromas, uterine fibroids, and goiters. Genitourinary tumors.
COWDEN SYNDROME

Trichilemmomas, papillomatous papules, and mucosal papules
COWDEN SYNDROME SURVEILLANCE

• Annual breast cancer screen: 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.
Position Paper for Health Care Providers

TESTING FOR HEREDITARY CANCER PREDISPOSITION SYNDROMES AND GENETIC COUNSELING

Summary

Genetic testing for Hereditary Cancer Predisposition Syndromes is a process and should be provided in the context of pre- and post-test genetic counseling. As described in published consensus guidelines and position statements, this process should include patient education, risk assessment, written informed consent prior to testing, psychological support, options for further medical care, and should be performed by those with professional expertise in recognizing the entire scope of Hereditary Cancer Syndromes (Appendix).

Background

Genetics is a rapidly changing field, affecting medical practice for health providers and the treatment options for patients. For example, prevention of certain types of cancer is possible in individuals found to have a much higher cancer risk than the general population. Although it is true that the mechanism behind genetic testing for hereditary cancer syndromes is a peripheral blood draw, the issues surrounding genetic testing for inherited susceptibility to cancer are much more complex. There is a wide array of potential risks and benefits, which includes but is not limited to medical, legal, and psychosocial risks. Written informed consent is mandated by Michigan state law prior to presymptomatic or predictive genetic testing. In addition to state law, numerous medical societies have concluded that any genetic testing for hereditary cancer syndromes should be performed in the context of informed consent, and be provided by a cancer genetics expert who is qualified to provide adequate, appropriate, and comprehensive pre-test and post-test genetic counseling and risk assessment for the complete spectrum of Hereditary Cancer Syndromes.

Genetic Testing is a Process

Many national societies have stated that identifying and testing individuals for hereditary cancer syndromes is a process. Based on these established societies’ guidelines, the following should be required as part of this process to standardize care in the state of Michigan:

1) Healthcare professionals in the state should recognize the NCHPEG Core Competencies in Genetics (Appendix), and examine their own cancer genomics competence to provide risk assessment, adequate, appropriate, and comprehensive pre- and post-test genetic counseling. If healthcare professionals deem that Hereditary Cancer Syndromes are beyond their expertise, referral of identified patients to a qualified genetics expert is recommended.

2) A healthcare professional with expertise in cancer genetics (an individual with a working knowledge of the syndromes listed in Tables 1 and 2 of Appendix) should be involved in risk assessment, ordering and interpreting the results of a genetic test. This individual should be able to provide:
   a. appropriate, adequate and comprehensive counseling
   b. a differential diagnosis of which hereditary cancer syndrome(s) is the most likely diagnosis
3) Written informed consent, as stated by Michigan state law, should be obtained by fully informing the patient the risks and benefits, as well as the limitations surrounding a genetic test.
4) Application of the ethical and legal aspects of autonomy, privacy, and confidentiality to each patient seeking genetic testing.
5) Addressing the psychosocial aspects of genetic testing during the pre-test and post-test counseling session.

Conclusions

The Michigan Cancer Genetics Alliance (MCGA) concludes that any Hereditary Cancer Syndrome testing should be offered to patients by following the current standard of care established by professional societies. All of these guidelines explicitly state that genetic testing is a process during which patients undergo pre- and post-test counseling with a qualified genetics expert. Centers performing genetic testing should provide patients with education (including about how to use and understand their individual test results), risk assessment, psychological support and options for further medical care.

References

### Appendix

#### Table 1: Hereditary Cancer Syndromes with an Increased Risk of Common Cancers

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features/Associated Cancer</th>
<th>Gene(s) Causing Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast cancer, Hereditary Breast-Ovarian Cancer (HBOC) Syndrome</td>
<td>Early-onset breast cancer, male breast cancer, ovarian, prostate cancer, pancreatic cancer</td>
<td>BRCA1, BRCA2, probably other gene(s)</td>
</tr>
<tr>
<td>Lynch Syndrome (HNPCC-Hereditary Nonpolyposis Colorectal Cancer)</td>
<td>Early-onset colorectal cancer, early-onset endometrial cancer, ovarian, stomach, small bowel, pancreas, ureter, renal pelvis cancer</td>
<td>DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS1, PMS2)</td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td>Breast, thyroid, and endometrial cancer, and benign hamartomatous lesions of skin, oral mucosa and kidney, and benign breast and thyroid disease</td>
<td>PTEN</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP)</td>
<td>Adenomatous polyposis (&gt;100 colorectal polypos), colorectal cancer, papillary thyroid cancer, pancreatic cancer, parotid malignancy; less than 100 colorectal polypos, later-onset colorectal cancer (&lt;40). May be increased risk of gastric and duodenal adenomas and/or cancer</td>
<td>APC</td>
</tr>
<tr>
<td>MTH-Associated Polyposis</td>
<td>Adenomatous polyposis with features ranging from AFAP to classic FAP. Recurrent adenomas.</td>
<td>MTH</td>
</tr>
<tr>
<td>Juvenile Polyposis Syndrome</td>
<td>Juvenile polyposis, increased risk colorectal, pancreatic, gastric and duodenal cancer</td>
<td>SMAD4, BMPRIA</td>
</tr>
<tr>
<td>Hereditary Breast Cancer</td>
<td>Breast cancer, possible increased risk of other cancers</td>
<td>BRCA1/2, BRCA2, BRCA2/ELAC2, MEC1, other gene(s)</td>
</tr>
<tr>
<td>Basal cell nevus syndrome, Gorlin syndrome</td>
<td>Basal cell nevus, characteristic facial, palmoplantar pits, odontogenic keratocyst, rib abnormalities, increased risk of basal cell carcinoma, ovarian cancer, ovarian fibromas</td>
<td>PTCH</td>
</tr>
<tr>
<td>Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)/Bleeding diaphanous synechiae</td>
<td>Multiple primary melanomas, dysplastic nevus, pancreatic cancer</td>
<td>CDKN2A (p10 / p14), CDK4</td>
</tr>
</tbody>
</table>

#### Table 2: Rare Hereditary Cancer Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Features/Associated Cancer</th>
<th>Gene(s) Causing Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li-Fraumeni Syndrome</td>
<td>Early-onset breast, soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, leukemia, brain tumors</td>
<td>TP53, CHEK2</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>Breast cancer, benign ovarian tumors, intestinal tumors, pancreatic cancer, polyps of the uterus, bladder, GI tract (hamartomatous polypos), oral palate, buccal mucosa, nasal passage, lactation</td>
<td>STK11 / LKB1</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>Adrenal medullary tumors, isolated phaeochromocytomas and/or paragangliomas</td>
<td>RET /VHL SDHD, SDHB</td>
</tr>
<tr>
<td>Neurofibromatosis type I</td>
<td>Paragangliomas, carotid body tumors, pheochromocytomas and other abnormalities</td>
<td>NF1 /NF2</td>
</tr>
<tr>
<td>Wilm's tumor</td>
<td>Nephroblastoma, can also be associated with Wilms, Beckwith-Wiedemann and other abnormal urogenital development syndromes</td>
<td>WT1</td>
</tr>
</tbody>
</table>
“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.