Hereditary Cancer Risk and Management: An Interactive Approach

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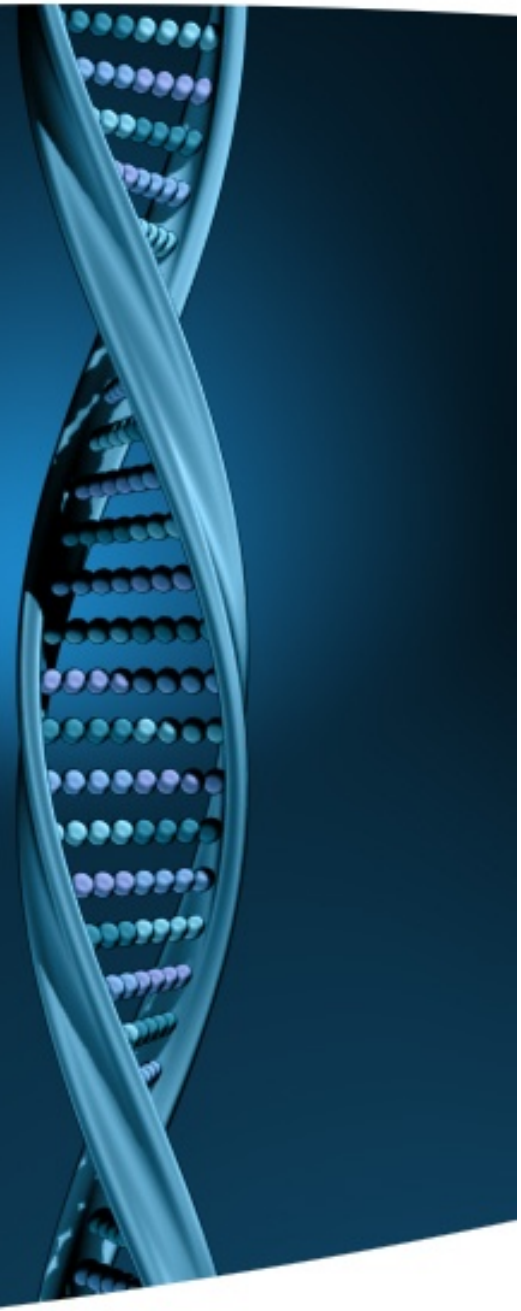


Chapter Index

1. Family History Background
2. The Case of the Frantic Cousin
3. The Case of the Hidden Cancer
4. The Case of the Anxious Grandmother
5. The Average Case of Colorectal Cancer
6. The Case of the Single Generation Cancer
7. The Case of the Family History Afterthought
8. Review and Post-Test
9. USPSTF Family History Guidelines
10. EGAPP Colorectal Cancer Recommendations
11. Resources and References

Chapter 1

"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

Cancer Registry Chart Reviews (2003-2004)

- 853 charts reviewed of Michigan residents with cancer
- 82% documented presence or absence of family history of cancer
  - 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

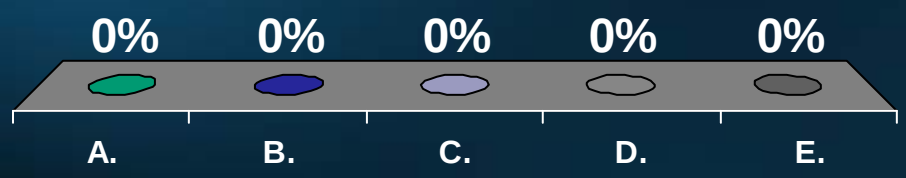
Health Plan Chart Reviews (2005-2007)

- 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

View the NCHPEG core competencies in genetics for all healthcare providers

How often do you collect / update a patient's family history?

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



Chapter Index

Demographics and Pretest

What is your current position?

1. Staff Physician
2. Resident Physician
3. Physician’s Assistant
4. Nurse
5. Student (including Medical Students)
6. Other Allied Healthcare Provider
7. State or Local Public Health Official
8. Not currently in clinical practice

In which area do you spend most of your time?

1. Family Medicine
2. Internal Medicine
3. Oncology
4. General or Specialized Surgery
5. Radiology
6. Genetics
7. Other Specialty Care
8. Medical School or Graduate Program

My knowledge level of common hereditary cancer syndromes and related issues is:

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

My confidence level in my ability to identify patients at risk for common hereditary cancer syndromes:

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

Which of the following evidence-based guidelines have you heard of?

1. EGAPP (Evaluation of Genomic Applications in Practice and Prevention) Review of Genetic Testing for Colorectal Cancer (2009)
2. USPSTF Guidelines (US Preventive Services Task Force) on Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility (2005)
3. Both
4. Neither

Which of the patients below is at greater risk for hereditary cancer?

A. Patient A whose mother and maternal aunt had ovarian cancer (age 65 and 70)
B. Patient B whose mother had breast cancer at age 45
C. Do not know

True or False: Breast cancer is only inherited from the mother’s side of the family.

A. True
B. False
C. Do not know

What percentage of individuals with colon cancer will have an inherited condition called Lynch Syndrome (regardless of family history)?

1. $<$ 1 %
2. 2-3%
3. 5-10%
4. Do Not Know

Which of the patients below has the greatest risk for hereditary cancer?

A. Patient A whose two paternal uncles had colon cancer (diagnosed at 62 and 65).
B. Father (dx. 45) with colon cancer.
C. Do Not Know

All of these increase a patient's risk for Hereditary Breast and Ovarian Cancer syndrome, except:

1. Ashkenazi Jewish Ancestry
2. Young ages at diagnosis in the family (< age 50)
3. Breastfeeding for a cumulative total of more than 1 year
4. A significant paternal family history of breast and ovarian cancer
5. A known BRCA mutation in the family
6. 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

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

In the past month, how many referrals have you made for genetic counseling services based on a patient's personal or family history of cancer?

A – 0

B – 1-2

C – 3-4

D – 5 or more

Goals of this experience are to increase provider:

- knowledge of hereditary cancer risk, family history "red flags" and genetic testing options for common hereditary cancer syndromes.
- confidence in obtaining and evaluating cancer family histories and providing appropriate medical follow up for hereditary risks.
- awareness of current evidence-based guidelines on genetic testing for hereditary cancer syndromes and gene expression profiling tests.

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
4. Provide appropriate referrals and follow up for patients at increased risk
5. Recognize the difference between germline testing for hereditary cancer and somatic testing through gene assay

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

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).

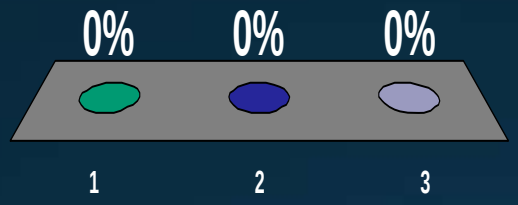
She says, “I’m so stressed about my cousin’s breast cancer diagnosis cause she’s my age.” Even though you’re running late, you decide to discuss her family history.

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 <u>and</u> ovarian cancer in her 70s.

What do you decide to do?

1. Draw her blood for genetic testing of the breast cancer genes (BRCA1/2)
2. 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.
3. Tell her that her family history is concerning and refer her for genetic counseling to discuss her risk and possible testing.



1: 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

POSITIVE RESULT

She is found to have a BRCA 2 gene mutation.

CONFIDENTIAL

Comprehensive BRACAnalysis®
***BRCA1* and *BRCA2* Analysis Result**

PHYSICIAN	SPECIMEN	PATIENT
John Smith, MD Comprehensive Medical Center 1100 Grand Ave Away, GA 12345	Specimen: Blood Draw date: Sept 27, 2008 Accession date: Oct 1, 2008 Report Date: Oct 15, 2008	Name: Doe, Jane Date of Birth: April 1, 1492 Patient ID: 000000 Gender: Female Accession #: 000-BLD Requisition #: 000000

Test Results and Interpretation

POSITIVE FOR A DELETERIOUS MUTATION

Test Performed:	Result:	Interpretation:
BRCA1 sequencing	No Mutation Detected	No Mutation Detected
5-site rearrangement panel	No Mutation Detected	No Mutation Detected
BRCA2 sequencing	S1970X	Deleterious

Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the *BRCA1* and *BRCA2* genes and a test for five specific *BRCA1* rearrangements.

The results of this analysis are consistent with the germline *BRCA2* mutation S1970X, resulting in premature truncation of the *BRCA2* protein at amino acid position 1970. Although the exact risk of breast and ovarian cancer conferred by this specific mutation has not been determined, studies of this type of mutation in high-risk families indicate that deleterious mutations in *BRCA2* may confer as much as an 84% risk of breast cancer and a 27% risk of ovarian cancer by age 70 in women (Am. J. Hum. Genet. 62:676-689, 1998). Mutations in *BRCA2* have been reported to confer a 12% risk of a second breast cancer within five years of the first (J Clin Oncol 17:3396-3402, 1998), as well as a 16% risk of subsequent ovarian cancer (J Natl Cancer Inst 91:1310-1315, 1999). This mutation may also confer up to a 6% risk of male breast cancer and 8% risk of prostate cancer by age 70 (J Natl Cancer Inst 91:1310-1315, 1999), as well as increased (albeit low) risks of some other cancers. Each first degree relative of this individual has a one-in-two chance of having this mutation. Family members can be tested for this specific mutation with a single site analysis.

Please contact Myriad Professional Support at 1-800-469-7423 to discuss any questions regarding this result.

Authorized Signature:

Director Name Here
Qualifications Here

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Qualifications Here

These test results should only be used in conjunction with the patient's clinical history and any previous analysis of appropriate family members. It is strongly recommended that these test results be communicated to the patient in a setting that includes appropriate counseling. The accompanying Technical Specifications summary describes the analysis, method, performance characteristics, nomenclature, and interpretive criteria of this test. This test may be considered investigational by some states. This test and its performance characteristics were determined by Myriad Genetic Laboratories. It has not been reviewed by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary.

SAMPLE

You disclose her test results and…

- After the initial shock, she says, “you know my cousin has a BRCA2 mutation too!”
- It turns out your patient was so anxious to start her mammograms that she forgot to mention that her cousin already underwent “that BRCA testing.”
- Full sequencing costs $3340 and site specific testing for a known family mutation costs ~ $475.

A difference of $2865 healthcare dollars that could have been saved!!

Return to choices

Not the best choice

#2. 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. She has a 1-year-old and a 3-year-old daughter at home.

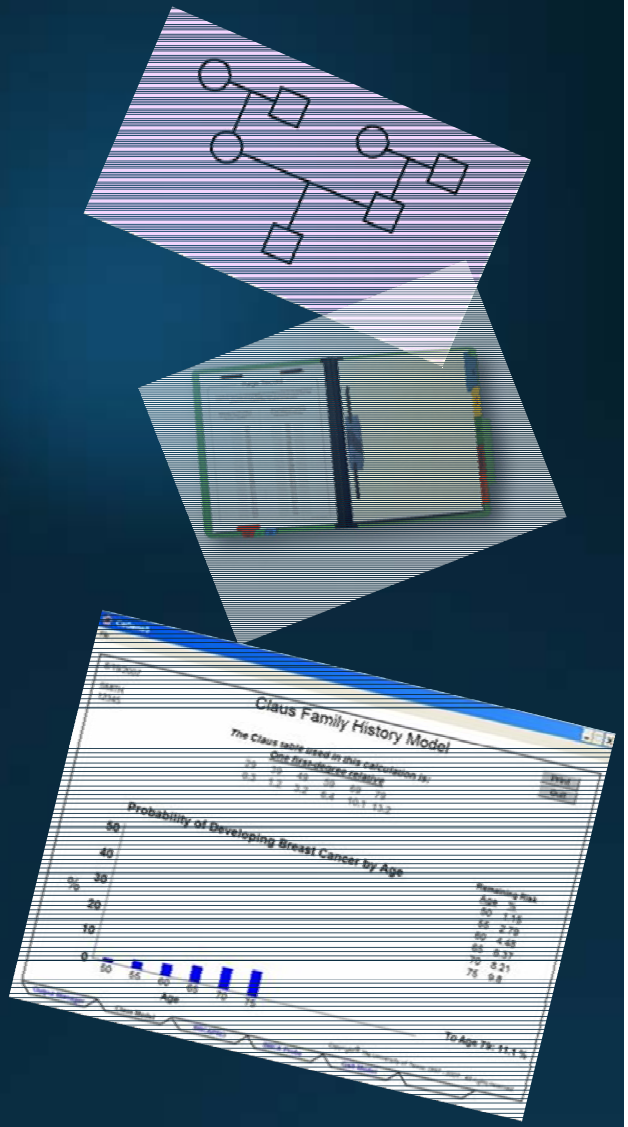
So what happened??

Return to choices 2

The Best Choice!

#3: She goes for genetic counseling…

- It is recommended that the patient's cousin undergo genetic testing for BRCA1/2.
- The patient recalls, "oh I think my cousin already had that!"
- The counselor obtains medical records and confirms a BRCA2 mutation in the cousin.
- Due to insurance issues, her father declines to be tested first, which would benefit all his children. Site-specific testing is ordered for your patient ($475).



- 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.

Return to choices 2

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)

View the USPSTF Family History Criteria

Chapter Index

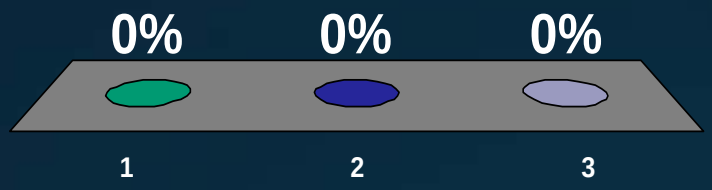
Chapter 3 : The Case of the Hidden Cancer

Your patient is a 30-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 60 and her sister recently had breast cancer at age 40. You ask if there are any other cancers in the family, and she reports "not that I can think of."

How do you proceed?

1. Her risk for hereditary cancer seems increased. You refer her for an early mammogram.
2. Strongly encourage that she have her mother or sister go for genetic counseling to discuss the family history and possibly have genetic testing.
3. This case really does seem clear cut. You draw the patient's blood for genetic testing (BRCA1/2).



Not the best choice

#1: 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.

Increased risk- begin surveillance

- She continues to have normal mammograms.
- At age 36 she begins to have pain during intercourse and heavy menstruation. After physical exam she is told she has uterine fibroids.

But wait, there's more…

Increased risk- begin surveillance

- At age 40, she has had irregular bleeding over the last 5 years and has recently developed pain with urination, continues to have pain during intercourse, and general malaise.
- An ultrasound is ordered to assess her uterine fibroids. A mass is seen and a biopsy is recommended.
- She is found to have endometrial cancer and a hysterectomy is performed to remove the tumor.
- The patient is devastated by the diagnosis, the need for a hysterectomy, and the discovery of cancer in one nearby lymph node.

Go back to the other choices and try again

Return to choices

The Best Choice!

2: She gets her mother to see a qualified healthcare professional for genetic counseling

Need to find genetic services?

Visit:
www.migeneticsconnection.org/cancer

Or view the directory here

Referral form statement:

- Breast cancer in her 60s
- Daughter – breast cancer age 40

Refer for Genetic Counseling

- 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).

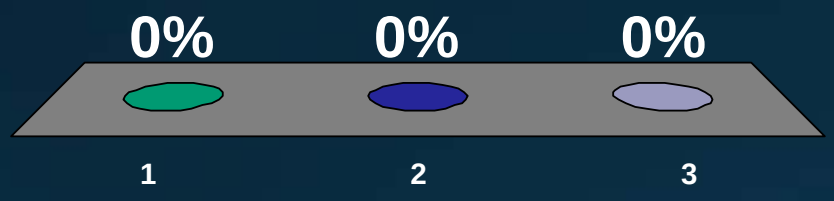
Refer for Genetic Counseling

- It is important to discuss and rule out BRCA1/2 and HBOC syndrome.
- However, based on the family history, it is much more likely that the 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



Refer for Genetic Counseling

- PTEN testing is carried out for your patient's mother and a gene mutation is identified. Your patient and her affected sister test positive as well. One other sister and her brother are negative.

- Although the risk for endometrial cancer is only 10%, your patient and her husband decide to have children right away.
- After having two healthy children at age 35, she begins having 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.

Return to choices

3: A clear cut case…

Not the best choice

- 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 thorough discussion, you draw the patient's blood and send it off for BRCA1/2 testing.
- 3 weeks later the results arrive

The Results Are In…

CONFIDENTIAL

Comprehensive BRACAnalysis®
***BRCA1* and *BRCA2* Analysis Result**

PHYSICIAN	SPECIMEN	PATIENT
John Smith, MD Comprehensive Medical Center 1100 Grand Ave Away, GA 12345	Specimen: Blood Draw date: Sept 27, 2008 Accession date: Oct 1, 2008 Report Date: Oct 15, 2008	Name: Doe, Jane Date of Birth: April 1, 1492 Patient ID: 000000 Gender: Female Accession #: 000-BLD Requisition #: 000000

Test Results and Interpretation

GENETIC VARIANT OF UNCERTAIN SIGNIFICANCE

Test Performed:	Result:	Interpretation:
BRCA1 sequencing	No Mutation Detected	No Mutation Detected
5-site rearrangement panel	No Mutation Detected	No Mutation Detected
BRCA2 sequencing	R18H	Uncertain Significance

Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the *BRCA1* and *BRCA2* genes and a test for five specific *BRCA1* rearrangements.

The *BRCA2* variant R18H results in the substitution of histidine for arginine at amino acid position 18 of the *BRCA2* protein. Variants of this type may or may not affect the function of the protein encoded by the gene in which it is found. Therefore, the contribution of this variant to the relative risk of breast or ovarian cancer cannot be established solely from this analysis.

SAMPLE

Please contact Myriad Professional Support at 1-800-469-7423 to discuss any questions regarding this result.

Authorized Signature:

Director Name Here
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She is found to have a variant in the BRCA 2 gene.

What does this mean?

VARIANT of uncertain significance

- 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 just more confused! So do I need screening or what?

Obtaining proper informed consent is the law in Michigan!

Return to choices

VARIANT of uncertain significance

This scenario leaves us with lots of questions:

- 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 sister tested negative for the patient's BRCA variant or any other mutations.?

Your patient never develops breast cancer, but she does develop endometrial cancer – a cancer that is not associated with the BRCA1 and BRCA2 genes.

Return to choices

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.

Chapter Index

Chapter 4

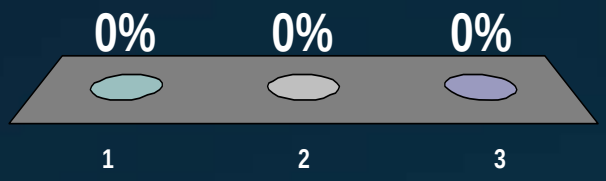
The Case of The Anxious Grandmother

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.



Now what if?

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.

Return to choices

Not the best choice

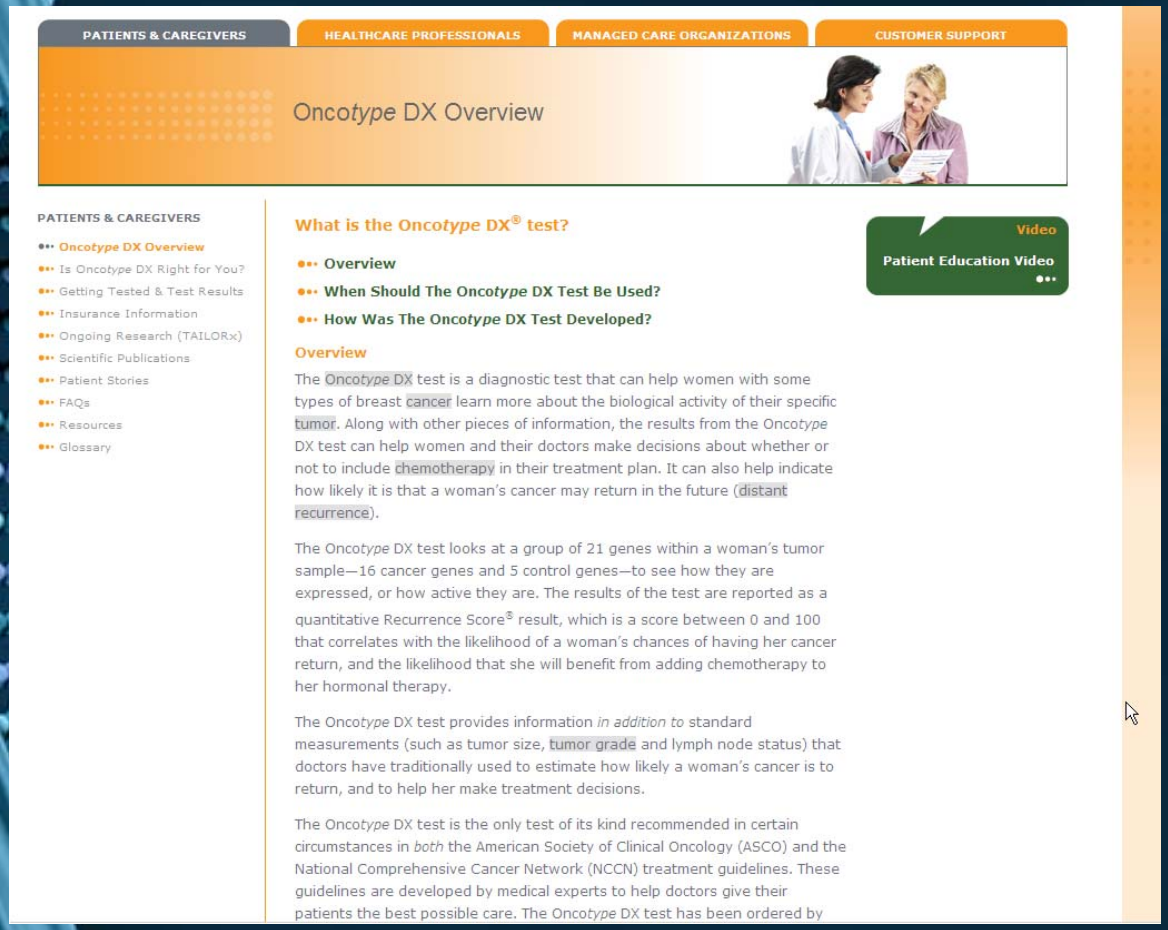
#2: Consult with the experts

- 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.

Return to choices

Not the best choice

#3: You tell the patient that she is at low risk based on her mother's "low risk" genetic test result.



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Oncotype DX Overview

PATIENTS & CAREGIVERS

- Oncotype DX Overview
- Is Oncotype DX Right for You?
- Getting Tested & Test Results
- Insurance Information
- Ongoing Research (TAILORx)
- Scientific Publications
- Patient Stories
- FAQs
- Resources
- Glossary

What is the Oncotype DX® test?

- Overview
- When Should The Oncotype DX Test Be Used?
- How Was The Oncotype DX Test Developed?

Video

Patient Education Video

Overview

The Oncotype DX test is a diagnostic test that can help women with some types of breast cancer learn more about the biological activity of their specific tumor. Along with other pieces of information, the results from the Oncotype DX test can help women and their doctors make decisions about whether or not to include chemotherapy in their treatment plan. It can also help indicate how likely it is that a woman's cancer may return in the future (distant recurrence).

The Oncotype DX test looks at a group of 21 genes within a woman's tumor sample—16 cancer genes and 5 control genes—to see how they are expressed, or how active they are. The results of the test are reported as a quantitative Recurrence Score® result, which is a score between 0 and 100 that correlates with the likelihood of a woman's chances of having her cancer return, and the likelihood that she will benefit from adding chemotherapy to her hormonal therapy.

The Oncotype DX test provides information *in addition to* standard measurements (such as tumor size, tumor grade and lymph node status) that doctors have traditionally used to estimate how likely a woman's cancer is to return, and to help her make treatment decisions.

The Oncotype DX test is the only test of its kind recommended in certain circumstances in *both* the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) treatment guidelines. These guidelines are developed by medical experts to help doctors give their patients the best possible care. The Oncotype DX test has been ordered by

- 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.

Return to choices

Review of the patient's history:

58-year-old female

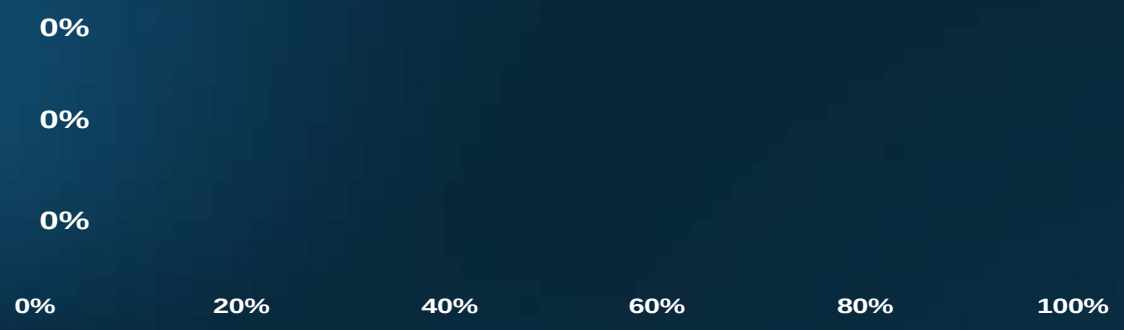
Mother with breast cancer at age 72.

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.

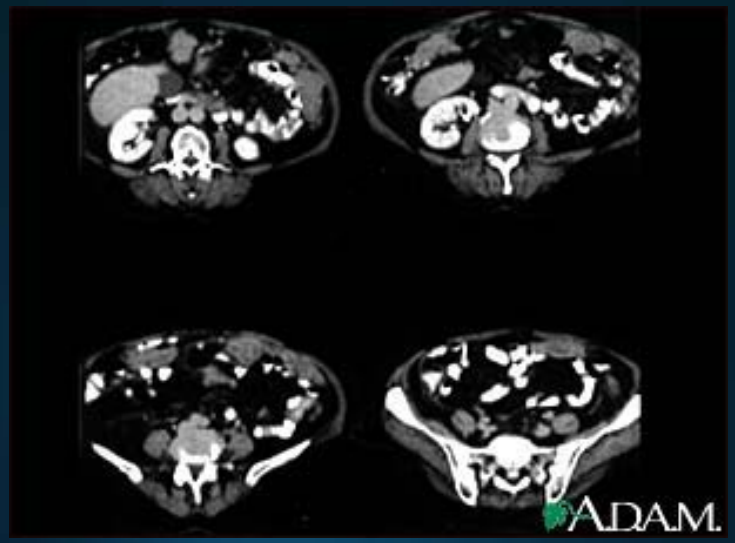


#1: Late onset / low risk

Not the best choice

- 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.

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.

Return to choices

#2: Consult with the experts

The Best Choice!

- 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.

Return to choices

Not the best choice

#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.

Return to choices

What did we learn?

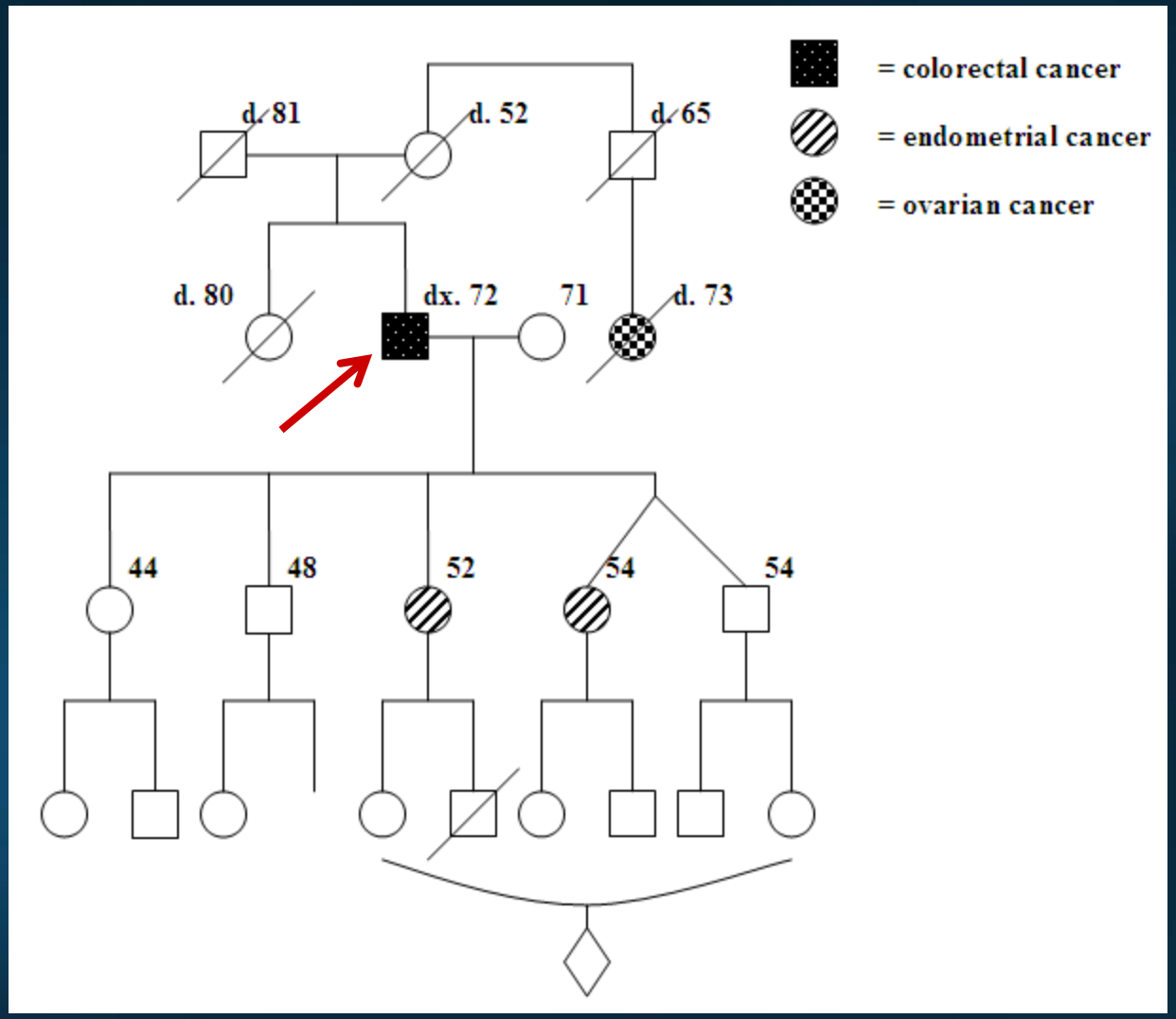
- A single diagnosis at an older age is most likely sporadic (or non-hereditary).
- Ashkenazi Jewish ancestry is important! Documenting ancestry can make the difference between identifying a family at risk and letting them slip through the cracks. View the USPSTF referral criteria for those with Ashkenazi 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.

Chapter Index

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.


= colorectal cancer
= endometrial cancer
= ovarian cancer
d. 81
d. 52
d. 65
d. 80
dx. 72
71
d. 73
44
48
52
54
54

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).

0%

0%

0%

0% 20% 40% 60% 80% 100%

#1: Consult with the experts

The Best Choice!

- 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.

Return to choices

#2: Late onset / low risk

Not the best choice

- 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).

An “ok” choice

#3: Increase screening for family

- 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.

Return to choices

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 EGAPP 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 Index

Chapter 6 The Case of the Single Generation Cancer

<u>Personal history:</u>

- 50 colon polyps
- colorectal cancer at age 27

<u>Parents:</u>

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

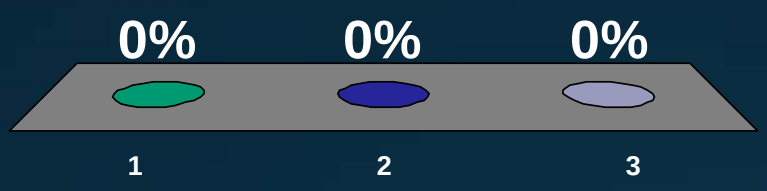
<u>Two brothers:</u>

- 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.



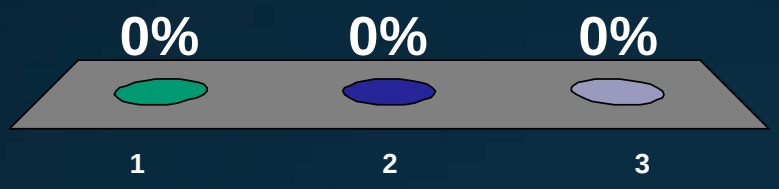
Not the best choice

#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



Return to choices

Not the best choice

#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)

Return to choices

The Best Choice!

#3: He would like more information and goes for genetic counseling…

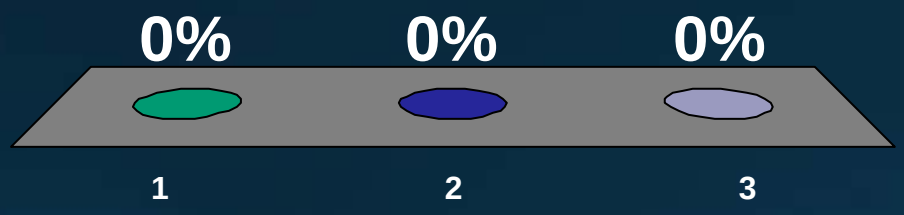
- Both Familial Adenomatous Polyposis (FAP) and MYH-Associated Polyposis (MAP) are discussed. Individuals with no family history can have a new mutation in the FAP gene (*APC*) or can have MAP which is an unusual recessive cancer condition.

- 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 Polyposis?

1. Yes
2. No
3. Don’t Know

View more information on MYH-Associated Polyposis



Return to choices

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.

Chapter Index

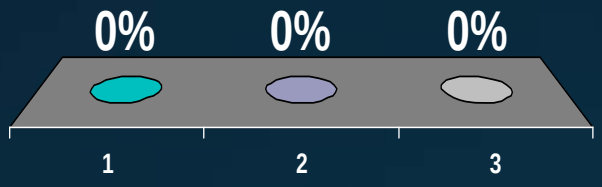
Chapter 7 The Case of the Family History Afterthought

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?”

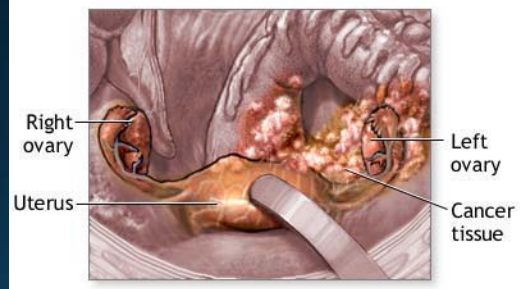
What do you do next?

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.

And…

She dies at age 49.

Return to choices

The Best Choice!

#2: Ask more about her family history and tell her you're not sure…

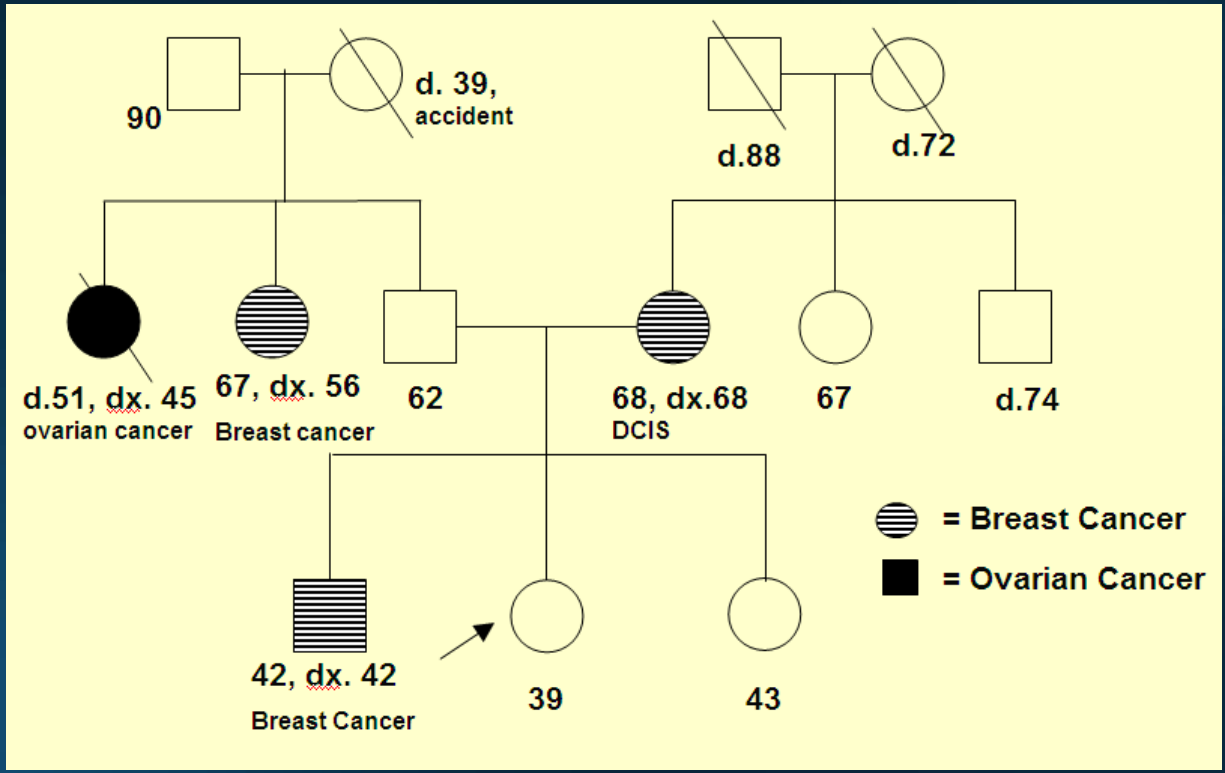
- Her mother was diagnosed at 68 years old.
- She reports no other family history until you specifically ask about paternal history.
- You review the importance of mammography and clinical breast exams beginning at age 40.
- You do not order genetic testing at this time, but <u>you strongly encourage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

She follows up with her physician who refers her to Genetics Clinic.

Return to choices

#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. <u>She would like to discuss having her ovaries removed in the future to reduce her risk.</u>

Return to choices

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%.

Chapter Index

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 coveys 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

Take the Post-Test

Chapter 8 Post-Test

My knowledge level of hereditary cancer genetics and related issues is:

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

My confidence level in my ability to identify patients at risk for hereditary cancer is:

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

Did this web-based training provide information that was appropriate and applicable in your current work?

1. Yes, very appropriate and applicable
2. Yes, somewhat appropriate and applicable
3. No, not at all appropriate or applicable

Will the content of this web-based training change your clinical practice in any way?

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

Which of the following evidence based guidelines have you ever heard of?

1. EGAPP (Evaluation of Genomic Applications in Practice and Prevention) Review of Genetic Testing for Colorectal Cancer (2009)
2. USPSTF Guidelines (US Preventive Services Task Force) on Genetic Risk Assessment and *BRCA* Mutation Testing for Breast and Ovarian Cancer Susceptibility (2005)
3. Both
4. Neither

Which of the patients below is at greater risk for hereditary cancer?

A. Patient A whose mother and maternal aunt had ovarian cancer (age 65 and 70)
B. Patient B whose mother had breast cancer at age 45
C. Do not know

True or False: Breast cancer is only inherited from the mother’s side of the family.

A. True
B. False
C. Do not know

What percentage of individuals with colon cancer will have an inherited condition called Lynch Syndrome (regardless of family history)?

1. $<$ 1 %
2. 2-3%
3. 5-10%
4. Do Not Know

Which of the patients below has the greatest risk for hereditary cancer?

A. Patient A whose two paternal uncles had colon cancer (diagnosed at 62 and 65).
B. Father (dx. 45) with colon cancer.
C. Do Not Know

All of these increase a patient's risk for Hereditary Breast and Ovarian Cancer syndrome, except:

1. Ashkenazi Jewish Ancestry
2. Young ages at diagnosis in the family
3. Breastfeeding for a cumulative total of more than 1 year
4. A significant paternal family history of breast and ovarian cancer
5. A known BRCA mutation in the family
6. 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

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

Your Specific Cancer Genetics Facility Report:

Questions and Discussion

Go Back

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

Go Back

9 USPSTF Family History Patterns

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

Go Back

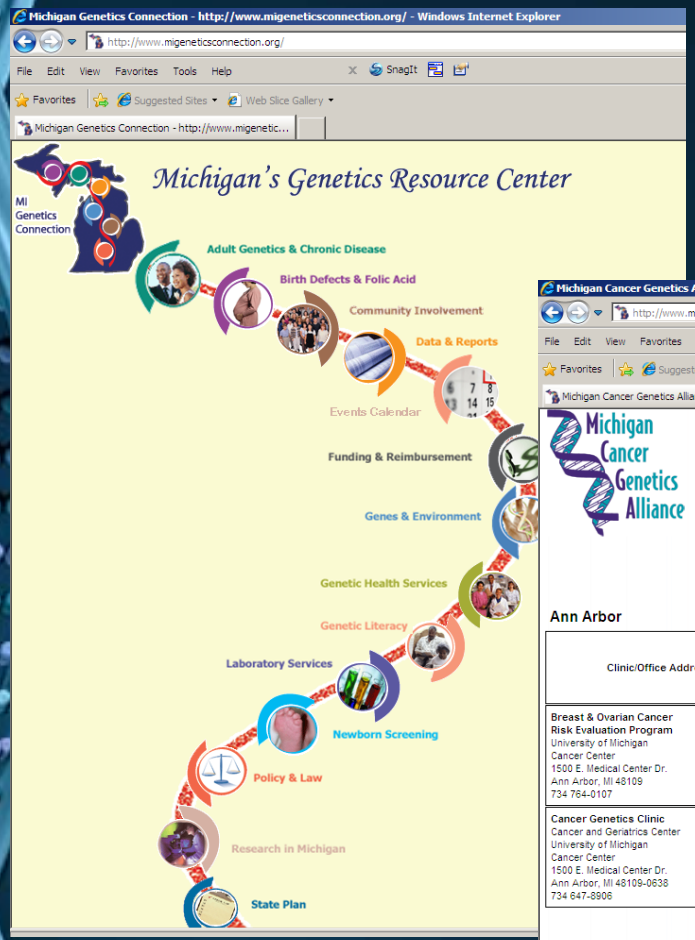
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Review of Genetic Testing for Colorectal Cancer

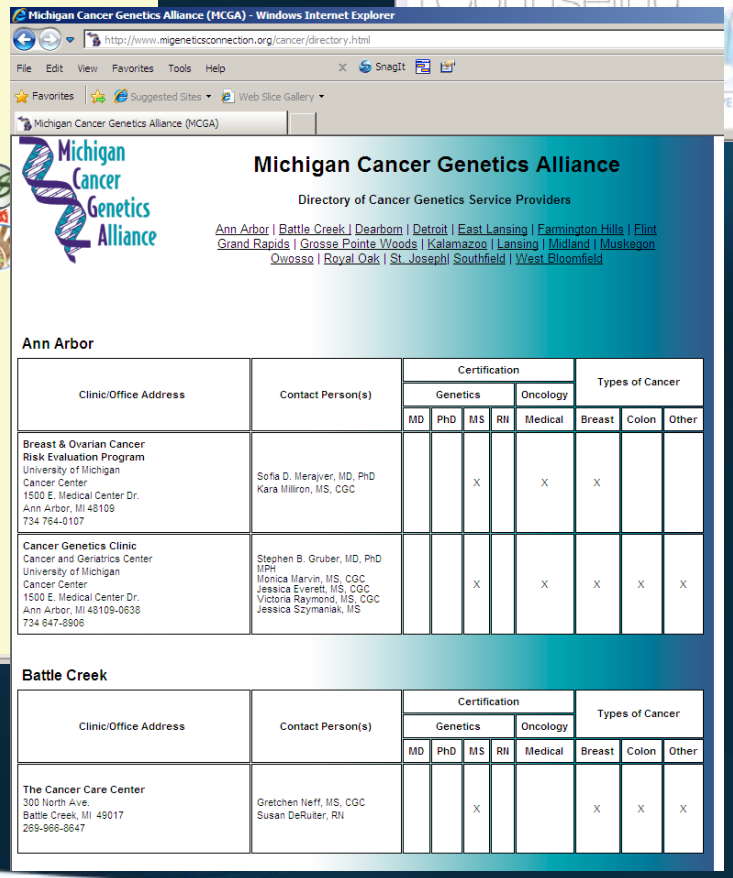
- "found sufficient evidence to recommend offering genetic testing for Lynch syndrome to all individuals with newly diagnosed colorectal cancer to reduce morbidity and mortality in relatives."
- MSI and IHC are both effective screening methods –no optimal testing strategy was identified.
- American College of Medical Genetics and the American Society of Human Genetics issued a joint statement to support that MSI/IHC are cost effective methods and should be offered to CRC patients

EGAPP Recommendations. AHRQ Publication No. 07-E008. Hereditary Non-Polyposis Colorectal Cancer: Diagnostic Strategies and Their Implications. May 2007.

Go Back

MCGA Cancer Genetics Directory





Michigan Cancer Genetics Alliance

Directory of Cancer Genetics Service Providers

Ann Arbor | Battle Creek | Dearborn | Detroit | East Lansing | Farmington Hills | Flint
Grand Rapids | Grosse Pointe Woods | Kalamazoo | Lansing | Midland | Muskegon
Owosso | Royal Oak | St. Joseph| Southfield | West Bloomfield

Ann Arbor

Clinic/Office Address	Contact Person(s)	Certification					Types of Cancer		
		Genetics				Oncology			
		MD	PhD	MS	RN	Medical	Breast	Colon	Other
Breast & Ovarian Cancer Risk Evaluation Program University of Michigan Cancer Center 1500 E. Medical Center Dr. Ann Arbor, MI 48109 734 764-0107	Sofia D. Merajver, MD, PhD Kara Milliron, MS, CGC			X		X	X		
Cancer Genetics Clinic Cancer and Geriatrics Center University of Michigan Cancer Center 1500 E. Medical Center Dr. Ann Arbor, MI 48109-0638 734 647-8906	Stephen B. Gruber, MD, PhD MPH Monica Marvin, MS, CGC Jessica Everett, MS, CGC Victoria Raymond, MS, CGC Jessica Szymaniak, MS			X		X	X	X	X

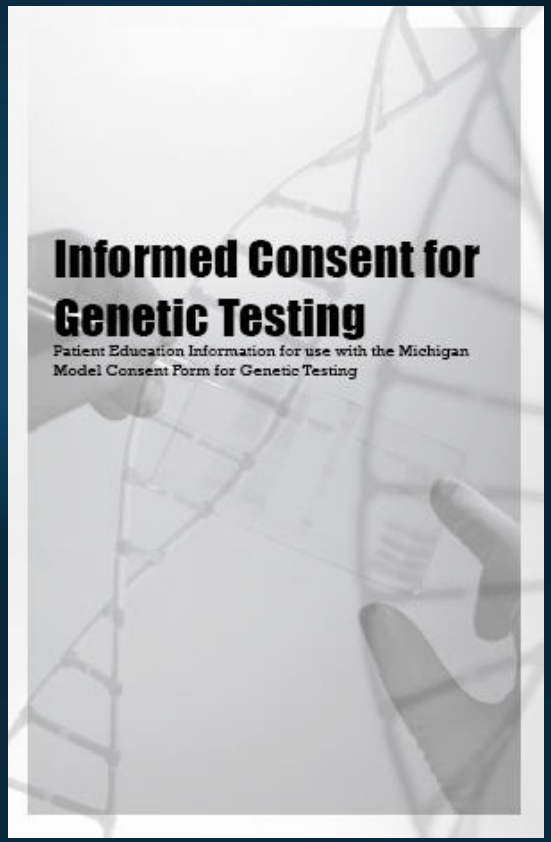
Battle Creek

Clinic/Office Address	Contact Person(s)	Certification					Types of Cancer		
		Genetics				Oncology			
		MD	PhD	MS	RN	Medical	Breast	Colon	Other
The Cancer Care Center 300 North Ave. Battle Creek, MI 49017 269-966-8647	Gretchen Neff, MS, CGC Susan DeRuiter, RN			X			X	X	X

Go Back

- 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).

- Major criteria -- breast and thyroid cancer, macrocephaly, endometrial cancer, and Lhermitte-Duclos disease (a benign cerebellar tumor).
- Minor criteria -- mental retardation, GI hamartomas, fibrocystic disease of the breast, lipomas, fibromas, uterine fibroids, and goiters. Genitourinary tumors.

Cowden syndrome

Cowden Syndrome

Cowden Syndrome Suveillance

- 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 (premenoapusal 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.

Go Back

Cowden Syndrome Suveillance

- 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.

Go Back

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 perotineal cancers as well.

Michigan Cancer Genetics Alliance

MCC
Michigan Cancer Consortium

November 2009

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*[3,4,5,7,8,14] and should be provided in the context of pre- and post- test genetic counseling. As described in published consensus guidelines[x] 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[1]).

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.[1] Written informed consent is mandated by Michigan state law[2] 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*.[3,4,7,8,14] 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[2]), 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.[15]
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[1]) should be involved in risk assessment, ordering and interpreting the results of a genetic test.[2] 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.[9]
4) Application of the ethical and legal aspects of autonomy, privacy, equity and confidentiality to each patient seeking genetic testing.[3]
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.[x] 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.[2]

[+] *See Appendix, Tables 1 and 2*

* *Genetic testing as defined here is in reference to germline testing for a hereditary cancer syndrome, and not for somatic genetic mutations such as in genetic profiling of a tumor.*

[x] *Such as the NCCN (National Comprehensive Cancer Network), ASCO (American Society of Clinical Oncology), ACOG (American College of Obstetrics and Gynecology), NSGC (National Society of Genetic Counselors), SGO (Society of Gynecologic Oncologists), and evidence-based recommendations such as USPSTF (U.S. Preventive Services Task Force).*

References:

1. Gray S: Direct-to-consumer marketing of genetic tests for cancer: buyer beware. J Clin Oncol 21:3191, 2003.
2. Statement of the American College of Medical Genetics: ACMG statement on direct-to-consumer genetic testing, adopted on April 7, 2008. www.acmg.net.
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5. Matloff E. Direct to confusion: lessons learned from marketing BRCA testing. Am J Bioethics 8:5, 2008.
6. Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility, adopted on March 1, 1996. J Clin Oncol 21:2397, 2003.
7. National Cancer Comprehensive Network Practice Guidelines: Genetic/familial high-risk assessment: breast and ovarian. V.1.2008 www.nccn.org.
8. Michigan Genetics Connection website: http://www.migeneticsconnection.org/geneticheath.shtml

Go Back

Appendix[1]

Table 1: Hereditary Cancer Syndromes with an Increased Risk of Common Cancers[3]

Syndrome	Features/Associated Cancers	Gene(s) Causing Syndrome
Hereditary breast cancer; Hereditary Breast/Ovarian Cancer (HBOC) Syndrome	Early-onset breast cancer, male breast cancer, ovarian, prostate cancer, pancreatic cancer	*BRCA1, BRCA2*, probably other gene(s)
Lynch Syndrome (HNPCC=Hereditary Nonpolyposis Colorectal Cancer)	Early-onset colorectal cancer, early-onset endometrium cancer, ovarian, stomach, small bowel, pancreas, ureter, renal pelvis cancers.	DNA mismatch repair genes- *MLH1, MSH2, MSH6, PMS1, PMS2*
Cowden Syndrome	Breast, thyroid, and endometrial cancer, and benign hamartomatous lesions of skin, oral mucosa and intestine, and benign breast and thyroid disease	*PTEN*
Familial Adenomatous Polyposis (FAP); Attenuated FAP (AFAP)	Adenomatous polyposis (>100 colonic polyps), colorectal cancer, papillary thyroid cancer, gastric cancer, periampullary cancer, adrenal cancer, hepatoblastoma, and extracolonic manifestations; Less than 100 colonic polyps, later-onset colorectal cancer (>40). May be increased risk of gastric and duodenal adenomas and/or cancer	*APC*
MYH-Associated Polyposis	Adenomatous polyposis with features ranging from AFAP to classic FAP. Recessive inheritance.	*MYH*
Juvenile Polyposis Syndrome	Hamartomatous polyps, increased risk colorectal, pancreatic, gastric, and duodenal cancer	*SMAD4, BMPR1A*
Hereditary Prostate Cancer	Prostate cancer, possible increased risk of other cancers	*HPC1/RNASEL, HPC2/ELAC2, MSR1*, other gene(s)
Basal cell nevus syndrome; Gorlin syndrome	Basal cell nevi, characteristic facies, palmar and plantar pits, odontogenic keratocysts, rib abnormalities, increased risk of basal cell carcinoma, ovarian cancer, ovarian fibromata	*PTCH*
Familial Atypical Mole Malignant Melanoma syndrome (FAMMM)/ Hereditary dysplastic nevus syndrome	Multiple primary melanomas, dysplastic nevi, pancreatic cancer	*CDKN2A (p16 / p14), CDK4*

Table 2: Rare Hereditary Cancer Syndromes

Syndrome	Features/Associated Cancers	Gene(s) Causing Syndrome
Li-Fraumeni Syndrome	Early-onset breast, soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, leukemia, brain tumors	*TP53, CHEK2*
Peutz-Jeghers Syndrome	Breast cancer, benign ovarian tumors, testicular tumors, pancreatic cancer, polyps of the ureter, bladder, GI tract (hamartomatous polyps), renal pelvis, bronchus, nasal passage. Melanin spots on lips, buccal mucosa and digits	*STK11/LKB1*
Hereditary Retinoblastoma	Retinoblastomas, often bilateral or multifocal, other malignancies like osteosarcomas, especially in response to radiation exposure	*RB1*
von Hippel-Lindau syndrome	Hemangioblastomas of the brain, spine, and retina, pheochromocytoma, renal cell carcinoma, epididymal cystadenoma, endolymphatic sac tumors	*VHL*
Multiple Endocrine Neoplasia type I; MENI	Zollinger-Ellison syndrome. Parathyroid tumors, hyperparathyroidism, pituitary tumors, pancreatic islet tumors	*MEN1*
Multiple Endocrine Neoplasia type II; MEN2	MEN2A: Medullary thyroid carcinoma (MTC), pheochromocytoma, parathyroid tumors/parathyroid hyperplasia. MEN2B: earlier onset of MTC and pheochromocytomas as well as mucosal neuromas and a Marfanoid habitus	*RET*
Pheochromocytoma	Adrenal medullary tumors, isolated pheochromocytomas and/or paragangliomas	*RET/VHL/SDHD, SDHB*
Nonchromaffin paraganglioma	Paragangliomas, chemodectomas, carotid body tumors, glomus jugular tumors, pheochromocytoma	*PGL1/SDHD PGL2, PGL3/SDHC*
Wilms tumor	Nephroblastoma; can also be associated with WAGR, Beckwith-Wiedmann and other abnormal urogenital development syndromes	*WT1*

Go Back

National Coalition for Health Professional Education in Genetics

Appendix[2]

National Coalition for Health Professional Education in Genetics=NCHPEG

NCHPEG's Core Competencies in Genetics – September 2007[15]

BASELINE COMPETENCIES:

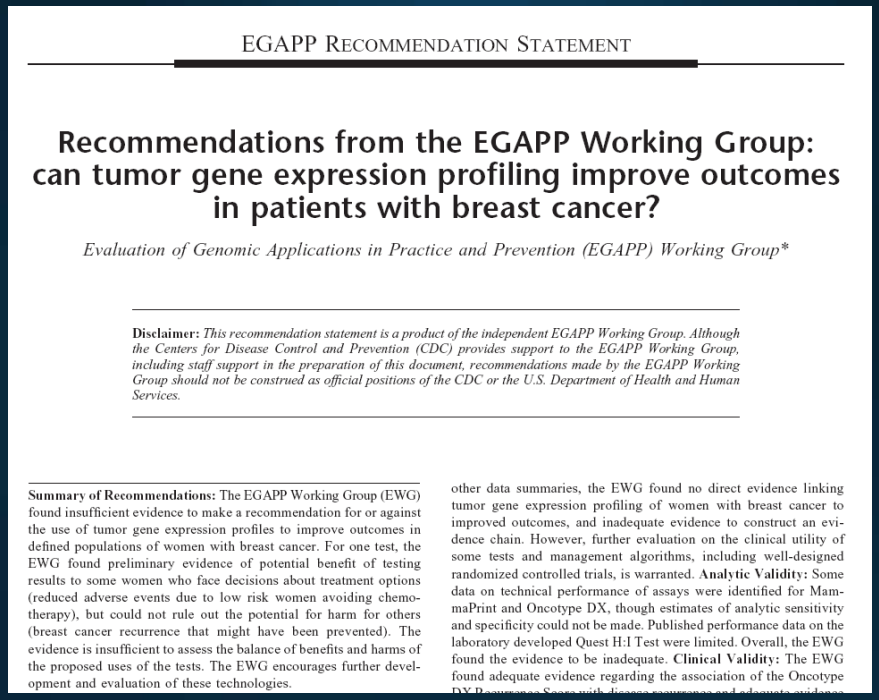
At a minimum, each health-care professional should be able to:
a. Examine one's competence of practice on a regular basis, identifying areas of strength and areas where professional development related to genetics and genomics would be beneficial.
b. Understand that health-related genetic information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

SKILLS:

All health professionals should be able to:
2.1 Gather genetic family history information, including at minimum a three-generation history.
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.
2.3 Explain effectively the reasons for and benefits of genetic services.
2.4 Use information technology to obtain credible, current information about genetics.
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.

Go Back

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Recommendation Statement: Tumor Gene Expression Profiling



EGAPP RECOMMENDATION STATEMENT

Recommendations from the EGAPP Working Group: can tumor gene expression profiling improve outcomes in patients with breast cancer?

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**

Disclaimer: *This recommendation statement is a product of the independent EGAPP Working Group. Although the Centers for Disease Control and Prevention (CDC) provides support to the EGAPP Working Group, including staff support in the preparation of this document, recommendations made by the EGAPP Working Group should not be construed as official positions of the CDC or the U.S. Department of Health and Human Services.*

Summary of Recommendations: The EGAPP Working Group (EWG) found insufficient evidence to make a recommendation for or against the use of tumor gene expression profiles to improve outcomes in defined populations of women with breast cancer. For one test, the EWG found preliminary evidence of potential benefit of testing results to some women who face decisions about treatment options (reduced adverse events due to low risk women avoiding chemotherapy), but could not rule out the potential for harm for others (breast cancer recurrence that might have been prevented). The evidence is insufficient to assess the balance of benefits and harms of the proposed uses of the tests. The EWG encourages further development and evaluation of these technologies.

other data summaries, the EWG found no direct evidence linking tumor gene expression profiling of women with breast cancer to improved outcomes, and inadequate evidence to construct an evidence chain. However, further evaluation on the clinical utility of some tests and management algorithms, including well-designed randomized controlled trials, is warranted. **Analytic Validity:** Some data on technical performance of assays were identified for MammaPrint and Oncotype DX, though estimates of analytic sensitivity and specificity could not be made. Published performance data on the laboratory developed Quest H:I Test were limited. Overall, the EWG found the evidence to be inadequate. **Clinical Validity:** The EWG found adequate evidence regarding the association of the Oncotype

"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%)

Lynch Syndrome

Cancer Risks in Individuals with HNPCC up to Age 70 Years Compared to the General Population			
Cancer	**General Population Risk**	**HNPCC**	
		Risks	**Mean Age of Onset**
Colon	5.5%	80%	44 years
Endometrium	2.7%	20%-60%	46 years
Stomach	<1%	11%-19%	56 years
Ovary	1.6%	9%-12%	42.5 years
Hepatobiliary tract	<1%	2%-7%	Not reported
Urinary tract	<1%	4%-5%	~55 years
Small bowel	<1%	1%-4%	49 years
Brain/central nervous system	<1%	1%-3%	~50 years

Aarnio et al 1995 , Davis & Cohen 1995 , Vasen et al 1996 , Rodriguez-Bigas et al 1998, Lin et al 1998 , Aarnio et al 1999 , Watson et al 2001 , American Cancer Society Surveillance Research 2002

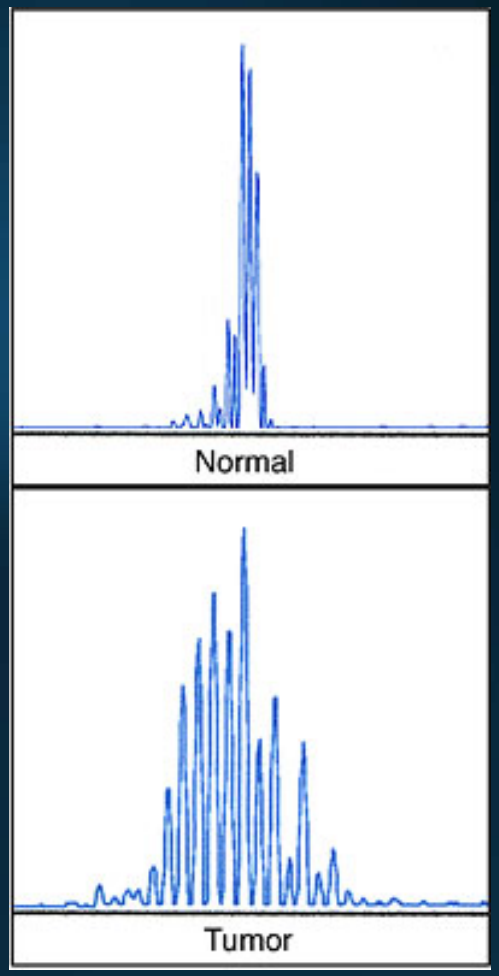
Lynch Syndrome

- 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)

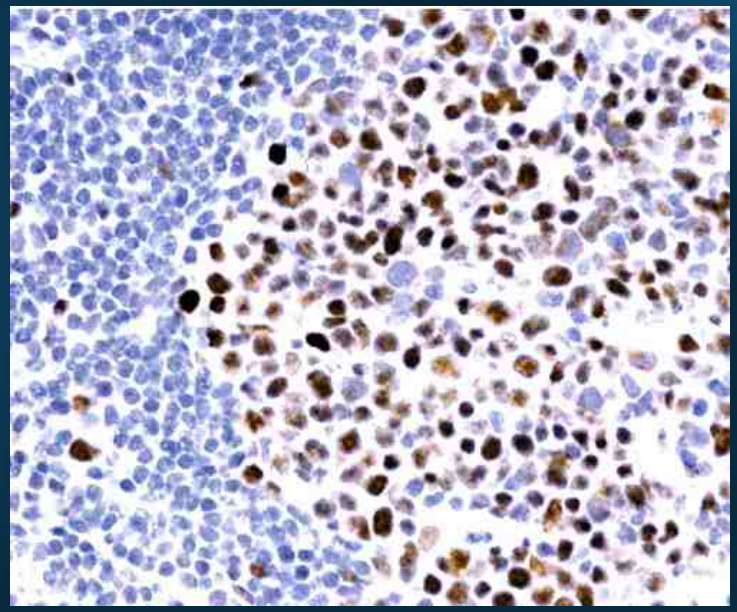
- Short repeats scattered throughout genome
- Can be repeated 10 to 100s of times
- Increased rate of mutation within these regions
- Mutations in MMR genes lead to unstable microsatellites indicating a high likelihood of Lynch Syndrome
- 95% of Lynch colon tumors will be MSI high (unstable)
- 90% of 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.

Go Back

Lynch Syndrome Surveillance

- **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 %.

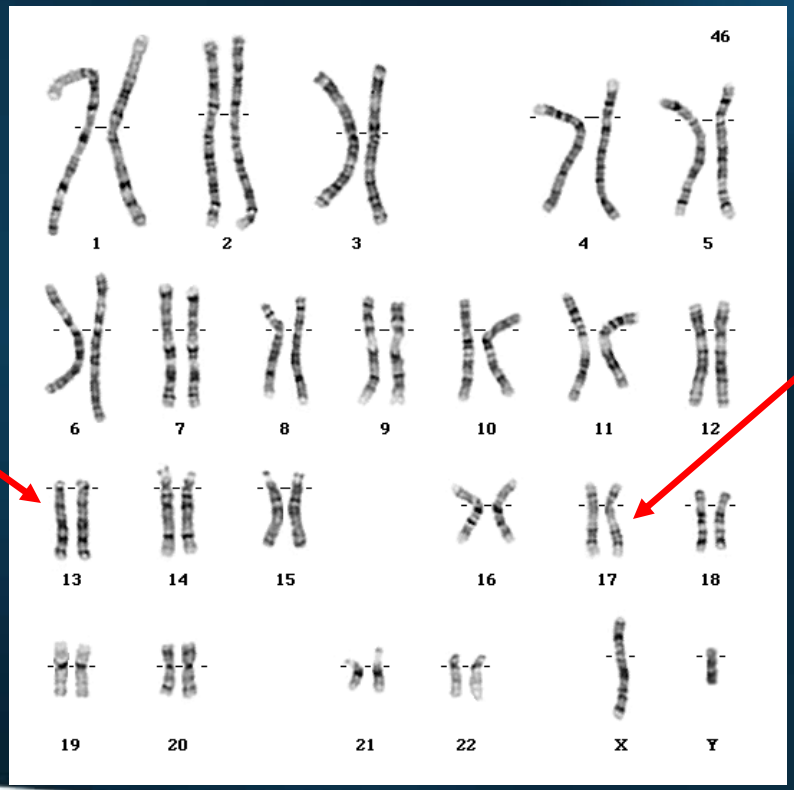
Hereditary Breast and Ovarian Cancer (HBOC)

- Accounts for 5-10% of all breast cancers. (And ~ 20% of Ashkenazi Jewish women diagnosed under age 45.)
- Approximately 1 in 200 are carriers in the general population.
- Caused by mutations in the BRCA1 or BRCA2 genes.

* 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 – meaning they are not located on the sex chromosomes.
- Both men and women can pass on changes in these genes to their children. Paternal history counts!

BRCA 2



BRCA 1

- General population risk for breast cancer is 1 in 8 or ~12%.

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

	BRCA1	*BRCA2*
30 yrs	3.2%	4.6%
40 yrs	19.1%	12%
50 yrs	50.8%	46%
60 yrs	54.2%	61%
70 yrs	85%	86%

- Men with BRCA1 or BRCA2 mutations have a 1.8% or 8% lifetime risk of breast cancer respectively (by age 80)

Go Back

Cancer	Lifetime Cancer risk General Population	Lifetime Cancer risk BRCA1/2 mutation carrier	2nd Cancer Risk within 5 yrs General Population	2nd Cancer Risk within 5 yrs BRCA1/2 mutation carrier
Breast	12%	36-85%	5%	12-20%
Ovary	1.6%	20-45%		
Pancreas		Slightly increased		
Prostate		20% Slightly increased		

Management of HBOC

POSITIVE TEST RESULTS

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.
- Breast ultrasound when needed.
- Concurrent transvaginal ultrasound and CA-125 every 6 months beginning at age 35. Best practice, however there is no evidence of efficacy in decreasing mortality.

Go Back

Management of HBOC

POSITIVE TEST RESULTS

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 age – decreases the ovarian cancer risk by 90-96% and decreases the breast cancer risk by 50%. Patient should be informed of this option.

Go Back

Management of HBOC

NEGATIVE / 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.

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.

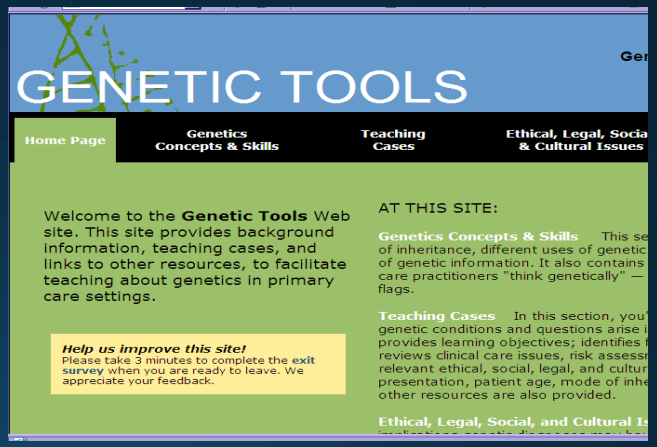
Go Back

MYH-Associated Polyposis (MAP)

- Typically Familial Adenomatous Polypsis (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.

Family History Resources for Providers

http://www.genetictools.org



http://www.cdc.gov/genomics/update/current.htm

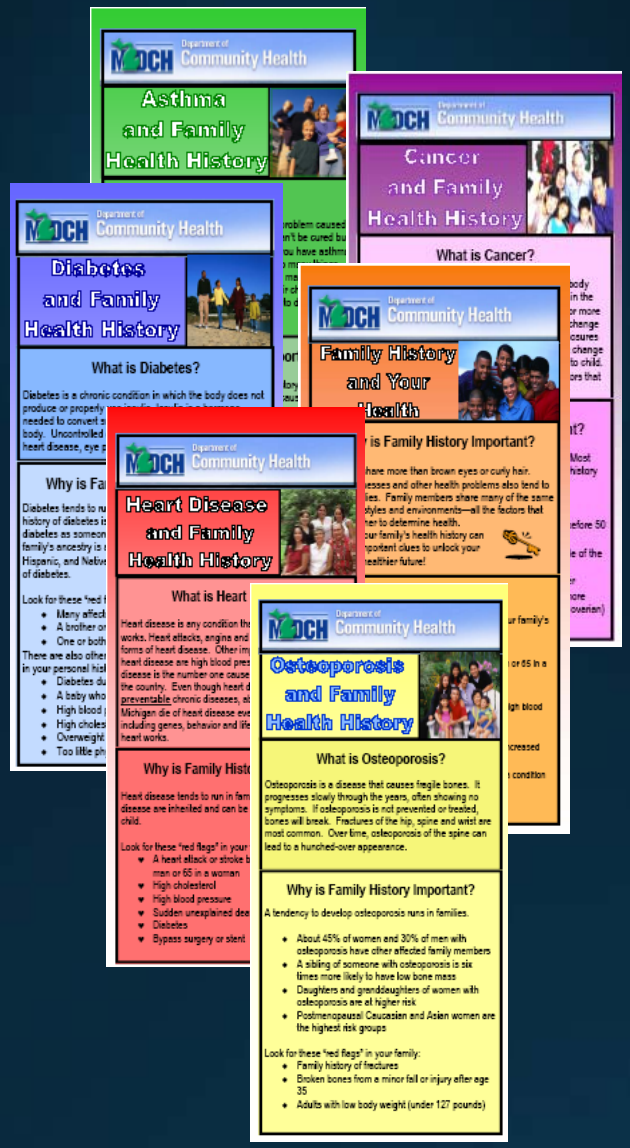
http://www.nchpeg.org/

http://www.aafp.org/afp/20050801/441.htmlww.nchpeg.org/

MDCH Family History Fact Cards

Developed in 2007 and distributed to public and health care providers

Series of 6 cards covering general family history, asthma, cancer, diabetes, heart disease and osteoporosis

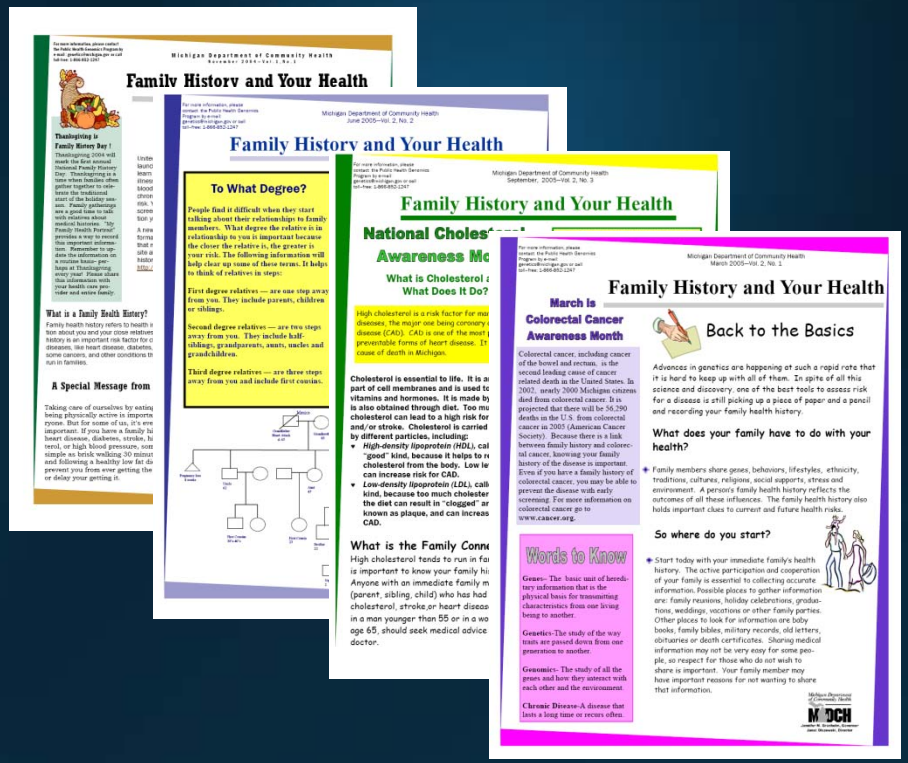


MDCH Family History and Your Health Newsletters

Developed and distributed quarterly since November 2004

Focus on awareness of disease or risk factor month

- *Number of hits to newsletters ~400-800/month*



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/cancer
- MI Cancer Consortium (MCC)
  - www.michigancancer.org

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- www.ccalliance.org