

Genetic Determinants, Risk Assessment and Management

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I have no disclosures.

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especially my partners in the
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Jacqueline Hale, APNC, AOCN, AGN-BC
Mary Vecchio, APNC, OCN, CTTS



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Objectives

At the conclusion of this session, the attendee should be able to:

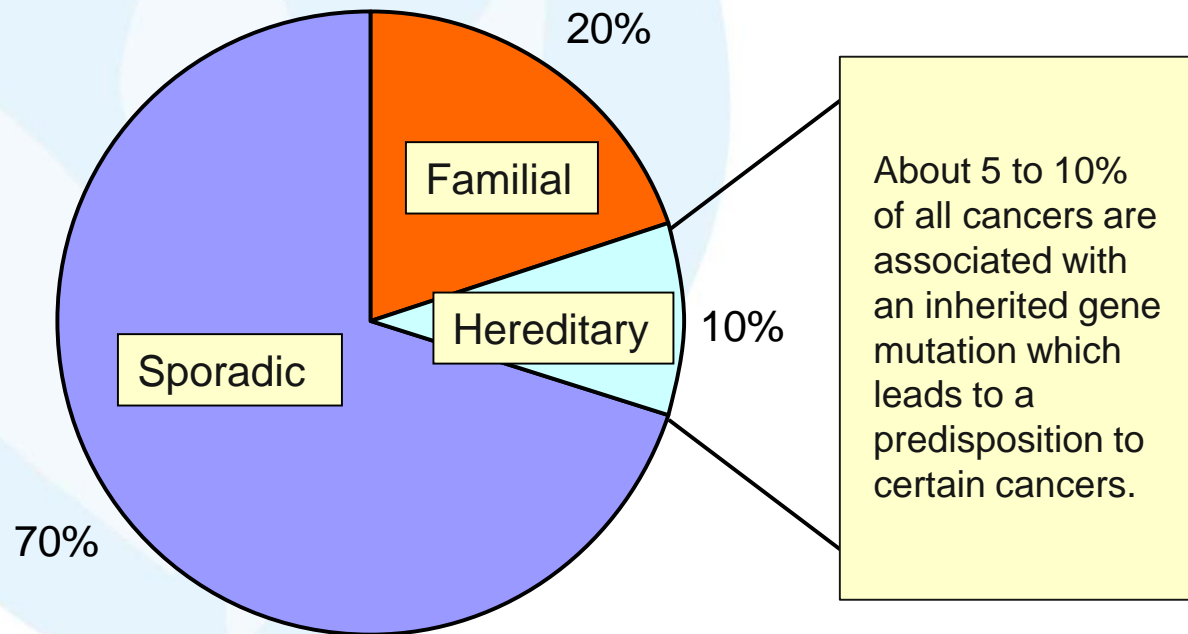
- Identify three features in a family history suggestive of hereditary risk for ovarian and/or uterine cancer
- Describe two potential benefits of genetic testing for cancer predisposition
- Describe two examples of risk management or risk reduction for high risk women



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Cancer Patterns in Families



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“Red Flags” ~

Some Indicators of a Possible Hereditary Cancer Syndrome

- 🚩 Personal or family history of cancer before the age of 50
- 🚩 Personal or family history of more than one type of cancer or the same cancer occurring more than once
- 🚩 Cancer in at least two generations in a family
- 🚩 Family history of certain types of cancers that fit a known hereditary pattern
- 🚩 Male breast cancer
- 🚩 Breast and/or ovarian cancer in an Eastern European Jewish family
- 🚩 Personal or family history of a large number of colon polyps



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Some of the More Common Hereditary Cancer Syndromes Involving Ovarian and Uterine Cancers

- Hereditary Breast and Ovarian Cancer Syndrome
(primarily breast, ovarian, prostate, and pancreatic cancers)
- Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer or HNPCC)
(primarily colorectal, uterine, ovarian, and stomach cancers; others less commonly)
- PTEN Hamartomatous Tumor Syndromes (Ex., Cowden Syndrome)
(primarily breast, uterine, thyroid, and colon cancers)
- Li-Fraumeni Syndrome
(primarily sarcomas, breast, brain, adrenocortical, and choroid plexus tumors; characterized by very early age of onset)
- Peutz-Jeghers Syndrome
(primarily breast, colon, pancreatic, gastric, ovarian, and uterine cancers; others less commonly)



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Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

- Results from a mutation in the BRCA1 or BRCA2 gene
- Females *and* males have the BRCA genes; a child can inherit a BRCA mutation from their mother *or* their father
- More common in families of Eastern European Jewish descent than in other ethnic groups
- First-degree relatives (siblings, children, parents) of a mutation carrier have a 50% chance of having the same mutation



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HBOC, cont'd

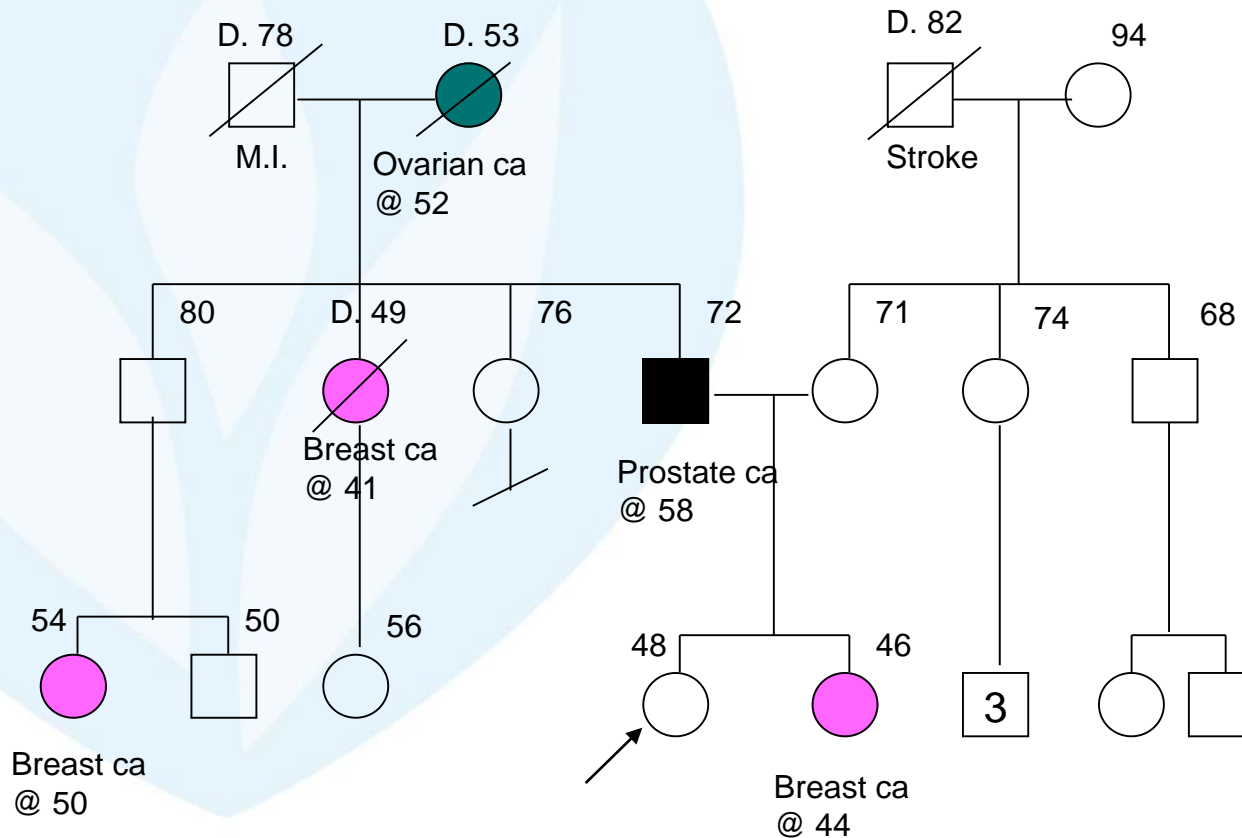
| Cancer Risk | BRCA Mutation Carrier | General Population |
|------------------------|-----------------------|--------------------|
| Breast cancer, females | Up to 87% | 12% |
| Ovarian cancer | Up to 44% | 1.5% |
| Prostate cancer | 20-25% | 10-15% |
| Breast cancer, males | Up to 8% | 0.5% |
| Pancreatic cancer | Up to 7% | <1% |



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Family History Suggestive of Hereditary Breast and Ovarian Cancer Syndrome



NOTE: The gene mutation can come from the maternal side *or* the paternal side of the family.

Lynch Syndrome (HNPCC)

- Results from a mutation in the MLH1, MSH2, MSH6, PMS2, or EPCAM gene
- Females *and* males have these genes; a child can inherit a mutation from their mother *or* their father.
- First-degree relatives (siblings, children, parents) of a mutation carrier have a 50% chance of having the same mutation.



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Lynch, cont'd.

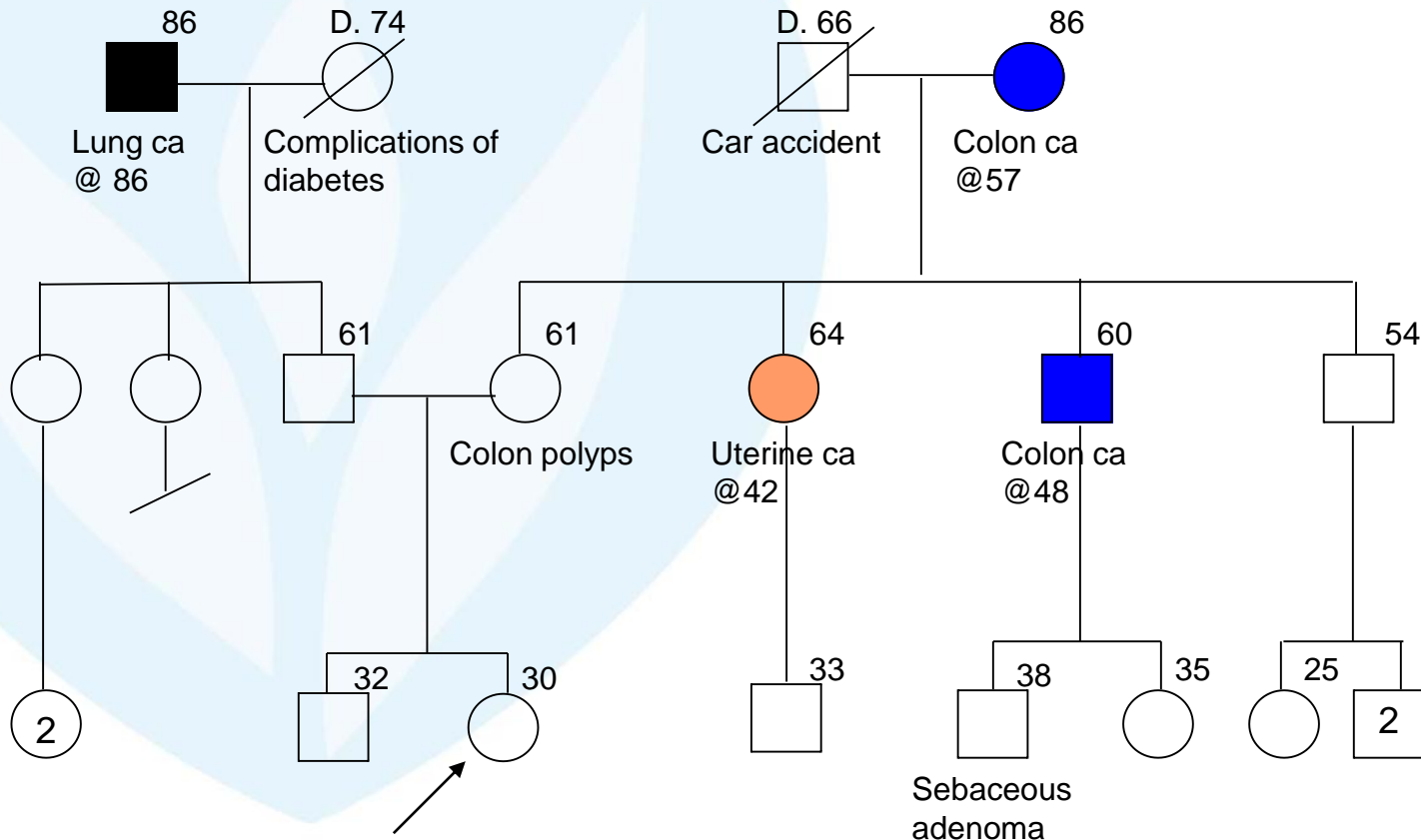
| Cancer Risk | Lynch Mutation Carrier | General Population |
|---|--|--------------------|
| Colorectal cancer | Up to 80% | 5.5% |
| Endometrial (uterine) cancer | Up to 70% | 2.5% |
| Stomach cancer | Up to 13% | <1% |
| Ovarian cancer | Up to 12% | 1.5% |
| Other cancers – urinary tract, brain, small bowel, pancreas, others | Risk is slightly elevated above that of the general population | <1% |



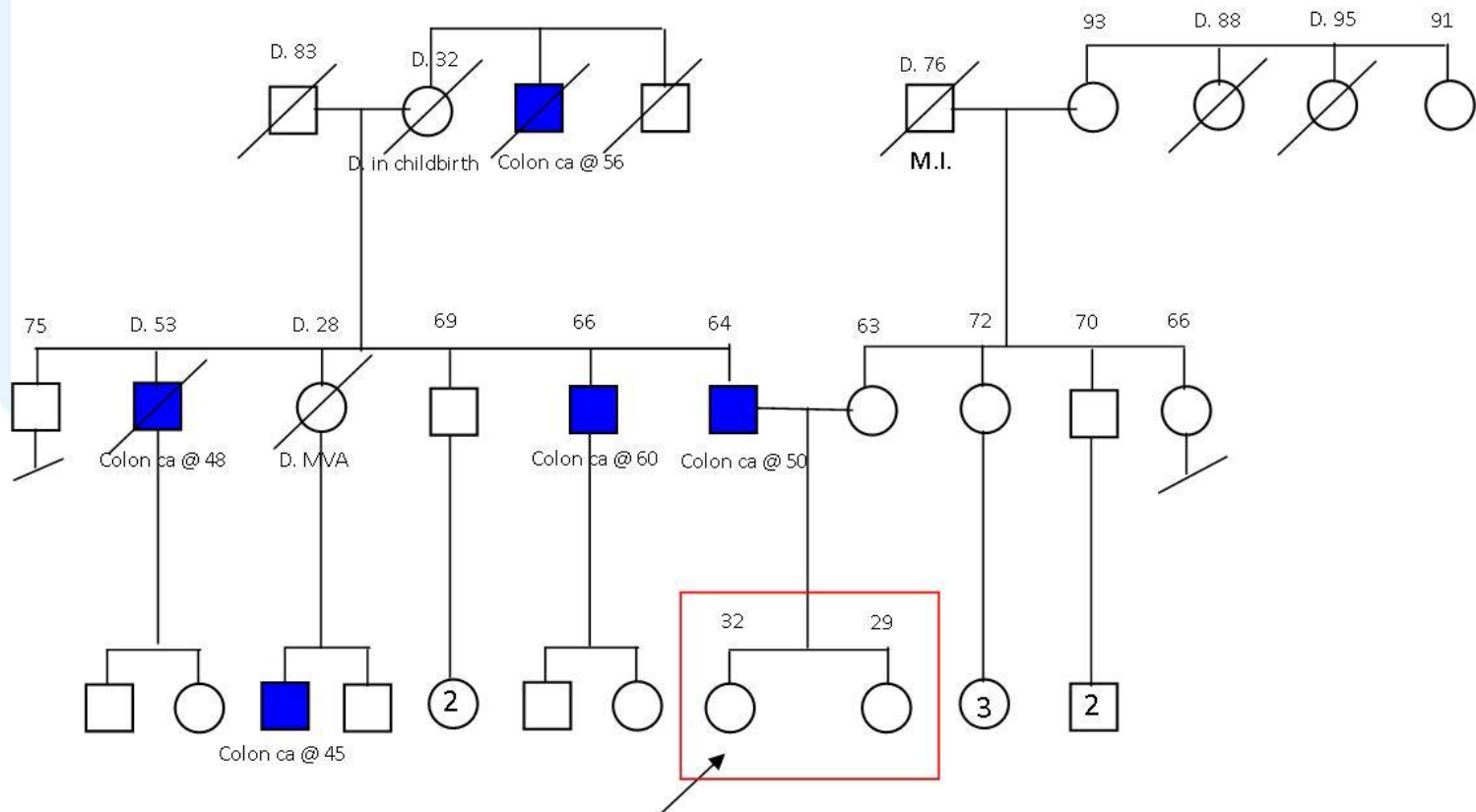
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Family History Suggestive of Lynch Syndrome



Looking At the Whole Picture and Asking the Right Questions – Why would these women need to worry about uterine or ovarian cancer?



Family History on *Both* Sides Matters!



GENETICS

This is how it works



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Genetic Testing

- Is available for many hereditary cancer syndromes
- Is one tool that can help determine if there is a hereditary predisposition to cancers in a family
- Usually involves just a blood test
- Is generally covered by insurance companies, Medicare, and Medicaid if there is a medical indication for the test
- May have implications for many family members



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Pre-Test Genetic Counseling

An integral part of the genetic testing process

- Helps determine if genetic testing is appropriate for the family
- Helps patients decide if they *want* testing
- Includes education about genetic testing, when relevant
 - Who is the most appropriate family member to test?
 - Advantages and disadvantages of testing
 - Possible results
 - Risk management options based on results
 - How results might impact other relatives
 - Explanation of insurance coverage
 - *Which* test(s) are indicated?
- Helps determine if records are needed from other family members
- Is required by some insurance companies



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Take Home Message

FOR Attendees

DATE Nov. 19, 2015

While You Were Out

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OF Hunterdon Regional Cancer Center

| | | | |
|-----------------|----------|-------------------|----------|
| TELEPHONED | | PLEASE CALL | |
| CAME TO SEE YOU | X | TAKE HOME MESSAGE | X |

MESSAGE Risk assessment does not always involve genetic testing.



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Post-Test Genetic Counseling

- Meet with patient in person to discuss test results
- Discuss implications of findings/cancer risks when a mutation is found
- Discuss recommendations based on findings
 - Based on the mutation, when present
 - With no mutation, risk calculations and risk management recommendations are based on family history and other risk factors
- Discussion of implications for other family members
 - Which family members would be impacted if patient has a mutation?
 - At what ages is testing appropriate?
 - With no mutation, should other family members still consider testing?
 - With no mutation, do other family members still have increased cancer risk?
- Explanation of ambiguous findings, such as “variants of unknown significance”
- When needed, assistance with communicating information to other family members
- Discussion of reproductive options
- Is enrollment in research appropriate?

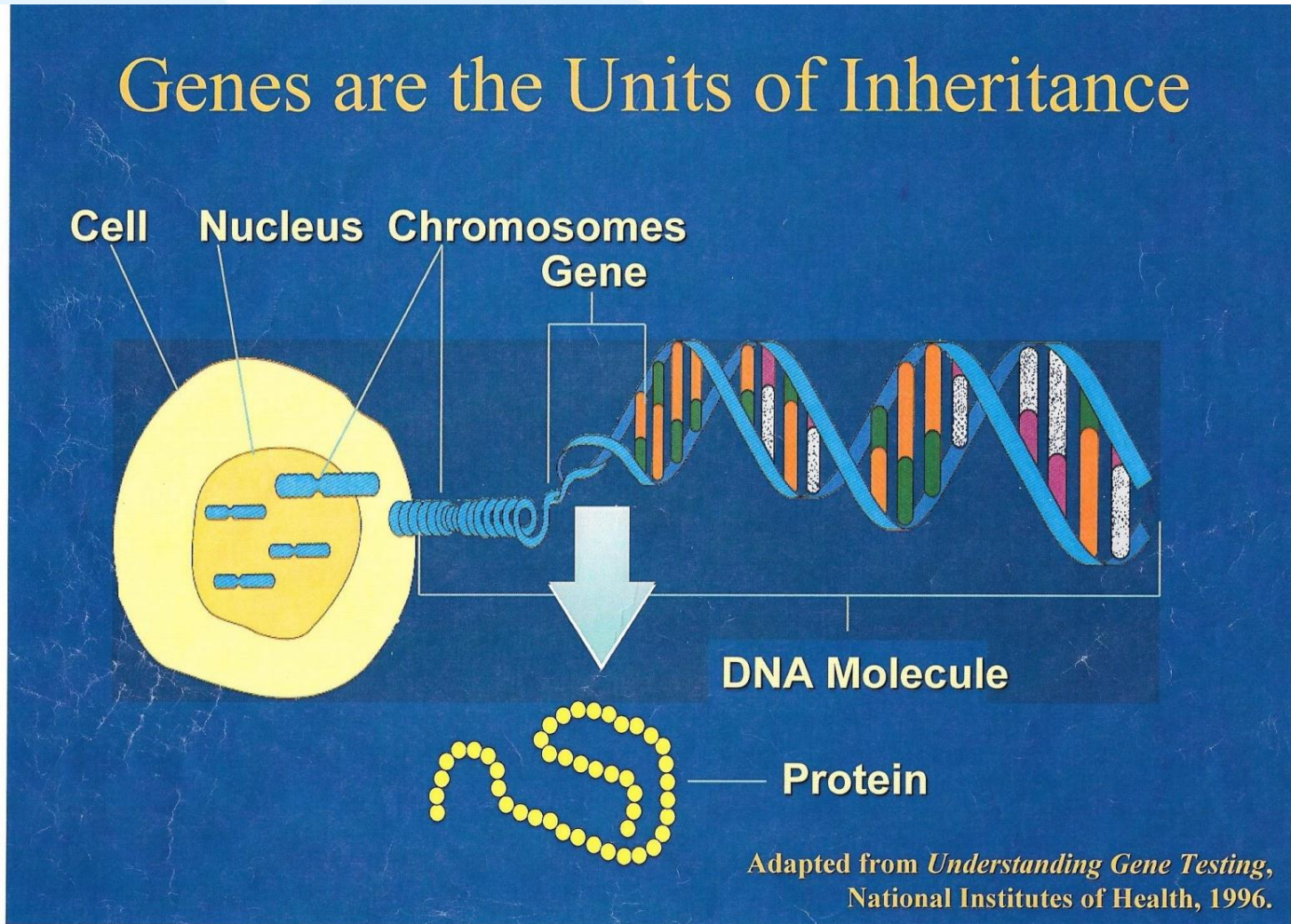


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Genes/DNA

Genes are the Units of Inheritance



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“Genes are the of inheritance”

“Mercer County Community College is located in”

ABC



What would “Spell Check” say about these sentences?



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Move From Single Syndrome Testing to Gene Panel Testing

Recent advent of tests which include *multiple* genes associated with hereditary predisposition to certain cancers

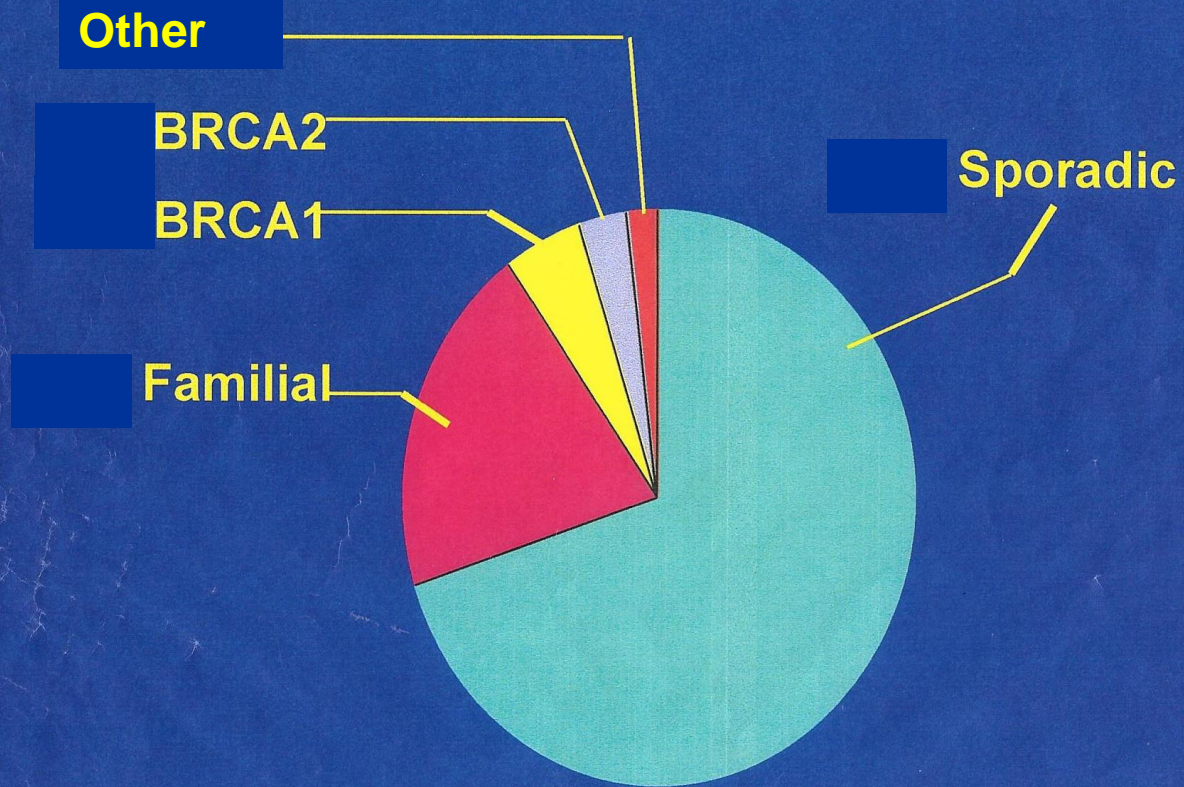
(vs. testing for one cancer syndrome at a time via “process of elimination” method)



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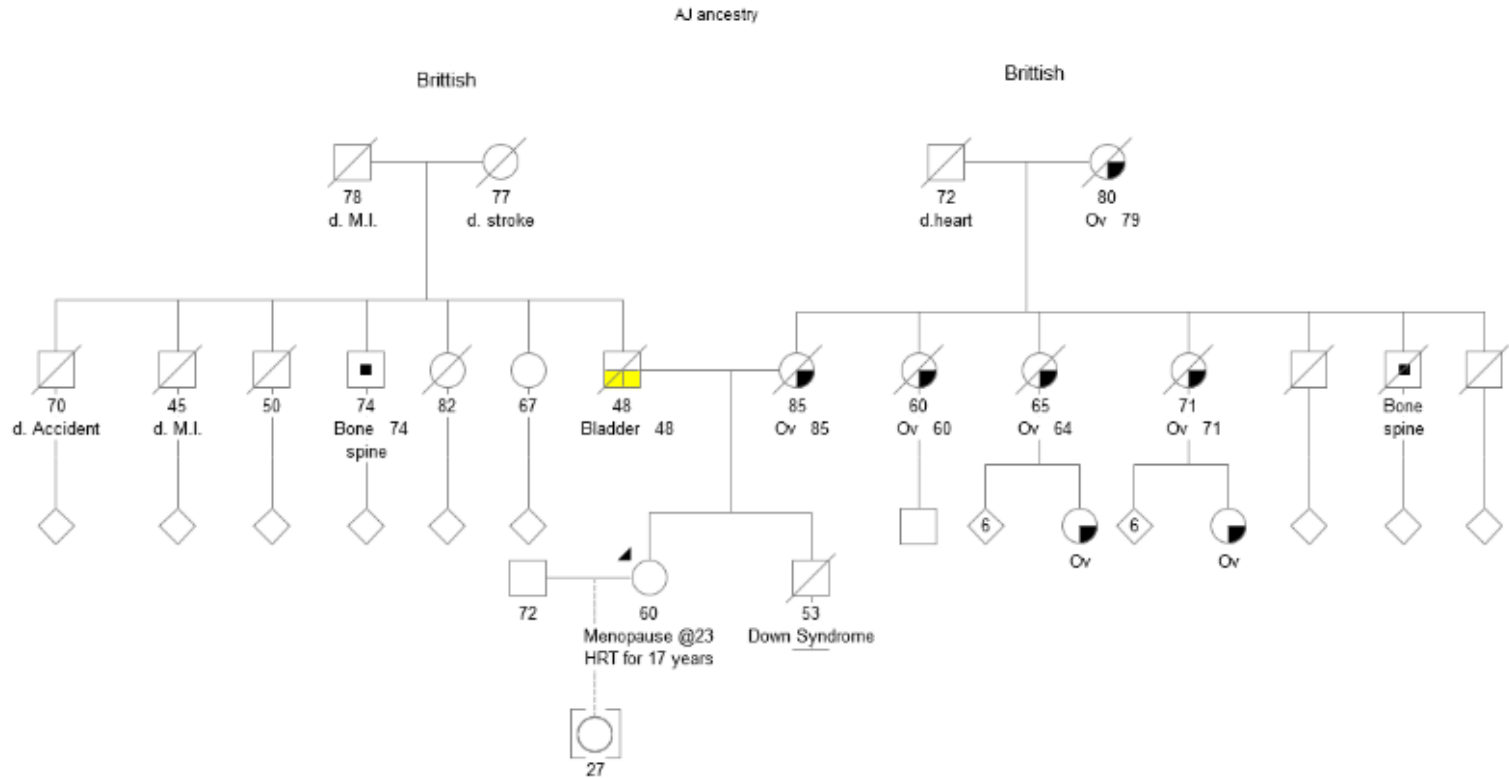
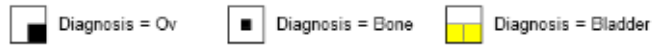
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Ovarian Cancer Patterns



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Multi Gene Tests

Ovarian Cancer Panel

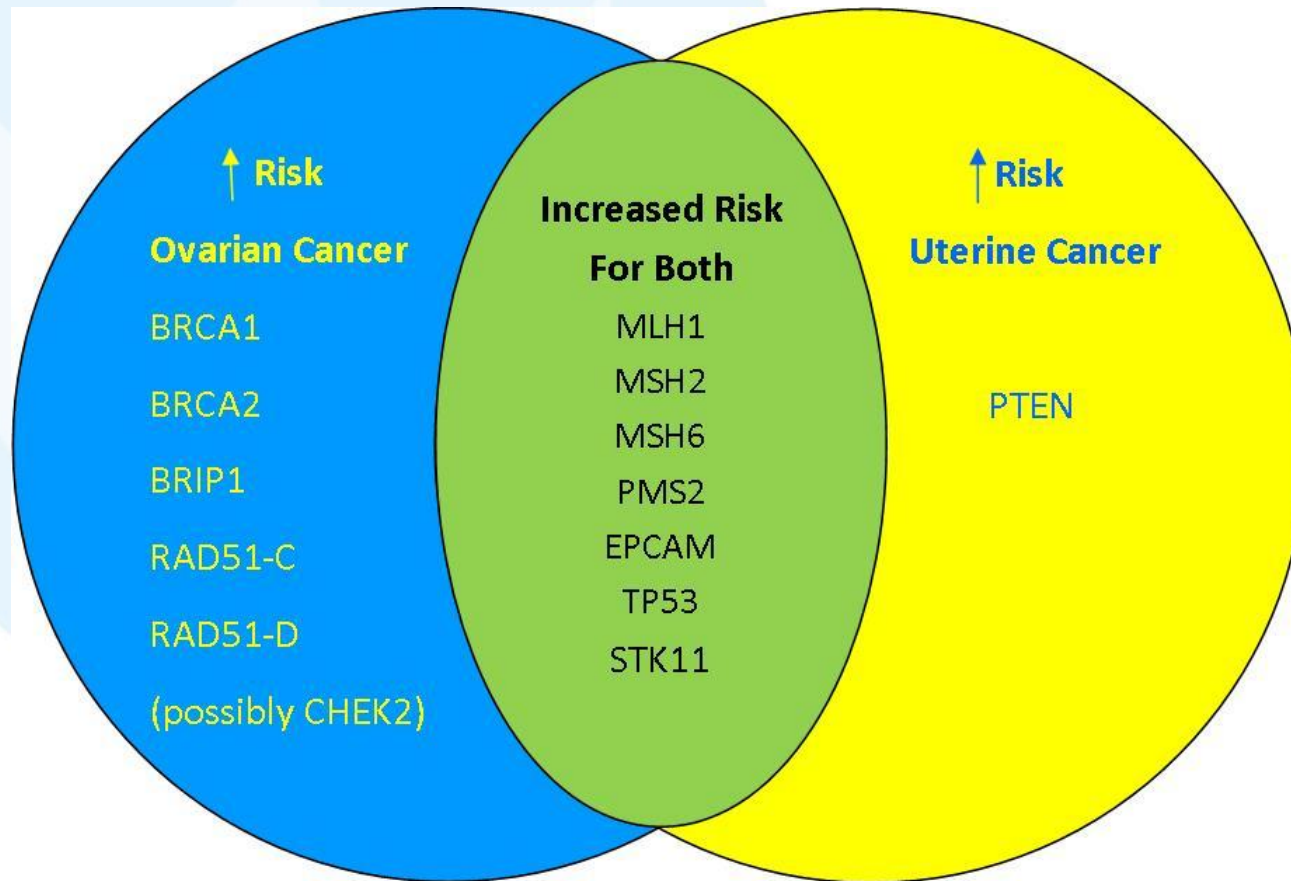
- **BRCA1**
- **BRCA2**
- **BRIP1**
- **CHEK2**
- **EPCAM**
- **MLH1**
- **MSH2**
- **MSH6**
- **PMS2**
- **RAD51C**
- **RAD51D**
- **STK11**
- **TP53**



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Overlap Between Ovarian and Uterine Cancer-Related Genes



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Application of Panel Tests

- Family history is highly suggestive of a hereditary cancer syndrome and single syndrome testing is uninformative
 - Ex: multiple cases of breast and ovarian cancer in a family but no mutation found on BRCA testing
- There are several hereditary cancer syndromes in the “differential diagnosis”
 - Ex: Multiple family members with uterine cancer plus:
 - colon cancer (suggestive of Lynch Syndrome)
 - breast cancer (suggestive of Cowden Syndrome)

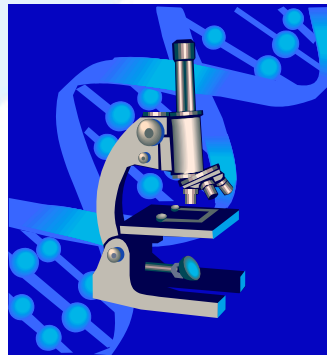


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Application of Panel Tests, cont'd.

- When insurance will pay for only one test – get the most information possible from that one test
- People who had genetic testing in the past with no mutation found may wish to consider re-assessment and additional testing
- Panel tests may be the way of the future for all genetic testing for hereditary cancer predisposition

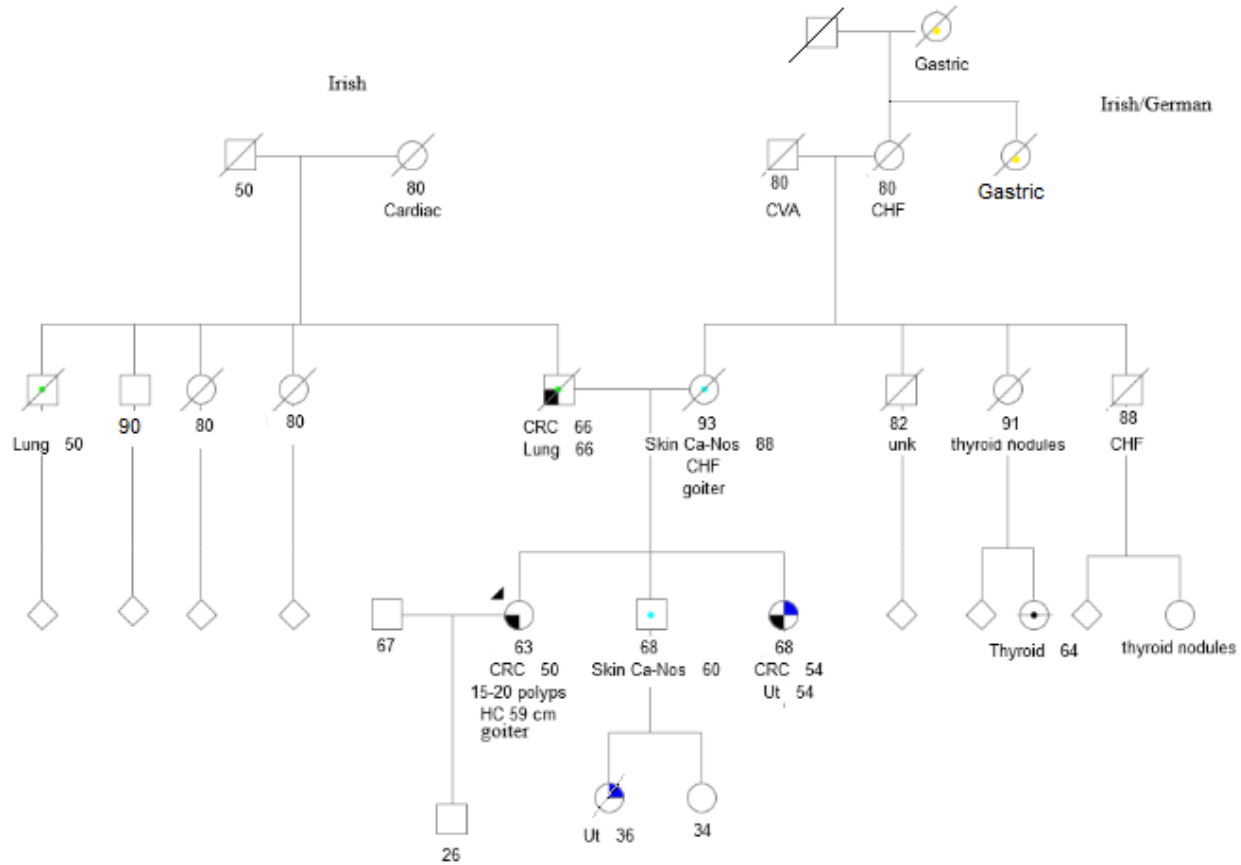


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- Diagnosis = Ut
- Diagnosis = Skin Ca-nos
- Diagnosis = Thyroid
- Diagnosis = CRC
- Diagnosis 2 = Ut
- Diagnosis = Lung
- Diagnosis 2 = Lung
- Diagnosis = Gastric



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Advantages of Panel Tests

- Answer more questions with one test
- Greatest amount of information in shortest amount of time
- Cost effective
- Good insurance coverage for tests



Disadvantages of Panel Tests

- For *some* genes on the panels, results could have limited utility
 - limited clinical data
 - no well-established guidelines for risk management upon finding of a mutation
- Greater likelihood (compared to single gene testing) of finding a variant of uncertain significance – inconclusive result



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MESSAGE Even if you have had risk assessment and/or testing in the past, you may benefit from an updated assessment.



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If You/A Family Member/A Patient Has Had Testing in the Past

Important to see an actual copy of the results

- *When* was the test done?
 - Type of testing – sequencing only or also large rearrangement testing?
- Which genes were tested?
- Was it completely negative, or was there a variant of unknown significance?



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Risk Management

- There are specific risk management recommendations for HBOC, Lynch Syndrome, Cowden's, and other hereditary cancer syndromes.
 - increased screening and surveillance
 - chemoprevention
 - risk-reducing surgeries
- Guidelines are updated every year.



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Risk Management for Ovarian Cancer

- Risk-reducing bilateral salpingo-oophorectomy (surgical removal of ovaries and fallopian tubes)
 - after completion of child-bearing; typically not before age 35
 - *Counseling is critical* re: psychosocial and quality-of-life issues
 - Removal of tubes alone is not standard of care; research is being done
- Screening: trans-vaginal ultrasound + ca-125 blood test
 - not highly accurate, but considered for high risk women over age 30 if child-bearing is not complete or if there are other reasons to not do surgery



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Risk Management for Uterine Cancer

- Prophylactic hysterectomy considered for women who have completed childbearing
 - For women at increased risk for both uterine *and* ovarian cancer (e.g., Lynch Syndrome), consideration of removal of uterus, ovaries, and fallopian tubes
- Screening: endometrial biopsies, trans-vaginal ultrasound
 - Not highly accurate, but may be considered; should be discussed with healthcare provider
- Education re: signs & symptoms of uterine and ovarian cancer is important for high risk women



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Ethical, Legal, and Social Issues

(there are many...these are just a few)

- Fundamental principles of bioethics apply to the cancer risk assessment process:
 - Respect for autonomy
 - Beneficence
 - Nonmaleficence (Do no harm)
 - Justice
- Genetic testing of children is indicated only if:
 - Onset of disease is likely to occur in childhood
 - Effective risk management interventions are available
 - The genetic test can be clearly interpreted
- Protection against genetic discrimination:
 - HIPAA offers some protections
 - Genetic Information Non-discrimination Act (GINA) – federal law that protects consumers from discrimination by health insurers and employers on the basis of genetic information (there are exceptions)
- Disclosure of genetic information to at-risk relatives
 - Does the healthcare provider have a duty to inform at-risk family members of a cancer-predisposing gene mutation in the family if the patient does not intend to share the information??
- Accidental discovery of non-paternity through genetic testing



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Advantages of Risk Assessment

Personalized,
interactive
education and
counseling

Information that
can benefit you
and your family
members

Individualized
prevention and
screening
recommendations

Assistance in obtaining
insurance coverage for
some screening
procedures

Peace of mind for
some family
members

Feeling of
empowerment from
being able to take
steps to reduce the
risk of cancer

Assistance with
communicating risk
information to
family members



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Questions?

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