The Role Genetic Counseling and Testing for the General Internist

23rd Annual Internal Medicine Board Review Course
Savannah, GA
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Objectives

• Understand the role of the general internist in genetic testing

• Recognize patients at high risk for genetic disorders

• Review ethical, legal and psychological impacts of genetic testing
Case Study

• 35 year old Mary, whose mother died of colon cancer at age 50, whose cousin died of colon cancer at age 45, and whose uncle was diagnosed with colon cancer a year ago (at age 52).
Case Study

• Is genetic testing appropriate?
### AAFP GENES Red Flags

<table>
<thead>
<tr>
<th>Features</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td><strong>Group of congenital anomalies</strong></td>
<td>While anatomic variation is normal, the presence of multiple variations may be indicative of a genetic syndrome.</td>
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<tr>
<td><strong>Extreme or exceptional presentation of common conditions</strong></td>
<td>Examples of this include the onset of disease at a younger than average age, unusually severe presentation of illness, multiple primary cancers, recurrent miscarriages.</td>
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<tr>
<td><strong>Neurodevelopmental delay or degeneration</strong></td>
<td>Developmental delay or regression in children and early onset dementia in adults may be a sign of a genetic condition.</td>
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<tr>
<td><strong>Extreme or exceptional pathology</strong></td>
<td>Some tumor pathologies may be suggestive of an inherited condition. Examples include medullary thyroid cancer, pheochromocytoma, plexiform neurofibromas, and multiple colon polyps.</td>
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<tr>
<td><strong>Surprising laboratory values</strong></td>
<td>Certain laboratory values may indicate an inherited defect in metabolic or clotting pathways. Examples include elevated fasting transferrin-iron saturation and cholesterol level &gt;500 mg/dL.</td>
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# Interpreting the History

<table>
<thead>
<tr>
<th>Average Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
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<tbody>
<tr>
<td>• No known family history, <strong>OR</strong></td>
<td>• One first degree relative (FDR) with onset of disease at an average age, <strong>OR</strong></td>
<td>• Premature disease or unusual presentation in an FDR</td>
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<tr>
<td>• Only one second or more distantly related relative</td>
<td>• Two second degree relatives (SDR) on the same side of the family*</td>
<td>• 2 ≥ affected FDRs*</td>
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<td></td>
<td></td>
<td>• 2 ≥ SDRs, with at least one having premature onset*</td>
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<td>• 3 ≥ affected relatives*</td>
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<td></td>
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<td>• Moderate risk status on both sides of the family</td>
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* Relatives must be on the same side of the family.
Case Study

• Mary and her doctor the first step to answering that question was the collection of Mary's family medical history.

• Mary had to call a few relatives to confirm cancer diagnoses and the ages that people were diagnosed with the cancer.
Case Study

• While talking to her aunt, she found out that another cousin had been diagnosed with endometrial cancer. Mary's doctor suggested that she collect medical records from her family members to help confirm the history. To do this, Mary sent medical release forms to the hospital that treated her mother and to her living uncle with cancer.
Case Study

• Upon review of Mary's history, it was clear to her doctor that there were many people in her family who had developed colon cancer at an early age.

• Mary's doctor felt that the pattern of cancers seen (colon and endometrial) fit a pattern of Hereditary Nonpolyposis Colorectal Cancer (HNPCC).
Case Study

• For HNPCC, there is a screening test called MSI testing that may be done before genetic testing.

• A positive MSI test gives clues that there may be an HNPCC mutation.

• MSI testing is done on tumor samples.
Case Study

• Mary's doctor explained this test to Mary and the implications for her and her family.
• Because Mary herself did not have cancer, Mary's doctor (with Mary's permission) requested tumor tissue from Mary's mother's tumor for MSI testing from the hospital where she had her colon cancer surgery.
Case Study

• After a few months, the results from MSI testing were completed.

• Mary's doctor explained that Mary's mother's tumor was MSI-high, which suggested that her mother might have had a mutation in one of the genes causing HNPCC.
Case Study

• The next question was who in the family, if anyone, should be tested for the actual genes involved in HNPCC.

• Mary wanted to be tested, but her doctor explained that if she tested negative they would not know if she was negative because she did not inherit the mutation in the family or if the mutation was in a gene that was not being tested.
Predictive values

• Penetrance - likelihood of developing disease given inheritance of a disease-causing mutation

• Variable expressivity - phenotypic variations in the way the disease is expressed
Validity and Utility

• Validity - the ability of a genetic test to predict a disease phenotype

• Examples:
  – APC gene - virtually all individuals who test positive will develop familial adenomatous polyposis (FAP)
  – APOE e4/e4 genotype - 30 percent chance of developing Alzheimer's disease
Case Study

• Mary agreed to ask if her affected uncle Evan would be willing to go through genetic testing first.
• If Evan tested positive, then Mary could go through testing.
• Evan agreed to consider testing, but wished to be seen at a medical facility closer to where he lived.
Case Study

• Evan's wife was worried about how this might affect their children and grandchildren.

• One of their children had previously died of colon cancer and another one had endometrial cancer.

• They had a third child who had not had cancer.
Case Study

• The genetic counselor explained that if the test result was positive that their living children could be tested for the mutation in the family.

• If it was negative, they would be "off the hook" and back to population risk.

• If the test was positive, surveillance guidelines would be recommended for them.
Case Study

• Evan asked about insurance discrimination based on genetic testing.
• The counselor said that although there were no good studies showing that genetic discrimination happened, they could keep his result confidential if he did not use his insurance to pay for the test.
Genetic Information Nondiscrimination Act (GINA)

- Enacted in 2008
- Prohibits discrimination by health insurers and employers on the basis of genetic information.
- Most states also have additional legislation protecting against the use of genetic information by health insurers and employers.
Case Study

- Evan and his wife reviewed their concerns and questions with the genetic counselor.

- Evan wanted black and white answers: should he be tested or not.
Case Study

• However, the genetic counselor could only tell him that this was a very personal decision and should be made based on and what benefit it might provide for Evan and his family, and with a thorough understanding of the risks involved.
Case Study

• Ultimately, Evan decided to go through genetic testing for HNPCC to benefit his children, grandchildren, nieces and nephews.
Case Study

• The next day DNA was extracted from the tube and over the next few weeks the lab sequenced the common genes that cause HNPCC.

• When a change was found in one of his genes, the laboratory resequenced the DNA to confirm their result.
Case Study

• To further ensure accuracy, the laboratory director reviewed the data and the result, and double-checked all the identification numbers.

• The result was sent back to Evan's genetic counselor with an explanation that the change in the gene was likely to be the cause of Evan's syndrome.
Case Study

- Evan returned to the genetic counseling clinic to receive his genetic test result.
- His niece Mary and his wife came with him.
- The genetic counselor that had seen Evan before told him that his genetic test had come back positive.
Case Study

• There was now a known mutation in the family that could explain the colon and endometrial cancers.
• The genetic counselor reviewed the value of this test.
• Evan is at increased risk for a secondary colon cancer.
Case Study

• Because of this, it is recommended that he have regular colonoscopies.

• He is also at slightly increased risk for some upper GI cancers.
Case Study

- The counselor explained that this mutation was likely the cause of the colon cancer and endometrial cancer seen in two of Evan's daughters.
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Case Study

• Although Evan was upset that he had passed on a faulty gene to his daughter who had died of colon cancer, his wife consoled him that now they could do something to protect their two younger children.
Case Study

• Because Evan was found to have a mutation known to cause HNPCC, other relatives in his family could now be tested for the same mutation.

• The genetic counselor reviewed the pros and cons of genetic testing for Mary.
Case Study

• If Mary tested negative for the mutation in the family, she would be at the same risk for colon cancer as other people in the general population.
Case Study

• Mary had her blood drawn and sent to the same laboratory that conducted the testing for her uncle.

• Because the laboratory only needed to look for the one mutation in the family rather than screening the genes for HNPCC for mutations, the test was less expensive and much quicker.
Case Study

• After a few weeks, Mary met with her doctor for results of the test.

• She did not inherit the mutation that her uncle and mother had shared.
Case Study

• Other family members, such as Mary's brother and sister, however were still at risk for inheriting the mutation.

• With her doctor's help, Mary drafted a letter to send to all of her at risk family members.

• The letter discussed the family's increased risk for colon and other cancers and that testing was available.
Case Study

• Her brother Tom decided that he would not have testing at this point, but would have regular colonoscopies for screening.

• Alice was found to carry the same mutation in the HNPCC gene as her uncle.
Case Study

• Because Evan and Alice tested positive for a known mutation, they were given specific medical recommendation for cancer screening.
Case Study

- Because genetic testing is new and medical information on genetic disorders is evolving, family members and individuals who have gone through testing need to keep up to date.
Case Study

• Some testing centers may offer the latest in clinical trials or be able to relay the results of clinical trials that are relevant to mutation carriers or high-risk individuals.
Review

• Testing can be diagnostic or predictive

• Primary care physicians are front line

• Family history is the first step

• High risk patients should be referred for genetic counseling
Review

• Ethical, legal and psychosocial ramifications are significant

• Consider the individual and the family

• Offer long term support
QUESTIONS?

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