Objectives:

What are your objectives?
The participant will be able to-
• Describe the underlying basis of the genetics of cancer
• Distinguish the role of gametic and somatic mutation in the etiology of cancer
• Understand the value of family history in defining risk for hereditary cancer syndromes
• Understand the value of genetic counseling in assisting the patient deciding if genetic testing will be helpful to them and their family

References

Genetics of Colorectal Cancer. NCI Bookshelf, Aug 14, 2017. PDQ Editorial Board. (818 references)-162 pgs
https://www.ncbi.nlm.nih.gov/books/NBK126744/

https://www.ncbi.nlm.nih.gov/books/NBK65784/

Genetics of Breast and Gynecologic Cancers. NCI Bookshelf, Aug 14, 2017. PDQ Editorial Board.215p (1324 refs.)
https://www.ncbi.nlm.nih.gov/books/NBK126744/

All cancers are genetic: involves gene change: mutation, deletion, duplication, rearrangement etc.
BUT

most cancers are not inherited from one's parents....but some are! 5-10% are Hereditary cancer syndromes
All Cancer Arises From Genetic Mutation

Germline
- Present in egg or sperm
- Can be inherited from mom or dad
- Cause cancer family syndrome

Somatic
- Occur in nongermline tissues
- Cannot be inherited
- “Acquired”

Parent
Harmful → Harmful
Mutation in egg or sperm all cells
Mutations in all cells in offspring
Child
Harmless → Harmless
Mutations in tumor only (for example ovary, breast)

NCI, ASCO, 2016

Mutations in Specific Genes are Responsible for Hereditary Risk of Cancer

Types of proteins

- Enzymes for mismatch or excision repair

- Repair DNA mutations

- Tumor suppressor gene

- Checkpoint molecules

- DNA repair gene mutation

- Growth factors

- DNA repair gene mutation

- Repair DNA mutations

- Tumor suppressor gene

- Checkpoint molecules

- Oncogene

- Tumor suppressor gene

- Growth factors

Complex Roles Of Cancer Genes: BRCA 1 & 2

6 Different Roles

Center for Genetic Counseling & CPN

3 Common types of cancer-causing genes

<table>
<thead>
<tr>
<th>Type of gene</th>
<th>Normal function</th>
<th>Mutated function</th>
<th>Types of proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncogene (proto-oncogene)</td>
<td>Promotes division</td>
<td>Promotes division - abnormal time or cell type</td>
<td>Enzymes for mismatch or excision repair</td>
</tr>
<tr>
<td>Tumor suppressor gene</td>
<td>Suppresses cell division</td>
<td>Fails to suppress division</td>
<td>Checkpoint molecules</td>
</tr>
<tr>
<td>DNA repair gene mutation</td>
<td>Repair DNA mutations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Center for Genetic Counseling

Probability of Developing Invasive Cancers Over Selected Age Intervals by Sex, United States 2000 to 2002

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Age Group</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>40-49</td>
<td>1.25</td>
<td>0.67</td>
</tr>
<tr>
<td>Lung</td>
<td>50-59</td>
<td>0.94</td>
<td>0.40</td>
</tr>
<tr>
<td>Colon</td>
<td>60-69</td>
<td>0.85</td>
<td>0.38</td>
</tr>
<tr>
<td>Prostate</td>
<td>70-79</td>
<td>0.70</td>
<td>0.34</td>
</tr>
<tr>
<td>Endometrium</td>
<td>80+</td>
<td>0.55</td>
<td>0.20</td>
</tr>
<tr>
<td>Skin</td>
<td>90+</td>
<td>0.40</td>
<td>0.14</td>
</tr>
<tr>
<td>Bone</td>
<td>90+</td>
<td>0.35</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Center for Genetic Counseling & CPN
What are the common hereditary cancer syndromes internists will encounter?

**HEREDITARY BREAST & OVARIAN CANCER**

**LYNCH SYNDROME: HNPCC**

**HEREDITARY PROSTATE CANCER**

List of Chromosome assignments for common hereditary cancer syndromes

- 2p16 MSH2 Lynch Syndrome colon cancer
- 2p16 MSH6 Lynch Syndrome colon cancer
- 3p21 MLH1 Lynch Syndrome colon cancer
- 7p22 PMS2 Lynch Syndrome colon cancer
- 13q12 BRCAl2 Hereditary Breast & Ovarian Cancer Syndrome (HBOC)-Prostate
- 17q21 BRCAl HBOC-Prostate
- 8q21.3 NBN Prostate and breast cancer

Half of the population have had a 1st or 2nd degree relative diagnosed with cancer

- 1st degree (parents, siblings, children)
- 2nd degree (grandparents, aunts, uncles, nieces, nephews)

Lynch Syndrome (Hereditary Non Polyposis Colon Cancer=HNPCC)

Accounts for 3-5% of colon cancer

1 in 300 carry one of the five mutated genes

Clinical Tip Offs: Colon cancer at 50 or younger; 1st degree relatives with colon, endometrial, breast cancer or other associated cancers

Variants: Muir-Torre (skin cancers) Turcot (glioma)

HNPCC associated Cancer Risks

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>52-82%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>24-66%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>20-24%</td>
</tr>
<tr>
<td>Stomach</td>
<td>11-19%</td>
</tr>
<tr>
<td>Liver, Bile Duct</td>
<td>2-7%</td>
</tr>
<tr>
<td>Urinary Tract</td>
<td>1-5%</td>
</tr>
<tr>
<td>Other</td>
<td>Pancreas, breast, sm bowel</td>
</tr>
</tbody>
</table>
Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

Tip Offs from Family History

- Breast Cancer <50 yo
- Triple Negative (Est/Prog/HER2<60
- Ovarian Cancer at any age
- Bilateral breast cancer
- Many relatives with breast cancer in several generations
- Male breast cancer
- Pancreas and prostate (>Gleason 7) in family
- Ashkenazi Jewish Ancestry in Family

Same High Penetrant-RISK BRCA 1 & 2

Gene Can Increase Risk of Other Non Breast Cancers

- OVARIAN; TUBAL OVARIAN; PERITONEAL
- PROSTATE (19-39%) BRCA 2 very aggressive
- PANCREATIC (1-8%)
- MELANOMA (5% BRCA 2) & GASTIC (BRCA 2)
Hereditary Prostate Cancer

5-10% of patients with prostate cancer have hereditary

BRCA 1 and 2 account for 50% of those with hereditary

Ethnic variation is great among sporadic cases 6 fold between African American and Asian men not as striking among hereditary predisposed men

RED FLAGS FOR HEREDITARY PROSTATE CANCER

Gleason Score >7

Metastatic Prostate Cancer

One or more Family Member:

Breast cancer = <50 yo onset

Ovarian cancer any age

Pancreatic cancer

Family History Tip Offs might be Hereditary PC

Hopkins Criteria Family History any one of

1. 3 or more 1st, Degree relatives
2. Prostate cancer in 3 or more generations
3. 2 relatives with onset before 55 years of age
4. Metastatic prostate cancer

12 Genes with reported HEREDITARY PROSTATE CANCER RISK

BRCA1  BRCA2  ATM  CHEK2  EPCAM  HOXB13
MLH1  MSH2  MSH6  NBN  PMS2  TP53

Choose the one patient who would not qualify for insurance coverage for genetic testing if they should want it.

A. Medicare Insurance only female 66yo and no cancer, but family history of breast cancer in 2 first degree and 2 second degree relatives.
B. Male with colon cancer at 45 whose father had colon cancer. Immunohistological pathology showing missing MSH2 and MSH6 gene proteins.
C. Son at 40 with markedly elevated PSA whose father had prostate cancer (PC) at 50 and grandfather died with PC at 55. Mother had breast cancer.
D. Adopted woman with ovarian cancer at 62.
E. Woman with breast cancer at 49; mother breast cancer at 62; two first degree relatives with melanoma.

Correct Ans=A

Medicare Regulations: Medicare.gov.

Medicare requires that the patient have cancer in order to undergo genetic cancer testing even though the patient may meet NCCN guidelines for HBOC or Lynch Syndrome or prostate cancer testing.
Audience Question:

Which one of the following IM patients should be referred for cancer genetic counseling?

A. 75 yo gentleman with colon cancer whose tumor upon oncotesting was found to have an APC variant gene with an allele freq. of 10% and no family hx of cancer.
B. Another 65 yo with colon cancer tumor immunochemistry showing: MSH2, MSH6, PMS2 and MLH1 proteins present and no family history of cancer.
C. 45 yo lady with ovarian cancer. Mother has breast cancer.
D. 70 yo with breast cancer and family history of basal cell skin cancer only.

Correct Answer=C


Why refer for genetic counseling?

• Counselor informs patient if genetic testing may benefit patient and other family members may be a risk, cost, and insurance coverage issues

1. May change treatment and prognosis
2. May change screening recommendations
3. May identify other family members at very significant risk for hereditary cancer syndromes
4. May prevent other cancers in patient and at risk family members
5. May relieve anxiety if no mutations identified.

Lets Demonstrate Genetic Counseling:

The Center for Genetic Counseling
Cara S Dresbold, MS, LCGC and Glenn Bingle, MD PhD
Breast and GYN Cancer Guideline-Based (19)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1, BRCA2</td>
<td>Hereditary Breast and Ovarian Cancer</td>
<td>Breast, Ovarian, Male Breast, Prostate, Pancreatic, Melanoma</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Lynch Syndrome</td>
<td>Colon, Uterine, Ovarian, Gastric, Hepatobiliary/Urinary tract, CNS, Skin</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden Syndrome</td>
<td>Breast, Thyroid, Uterine, Colon, Kidney, Skin, benign findings</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni Syndrome</td>
<td>Breast, Sarcoma, Leukemia, Brain, Adrenocortical, Others</td>
</tr>
<tr>
<td>CDH1</td>
<td>Hereditary Diffuse Gastric Cancer</td>
<td>Diffuse Gastric, Lobular Breast</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jegher Syndrome</td>
<td>Breast, Colon, Pancreatic, Gastric, polyps</td>
</tr>
<tr>
<td>PALB2</td>
<td></td>
<td>Breast, Pancreatic</td>
</tr>
<tr>
<td>CHEK2</td>
<td></td>
<td>Breast, Colon, Prostate, Thyroid, Uterine, Ovarian</td>
</tr>
<tr>
<td>ATM</td>
<td></td>
<td>Breast, Pancreatic</td>
</tr>
<tr>
<td>NBN</td>
<td></td>
<td>Breast, Ovarian</td>
</tr>
<tr>
<td>BRIP1</td>
<td></td>
<td>Ovarian, Breast</td>
</tr>
<tr>
<td>RAD51C, RAD51D</td>
<td></td>
<td>Ovarian, Breast</td>
</tr>
<tr>
<td>NF1</td>
<td>Neurofibromatosis type 1</td>
<td>Breast, Neurofibromas</td>
</tr>
</tbody>
</table>

Breast, GYN, and Colon Cancer (33)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Familial Adenomatous Polyposis (FAP)</td>
<td>Colon, colon polyps, thyroid, duodenal</td>
</tr>
<tr>
<td>BMPR1A, SMAD4</td>
<td>Juvenile Polyposis</td>
<td>Colon, colon polyps, gastric, pancreatic</td>
</tr>
<tr>
<td>MUTYH</td>
<td>MUTYH-Associated Polyposis (MAP)</td>
<td>Colon, colon polyps, duodenal, uterine</td>
</tr>
<tr>
<td>PALB2</td>
<td></td>
<td>Breast, Pancreatic</td>
</tr>
<tr>
<td>CHEK2</td>
<td></td>
<td>Breast, Colon, Prostate, Thyroid, Uterine, Ovarian</td>
</tr>
<tr>
<td>ATM</td>
<td></td>
<td>Breast, Pancreatic</td>
</tr>
<tr>
<td>BRIP1, RAD51C</td>
<td></td>
<td>Breast, Ovarian</td>
</tr>
<tr>
<td>POLD1</td>
<td></td>
<td>Colon cancer, polyps, other</td>
</tr>
<tr>
<td>POLE</td>
<td></td>
<td>Colon cancer, polyps, other</td>
</tr>
<tr>
<td>GREM1</td>
<td></td>
<td>Colon Cancer, Colon polyps</td>
</tr>
<tr>
<td>BLM</td>
<td></td>
<td>Colon Cancer</td>
</tr>
<tr>
<td>GALNT12</td>
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<td>Colon Cancer</td>
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<tr>
<td>BARD1</td>
<td></td>
<td>Breast, Ovarian</td>
</tr>
<tr>
<td>DICER1</td>
<td></td>
<td>Ovarian</td>
</tr>
<tr>
<td>NBN, RAD50</td>
<td></td>
<td>Breast, Ovarian</td>
</tr>
<tr>
<td>SMARCA4</td>
<td></td>
<td>Ovarian</td>
</tr>
<tr>
<td>AXIN2</td>
<td></td>
<td>Colon Cancer</td>
</tr>
</tbody>
</table>

Limitations of Panel Testing

- Incidental findings, or “surprising” results
- Pathogenic mutations in genes with limited data on cancer risk
- Higher rate of variants of unknown significance