Objectives:
- Participants should be able to recognize appropriate patients to refer for genetic counseling and testing.
- Participants should be able to discriminate amongst the presented cancer genetic syndromes and select appropriately associated cancers.
- Participants should be able to question patients to determine whether genetic counseling and/or testing is relevant.

Learning Assessment:
- Which theory explains why autosomal dominant, hereditary cancer occurs at a younger age than sporadic cancer?
  1. Theory of Relativity
  2. Knudson’s Two Hit Hypothesis
  3. Vogelstein’s Model of Colon Cancer
  4. Law of Gravity

Learning Assessment:
- Pancreatic Cancer is associated with which hereditary cancer syndrome?
  1. Hereditary Breast and Ovarian Cancer Syndrome
  2. Hereditary Non-Polyposis Colorectal Cancer
  3. Peutz-Jeghers Syndrome
  4. All of the above

Learning Assessment:
- Which hereditary cancer syndrome is Autosomal Recessive in inheritance pattern?
  1. Li-Fraumeni Syndrome
  2. Hereditary Diffuse Gastric Cancer
  3. PMS2
  4. Familial Adenomatous Polyposis

Learning Assessment:
- Men cannot inherit hereditary breast and ovarian cancer, nor can they pass it on.
  True
  False
Identifying Genetics Referrals:
- Young age at onset
- High frequency of cancer
- Multiple affected generations
- Ethnicity
- Multiple primaries
- Bilateral cancers
- Clustering of specific cancers
- Rare cancers or unusual presentations

How to Interpret a Family History of Cancer:
Concerned?
- Discuss it with doctor
- Contact a Genetics Professional (counselor or physician)
Evaluate for:
- Number of cancers
- Type of cancers
- Age at diagnosis of cancers
- Number of generations with cancer
- Patient’s level of concern

A Genetics Professional Can Help Patients by:
- Explaining risks
- Guiding screening and management decisions
- Offering appropriate genetic testing
- Encouraging contact with family members who may also be at risk
- Coping with everyday concerns by suggesting lifestyle changes

Review of Genetics Basics!

Genetic Inheritance:

**Single Gene Disorders**

- Mendelian Inheritance

- **Autosomal Dominant**
  - One Copy of One Gene

- **Autosomal Recessive**
  - Two Copies of One Gene

- **Sex Linked On a Sex Chromosome**
  - (Men and Women)

Cancer Genetics:

Up to 10% of all cancers are inherited in a simple fashion
Most with Autosomal Dominant Inheritance
Development Pathway of Hereditary Cancer: Tumor Suppressor Genes

In hereditary cancer, one damaged gene is inherited in every cell of the body:

- 1 damaged gene 1 damaged gene
- 1 normal gene 1 normal gene
- Tumor develops

Tumor develops

Hallmarks of HBOC:

- Family history of:
  - Young Breast Cancer
  - Ovarian Cancer Any Age
  - Male Breast Cancer
  - Bilateral Breast Cancer
  - Multiple Primaries
  - Multiple Generations
- Sometimes seen:
  - Pancreatic Cancer
  - Melanoma
  - Colorectal Cancer
  - Prostate Cancer

BRCA1/2 Carriers

- Prophylactic oopherectomy best option for carriers
  - Reck et al., UGO, Vol. 16, 2006
- BRCA1/2 breast tissue studies indicate early anti-oestrogen treatment should prevent breast cancer
  - Bramley et al, BJC, Vol. 94, 2006
- HRT-Unaffected carriers can take HRT (low dose) until age 50 for symptoms from prophy BSO.
  - Affected carriers report similar QOL and depression symptoms to general Population of BSO’s.
  - Rebbeck et al, JCO, Vol. 23(31), 2005

Hereditary Breast (Ovarian) Cancer (negative BRCA1/2)

- 13% of BRCA negative families with strong history have mutation not detected by current clinical testing
- Screening under 50 is cost-effective in high-risk BRCA negative families
- Women from high risk non-BRCA families have as high as a 40% risk of breast cancer in the contralateral breast within 15 years
  - Shahidi et al., CANCER, Vol. 106, 2006
- Families with only breast cancer and a negative genetic test are not at increased risk for ovarian cancer
  - Requires further confirmation
  - Kauff et al, JNCI, Vol. 97(19), 2005
With Positive Test Result Members Can Have their Personal Risk Defined

Inherited Colon Cancer:

- Polyps Count!
- Important to note:
  - Number of polyps at each scope
  - Total number of polyps over a lifetime
  - Type of polyp
  - Location of polyp
  - Size of polyp
  - Age when polyps were found

Hereditary Non-Polyposis Colorectal Cancer (HNPCC):

- Colon/Rectal Adenocarcinoma
- Uterine Carcinoma
- Larynx Carcinoma
- Bile Duct Carcinoma
- Colon Polyps-Adenomas
- Small Intestine Adenocarcinoma
- Stomach Adenocarcinoma
- Breast Adenocarcinoma
- Ovarian Adenocarcinoma
- Renal Cell Carcinoma
- Renal Pelvis Transitional Cell
- Pancreatic Cancer

Muir Torre Variant:
- Sebaceous Neoplasia
- Breast Cancer

Turcot Variant:
- Brain Tumors-Glioblastoma

HNPCC Family History:

HNPCC Related Cancers

- Colon cancer: avg age at dx 45 yrs
  - 68-75% risk by age 65 yrs
  - 50% risk new primary
  - right-sided tumors
- Endometrial cancer: 40-60 yrs
  - 60% risk by age 70 yrs
- Ovarian cancer: avg age at dx 45 yrs
  - 12% risk by 70 yrs
Microsatellite Instability (MSI):

- Normal cells: Stable microsatellite patterns
- Tumor cells: MSIs

HNPCC:
- Sebaceous gland tumors can direct clinicians to inquire about family history and in turn lead patients to early screening and detection
  - Tsai et al., WUSO, Vol. 4, 2006
- MLH1 de novo mutation reported
  - Stulp et al., WJG, Vol. 12(5), 2006

HNPCC associated $PMS2$:
- Gene: $PMS2$
- Syndrome: Childhood Cancer and CRC
- Presentation:
  - AD; low penetrance
  - CRC appears sporadic
  - AR; childhood cancers and clinical spectrum
- Homozygous $PMS2$:
  - Café-au-lait spots/patches
  - Unusual tumor spectrum:
    - T-cell ALL
    - NHL
    - Supratentorial Primitive Neuroectodermal Tumors
    - Intracerebral Glioma
    - Medulloblastoma
  - Colon polyps/CRC
  - Increased risk of second primary malignancy

FAP:
- Colon: 100’s of polyps
- Desmoid
- Osteomas
- Bilateral CHRPE
- Small bowel
- Stomach
- Thyroid
- CNS
- Liver
- Bile duct
- Adrenal gland
- Attenuated FAP:
  - usually less than 100 cumulative polyps
  - often right-sided
  - mean age of polyph onset in 40’s – 50’s

AFAP is caused by mutations in the same gene that causes FAP, APC, the AFAP mutations tend to be in a different area of the gene, we do not understand why this makes a different disease.

Peutz-Jeghers Syndrome:
- Colon/Rectum Cancer
  - Polyps-Hamartomas
- Cervical Cancer
- Breast Cancer
- Lung Cancer
- Anemia
- Pancreatic Cancer
- Small Intestine
- Stomach-Hamartomas
- Pigmented spots

Li-Fraumeni Syndrome:
- Gene: $p53$
- Presentation:
  - Sarcoma (non Ewings)
  - Early-onset breast cancer
  - Brain tumor
  - Adrenocortical carcinoma
  - Acute leukemias
  - CRC, lung, stomach, melanoma, neuroblastoma
- Pathway: LOF, Tumor supressor gene-involved in cell repair, apoptosis, and genome stability
Li-Fraumeni Syndrome

Diagnostic criteria:
- A proband with a sarcoma diagnosed before 45 years of age.
- A first-degree relative with any cancer under 45 years of age.
- A first- or second-degree relative with any cancer under 45 years of age or a sarcoma at any age.

Germline testing of the p53 gene will identify a mutation in ~70% of families who meet this criteria; there may be other causative genes.

NEW: Early onset CRC is a part of the spectrum, pay close attention to patients with CRC <50. *Family History*

Wong et al, Gastroenterology, Vol. 130, 2006

Cowden Syndrome:

- PTEN gene
- Colon Polyps-Hamartomas
- Breast Cancer
- Thyroid Cancer
- Endometrial Cancer
- Fibroids of the Endometrium
- Benign Breast Disease
- Enlarged OFC
- Skin changes

Hereditary Diffuse Gastric Cancer (HDGC):

Gene: CDH1 (AD, E-Cadherin)

Presentation:
- Diffuse gastric cancer
- Lobular breast cancer
- CRC

Pathway: LOF, tumor suppressor, adherens junction (joins cells together)

Diagnostic Criteria: Aggregation of gastric cancer (2+ cases in family) with one diffuse gastric cancer diagnosed under 50

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

Gene: FH (AD, Fumarate Hydratase)

Presentation: Renal Cell Carcinoma, Cutaneous and Uterine Leiomyomata, Leiomyosarcoma and Uterine Sarcoma

Pathway: LOF, tumor suppressor gene, pathway

Unexpected, gene encodes enzyme for Krebs cycle

Testing: NIH study, 03-C-0066

Stewart et al., OB and GYN, Vol. 107(4), 2006

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Learning Assessment:

Men cannot inherit hereditary breast and ovarian cancer, nor can they pass it on.
True
False

Bonus Question:

What is Maggie’s FAVORITE gene?

Questions:

Thank you for having me!
I can be reached at: 212-6889 for questions
To schedule an appointment call: 212-6874 to reach Joy