Genetics of Gyn Cancer

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Hereditary Cancer
- Not a single gene
- Not a single mutation
- Not like sickle cell anemia
- Autosomal dominant

Genetic Testing
- Positive
- Negative
  - May yes and maybe no
- VUS
Genetic Testing
- Positive
- Deleterious mutation
- Known risks
- Recommended management plan
- Family members should be tested

Genetic Testing
- Negative
  - Maybe yes and maybe no
- True negative
- Maybe negative

Genetic Testing
- Variant of uncertain significance
  - VUS
- Change is present
- Benign vs potentially bad
- Follow-up
NCCN
- National Comprehensive Cancer Network
- Guidelines
  - Counseling
  - Testing
  - Management
- Police (Ish)

Women’s Health Cancer
- Lynch Syndrome
- Hereditary Breast and Ovarian Cancer
Colorectal Cancer

- 135,430 new cases annually
- ~50,260 deaths annually
- 9% of all cancer deaths

Colorectal Cancer

- Population risk
- Men
  - 1 in 21, 4.7%
- Women
  - 1 in 23, 4.4%

Colorectal Cancer

- Sporadic
  - No family history
  - 70% of the cases
  - Over the age 50
  - Dietary and environmental factors
Lynch Syndrome
- Dr. Henry Lynch
  - Nebraska family
- Dr. Marjorie Shaw
  - Michigan family
- Landmark paper 1966
- HNPCC
  - Hereditary Non-polyposis Colon Cancer

Lynch Syndrome
- Lynch Syndrome
  - CRC
  - Endometrial
  - Ovarian
  - Small intestine
  - Hepatobiliary
  - Urologic
  - Skin
  - Brain

Lynch Syndrome
- Most common cause of inherited CRC
- Associated
  - Endometrial cancer
  - Ovarian cancer
Lynch Syndrome

- Life time risk
- CRC
  - 52-82%
    - Mean age at diagnosis 44-61

- Endometrial cancer 1st malignancy
- If Lynch, then ~50% present with EC
- High incidence of metasynchronous or synchronous CRC or other Lynch tumor

- Autosomal Dominant with incomplete penetrance
- Population frequency
  - ~ 1 in 279
Lynch Syndrome

- Germline mutation in one allele
- Second allele inactivated somatically
  - Mutation
  - Loss of heterozygosity
  - Epigenetic silencing by promoter hypermethylation

2-Hit Theory

- Mutation
- Wild type
- 1st hit
- 2nd hit
- Early onset Cancer
- Late onset Cancer

Lynch Syndrome

- 3% of newly dx CRC
- 3% of endometrial cancer
Lynch Syndrome

- DNA mismatch repair genes, MMR
- Identification and repair of DNA replication errors
  - Deletions
  - Insertions
  - Substitutions

Lynch Syndrome

- DNA mismatch repair genes, MMR
  - MSH2
  - MLH1
  - MSH6
  - PMS2
  - EPCAM (not a MMR gene)

Lynch Syndrome

- Microsatellites
- Stretches of 2-5 nucleotides repeated multiple times
- Microsatellite Instability High (MSI Hi)
  - Accumulations of these stretches
Lynch Syndrome

- If mutation in MMR gene
- Then High MSI
- Then
  - Frameshift mutations
  - Protein truncation
  - Inactivation of the cancer regulatory genes

Lynch Syndrome

- Bottom line
- Increase mutation rate
- Failure of repair
- Microsatellite instability, MSI

Lynch Syndrome

- Tumor testing
- Can be done on paraffin tissue blocks
- MSI by PCR
- IHC by immunohistochemistry
  - MMR proteins
  - MLH1 methylations analysis
Lynch Syndrome

- Tumor tissue compared to normal tissue
- MSI/IHC
  - MSI high >30% with instability
  - MSI Low <30% with instability
  - MSI stable 0% instability

11% of sporadic CRC tumors have MSI instability

20-30% of endometrial cancers exhibit MSI
  - Majority are due to somatic MLH1 promotor methylation

Diagnosis by personal and family history
- Young age
- Multiple family members with a LS tumor
- Amsterdam criteria
Lynch Syndrome

- Amsterdam II criteria
- At least 3 relatives with LS related cancer
- One should be a 1st degree relative of the other 2
- AND

Lynch Syndrome

- AND
  - At least 2 successive generations affected
  - At least 1 DX before 50
  - FA excluded
  - Tumors verified by path exam

Lynch Syndrome

- Universal tumor testing for MSI/IHC
- CRC and Endometrial cancer
- Significant number of LS patient’s ID’d who do not Amsterdam criteria
Lynch Syndrome

- DNA testing if
  - MSI suggestive of a mutation
  - FHX suggestive of Lynch
  - Suspicious history and no tumor available

Lynch Syndrome
Endometrial cancer

- Population risk for Endometrial CA
  - 1 in 41, 2.8%
- Increasing since 1990 due to obesity

Lynch Syndrome
Endometrial cancer

- Risk depends on which gene is mutated
  - MSH6 64-72%
  - MSH1 or MLH1 40-50%
  - PMS2 15%
Lynch Syndrome
Endometrial cancer

- If diagnosed less than 50
- 9% with a mutation

Lynch Syndrome
Endometrial cancer

- Majority well differentiated endometrioid adenocarcinoma
- DX early stage
- Arise in the LUS

Lynch Syndrome
Endometrial cancer

- If Lynch NCCN guidelines
  - Yearly endometrial biopsy
  - 30-35 or 10 years younger than earliest family case
  - Pelvic ultrasound often done but controversial
Lynch Syndrome
Endometrial cancer

- Prevention
- Chemoprevention
  - OCPs
  - Depo
- Limited data

Lynch Syndrome
Endometrial cancer

- Prevention
- Surgery
  - Hysterectomy and BSO
  - At time of CRC surgery
  - Finished child bearing

Lynch Syndrome
Endometrial cancer

- 108 women with hyst and or BSO
- 433 no prophylactic surgery
- Median follow-up 13 years
**Lynch Syndrome**

**Endometrial cancer**

- Prophylactic surgery
  - 3 with occult EC at time of hyst
  - No EC, ovarian Ca or primary peritoneal cancer
- No surgery
  - 33% endometrial cancer
  - 5% ovarian cancer

**Ovarian Cancer**

- Ovarian
- Tubal
- Primary peritoneal

**Ovarian Cancer**

- Sporadic
- BRCA 1 or 2
- Lynch syndrome
- Other
Ovarian Cancer

- Second most common GYN malignancy
- Population risk 1.5%
- Lynch Syndrome risk 3-20%

Ovarian Cancer

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Lifetime Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>1.0</td>
</tr>
<tr>
<td>BRCA1 Mutation</td>
<td>35-46%</td>
</tr>
<tr>
<td>BRCA2 Mutation</td>
<td>13-23%</td>
</tr>
<tr>
<td>Lynch mutation</td>
<td>3-20%</td>
</tr>
</tbody>
</table>

Ovarian Cancer

Lynch Syndrome

- Age at dx 43-50 vs 60
- MHL1 and MSH2 most common
Ovarian Cancer
Lynch Syndrome

- Histopathology and survival similar
- Path
  - Serous
  - Endometrioid
  - Mucinous
  - Clear cell

Ovarian Cancer
Lynch Syndrome

- Earlier stage at diagnosis
  - I or II
  - No 5 year survival advantage

Ovarian Cancer
Lynch Syndrome

- Average age of OC dx in US is 63 years
- If young, think hereditary etiology
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>Any</td>
<td>44-79%</td>
<td>38-78%</td>
<td>25-47%</td>
</tr>
<tr>
<td>Women</td>
<td>Any</td>
<td>44-79%</td>
<td>38-78%</td>
<td>25-47%</td>
</tr>
<tr>
<td>CRC</td>
<td>60-65%</td>
<td>40-65%</td>
<td>50-60%</td>
<td>18-30%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>17-48%</td>
<td>27%</td>
<td>17-48%</td>
<td>39%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>20%</td>
<td>20%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Hereditary Breast and Ovarian Cancer

- BRCA 1 and 2 mutations
- Tumor suppressor genes
- DNA repair pathways
- Two hit
- BRCA1 (17) and BRCA2 (13)

HBOC

- Population frequency
  - 1 in 400 to 1 in 800
HBOC

- Epithelial ovarian cancer
  - ~9-24%
- Breast Cancer
  - ~4.5%

5-10% unselected women with breast cancer
20% with family history of breast cancer
BRCA1 and 2 TIP OF THE ICEBERG
Bunch of genes besides BRCA 1 and are associated with breast cancer

Li-Fraumeni syndrome
Peutz-Jeghers syndrome
PTEN Hamartoma tumor syndrome
Hereditary diffuse gastric cancer syndrome
Lynch syndrome
CHEK2
ATM
PALB2
And on and on
Up to 25% non-BRCA 1 or 2 genes
Breast Cancer

- 1 in 8 by 85
- 1 in 12 by 70
- Most not due to HBOC

BRCA Mutations

- Population Risk
  - 1 in 400-1 in 800
- Ashkenazi Jewish
  - 1 in 40
  - 3 founder mutations
  - If AJ and Breast cancer, risk high

NCCN

- Personal history of breast cancer
  - Young age, ≤ 45
  - Two breast primaries
  - Triple negative breast cancer, ≤ 60
NCCN

- Personal history of breast cancer
  - Family hx multiple breast cancers
  - AJ ancestry
  - Ovarian cancer, fallopian tube cancer, 1* peritoneal cancer

NCCN

- Known Genetic mutation
- Family hx multiple breast cancers
- AJ ancestry and BRCA 1 or 2 associated cancer
- Ovarian cancer, fallopian tube cancer, 1* peritoneal cancer
- Family history of male breast cancer

NCCN

- PHx or FHx of 3 or more associated cancers
  - Pancreatic
  - Prostate
  - Melanoma
  - Sarcoma
  - Adrenal
  - Brain
  - Leukemia
  - Gastro
  - Colon
  - Endometrial
  - Thyroid
  - Kidney
Risk Assessment Tools

- BRCAPRO
- BOADICEA
- Tyer-Cuzick
- Breast Cancer Surveillance Consortium
- Don’t use GAIL

Risk

- Ovarian cancer
- Regardless of age and family history
- 15% BRCA 1 or 2 mutation
- AJ and Ovarian cancer
  - Up to 40% will have a mutation

HBOC

Lifetime risks

- BRCA 1 mutation
  - Breast 72%
  - Ovarian 44%
- BRCA 2 mutation
  - Breast 69%
  - Ovarian 17%
BRCA Mutation

- Population Risk
  - 1 in 300 to 1 in 800
- Ashkenazi Jewish
  - 1 in 40
  - 3 founder mutations

BRCA Mutation

- Stage at presentation
  - Ovarian cancer
  - 70% III or IV
- BRCA 1 or 2 carriers, breast cancer
  - Similar to non-carriers

BRCA Mutation

Ovarian Cancer

- Tend to be higher grade tumors
- Histology similar to non-carriers
- Serous adenocarcinoma the most common
- Mucinous and borderline rare
BRCA Mutation
Ovarian Cancer
- Mutation carriers tend to have a better prognosis than non-carriers
- More sensitive to platinum based treatment

Lynparza
- Olaparib
- PARP Inhibitor
  - Poly (ADP-ribose) Polymerase (PARP) Inhibitor
- Recurrent ovarian cancer
- BRCA ½ mutation

Lynparza
- Recurrent ovarian cancer
- BRCA ½ mutation
- CDX – Myriad
  - FDA approved BRCA ½ test
- Reflex to MyRisk panel
Lynparza

Never stop at CDX

BRCA Mutation
Pancreatic Cancer

- BRCA1
  - ~1%
- BRCA2
  - ~4.9%

BRCA Mutation
CRC

- BRCA1
  - 4 fold increased risk in carriers less than 50
- BRCA2 and non-carriers
  - No increased risk over the population risk
**Risks**

- Triple Negative Breast cancer
  - ER/PR/HER2 negative
  - Less than or equal to 60
- 5 fold increased risk of a mutation
  - 8.5% BRCA1 mutation
  - 2.7% BRCA2

**Risks**

- Triple Negative Breast cancer
- African American
- DX 50-59
  - No family history
  - 7.5% BRCA1 or 2 mutation
- Other mutations
  - 3.7%

**Lifetime Risks**

- BRCA 1 mutation
  - Breast 72%
  - Ovarian 44%
- BRCA 2 mutation
  - Breast 69%
  - Ovarian 17%
Second Breast Cancer

- BRCA 1 mutation
  - First cancer 25-29
    - 5 year risk 16%
    - 10 year risk 29%
  - First cancer 50-54
    - 5 year 6%
    - 10 year 11.7%

Second Breast Cancer

- BRCA 2 mutation
  - First cancer 25-29
    - 5 year risk 14.6%
    - 10 year risk 26.6%
  - First cancer 50-54
    - 5 year 5.3%
    - 10 year 10.4%

Fallopian Tube Cancer

- BRCA 1 or 2 carriers
- 50% of serous “ovarian Cancer”
- Distal fallopian tube
Fallopian Tube Cancer
- IF FTC
- Then ~30% with a mutation
  - BRCA1 greater than BRCA2
- IF AJ
  - Then up to 55%

Primary Peritoneal Cancer
- Risk increased
- AJ with founder mutation
  - 1.3%
- Non-AJ
  - ?

Uterine Papillary Serous Carcinoma
- Part of the disease spectrum
  - Maybe
- Actual risk not known
  - Low
  - NON-BRCA 1 or 2 mutations
Pancreatic Cancer

- BRCA1
  - ~1%
- BRCA2
  - ~4.9%

Colorectal Cancer

- BRCA 1
  - 4 fold increased risk in carriers less than 50
- BRCA 2 and non-carriers
  - No increased risk over population risk

<table>
<thead>
<tr>
<th>BRCA 1 and 2 Risks</th>
</tr>
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<tbody>
<tr>
<td><strong>CANCER</strong></td>
</tr>
<tr>
<td>Breast</td>
</tr>
<tr>
<td>Contralateral breast</td>
</tr>
<tr>
<td>Ovarian</td>
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</table>
Other Stuff

- Male breast cancer
- Prostate cancer
- Melanoma
  - Especially ocular
- Stomach and biliary cancer
- Endometrial cancer

Panels

<table>
<thead>
<tr>
<th>HBOC</th>
<th>BRCA 1 and 2</th>
</tr>
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<tbody>
<tr>
<td>Breast Cancer panel</td>
<td>ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEF, TP53</td>
</tr>
</tbody>
</table>

Panels

<table>
<thead>
<tr>
<th>Lynch Panel</th>
<th>MLH1, MSH2, MSH6, PMS2 + EPCAM del/dup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon Panel</td>
<td>(17 genes) APC, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH6, MUTYH, PMS2, POLD1, POLE, PTEF, SMAD4, STK11, TP53</td>
</tr>
<tr>
<td>Panels</td>
<td></td>
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</tr>
<tr>
<td><strong>GYN Panel</strong> (13 genes)</td>
<td>BRCA1, BRCA2, BRIPI, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, TP53</td>
</tr>
<tr>
<td><strong>Ovarian Cancer Panel</strong> (25 genes)</td>
<td>BRCA1, BRCA2, BRIPI, CDH1, CHEK2, DCCER1, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TP53</td>
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<tbody>
<tr>
<td><strong>Cancer Panel</strong> (34 genes)</td>
</tr>
<tr>
<td><strong>CancerNext-Expanded (67 genes)</strong></td>
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