Primary Care Approach to Genetic Cancer Syndromes

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Syndromes

- Hereditary Breast and Ovarian Cancer (HBOC)
- Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
- Familial Adenomatous Polyposis (FAP)
- Melanoma
Objectives

- Identify Risk Factors for BRCA gene mutations
- Identify patients at risk for Hereditary Breast and Ovarian Cancer Syndrome (HBOC)
- Clinical features of HBOC
- Management of HBOC
- Interpretation of BRCA test results
- Utilize BRCA testing in the clinical setting
Overview

• Relative Risk
• Why test
• Who to test
• Results
• Management
HBOC Risk

Patients with a personal history of cancer

- About 22% of breast cancer patients at risk for HBOC
- 100% of ovarian cancer patients at risk for HBOC

- 1 in 400 people in general population have BRCA mutation
- 1 in 40 Ashkenazi Jewish ancestry have BRCA mutation

Patients with only a Family History of Cancer

- 6% of all patients are considered high risk and need evaluation
- 9% of a primary care practice have family history of breast or ovarian cancer

References:
- Journal of General Internal Medicine 2009;24(7):822-28
- Breast J 2003 Jan-Feb;9(1):19-25
- Genet in Med 2009;11:783-789
- Gynecology Oncol 2011;121(2):352-7
- Cancer 2005;104(12):2807-16
- Nat Rev Cancer 2004;4(9):665-76
- Cancer 2005;104(9):1849-53
WHY TEST?
Increased Cancer Risk

- Positive female patients have up to 87% chance of getting breast cancer
- Positive female patients have up to 44% chance of ovarian cancer
- 10 fold ovarian cancer risk after breast cancer
- Positive male patients have up to 10% chance of male breast cancer
- Positive male patients have up to 20% chance of prostate cancer
- Significant increase in other cancers including Pancreatic and Melanoma
- Appropriate Intervention Improves outcome
Increase risk of Breast and Ovarian Cancer with BRCA mutation

- Breast Cancer by age 50: 50% (BRCA) vs. 2% (General Population)
- Breast Cancer by age 70: 87% (BRCA) vs. 8% (General Population)
- Ovarian Cancer by age 70: 44% (BRCA) vs. 1% (General Population)
Risk of Second Cancer with BRCA mutation

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>BRCA Mutation</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer after 5 years</td>
<td>27.0%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Breast Cancer by age 70</td>
<td>64.0%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Ovarian Cancer 10 years after</td>
<td>13.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>breast cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

JNCI 1999;15:1310-6
JCO 1998;16:2417-25
Lancet 1998;351:1316-21
JCO 2004;22:2328-35
Gynecol Oncol 2005 Jan;96(1):222-6
JCO 2010;28(14):2404-10
Male Cancer Risk with BRCA mutation

- Breast Cancer by age 80: 8.0% (BRCA Mutation), 0.1% (General Population)
- Prostate Cancer by age 80: 20.0% (BRCA Mutation), 14.0% (General Population)
Other Cancer risk with BRCA mutation

- Pancreatic Cancer by age 80
  - BRCA Mutation: 7.0%
  - General Population: 1.0%

- Melanoma by age 80
  - BRCA Mutation: 4.0%
  - General Population: 2.0%
Who To Test
Risk Factors Based on Family History

- Family history includes up to third degree relative
- Any ovarian cancer
- Any breast cancer diagnosed before age 50
- 2 breast cancers on the same side of the family or in one individual
- Any male breast cancer
- Any BRCA mutation in the family
- Pancreatic cancer and additional Breast or ovarian cancer
- Ashkenazi Jewish ancestry with any HBOC cancer (Breast, Ovarian, Pancreatic)
- Triple Negative (Estrogen, Progesterone, Her2Neu)
Key Points

- Mutation is Autosomal Dominant
- One gene from mother and one from father
- Each offspring has 50% risk of inheritance from affected parent
- Men and Women should be screened for risk and tested appropriately
- Men have equal chance of carrying the genetic mutation
- Family history should include third degree relatives
Ductal Carcinoma in Situ (DCIS)

- 3.2% of women with DCIS had BRCA1 or BRCA2
- 5.9% of women with Carcinoma in Situ have BRCA1 or BRCA2 mutation
- DCIS must be considered as a risk factor for HBOC
Results
Possible Results

• Positive for deleterious mutation
  – BRCA 1 or BRCA 2 present
• Negative for deleterious Mutation
  – No mutation present
• Polymorphism
  – Mutation present but not associated with increased cancer risk
• Genetic Variant of Unknown Significance
  – Mutation present but not enough data to determine if cancer risk is increased
Histology and Prognosis

• Breast Cancer
  – BRCA1
    • Prognosis needs further study
    • Majority triple negative
    • More likely basal phenotype
  – BRCA2
    • Similar to non-BRCA tumors

• Ovarian Cancer
  – Majority papillary serous
  – May improve survival compared to non BRCA ovarian cancer
Management options

- Increased Surveillance
- Surgery
- Chemoprevention
Surveillance Options

- Self-Breast Exam
- Clinical Breast Exam
- Mammogram
- Ultrasound
- MRI
- Pelvic Exam
- CA-125
## Female BRCA Carriers

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Age to start</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>Self-exam</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Clinical Exam</td>
<td>25 Every 6-12 months</td>
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<tr>
<td></td>
<td>Mammogram</td>
<td>25 Yearly</td>
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<tr>
<td></td>
<td>MRI</td>
<td>25 Yearly</td>
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<tr>
<td>Ovarian Cancer</td>
<td>Pelvic exam</td>
<td>35 Every 6 months</td>
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<tr>
<td></td>
<td>Ultrasound and CA-125</td>
<td>35 Every 6 months</td>
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- Mammogram and ultrasound should alternate every 6 months with MRI
- CA-125 and transvaginal ultrasound of limited efficacy and data
- Ovarian cancer surveillance is not primary treatment
### Male BRCA carriers

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<td>Clinical Exam</td>
<td>35 Every 6-12 months</td>
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<td></td>
<td>Mammogram</td>
<td>40 Yearly</td>
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<tr>
<td>Prostate Cancer</td>
<td>PSA</td>
<td>40 Yearly</td>
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<tr>
<td></td>
<td>Digital Rectal Exam</td>
<td>40 Yearly</td>
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</table>
Surgical Management

- Bilateral Mastectomy has 90% cancer risk reduction
- Bilateral Salpingo-oophorectomy (BSO) has 96% cancer risk reduction
- BSO advised after childbearing years but by age 40
- Risk reducing BSO considerations
  - Ovaries and fallopian tubes to level of cornu
  - Ligation of ovarian vessels at pelvic brim
  - Thorough pelvic inspection and washing
  - Complete serial sections

- Studies show 2%-26% occult tumors found in surgery
Chemoprevention
Breast Cancer
• Tamoxifen
  – Possible 45% risk reduction for unaffected BRCA positive
  – Possible 62% reduction in BRCA2
  – Affected BRCA carriers possible 53% reduction in opposite breast
• Raloxifene and Aromatase Inhibitors
  – No specific data for BRCA
  – Risk reduction in post menopausal women

Ovarian Cancer
• Oral contraceptive
  – Possible 60% reduction
  – Unclear risk for increase breast cancer

Int J Cancer. 2006;118(9):2281-4
Lancet 2000;356:1876-81
JAMA 2001;286:2251-6
JNCI 1998; 90:1371-88
Cancer Prevention Research 2011;3(6):696-706
NEJM 1998; 339:424-8
JNCI 2002;94:1773-9
JCO. 2007 ;112(S3):700-709
Cancer Epidemiol Biomarkers Prev. 2006;15(10)
Breast Cancer Res Treat 2010 Feb;120(1):175-83
Eur J Cancer 2010;46:2275-84
www.nccn.org
Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer: HNPCC)
Objectives

- Identify Risk Factors for HNPCC gene mutations
- Identify patients at risk for HNPCC
- Clinical features of HNPCC
- Management of HNPCC
- Interpretation of HNPCC test results
- Utilize HNPCC testing in the clinical setting
Overview

• Relative Risk
• Why test
• Who to test
• Results
• Management
Relative Risk, Prevalence and Facts

- About 1 in 300 to 1 in 500 people affected
- Increased colon and endometrial cancer risk
- Mutations: MLH1, MSH2, MSH6, PMS2, EPCAM
- Autosomal dominance
- 2-4% of colorectal cancer caused by mutation
- Age of onset usually under age 58
- About 6% of colon cancer under age 50 is Lynch related
- 2-4% of endometrial cancer caused by Lynch
- 9% of endometrial cancers under age 50 caused by Lynch
- 50% of women with Lynch will present with gynecologic malignancy first
Relative Risk for Colorectal Cancer

- Lynch Syndrome: 40
- Obesity: 1.7
- IBD: 1.5
- Alcohol: 1.2
- Red meat: 1.2

Sources:
Seer.cancer.gov/statistics/
Relative Risk for Endometrial Cancer

- Lynch Syndrome MSH6: 79
- Lynch Syndrome MLH1 and MSH2: 48.5
- Tamoxifen: 2.6
- Obesity: 2.23
- Diabetes: 2.18
- Metabolic Syndrome: 1.67

References:
Lancet Oncol 2009;10:400-408.
Conclusion

Lynch syndrome is the single most common explanation for hereditary colon and gynecologic malignancies.
Gene Mutation Prevalence

- MLH1 and MSH2: 71%
- MSH6: 14%
- PMS2: 14%
- EPCAM: 1%

References:
WHY TEST?
Increase risk of Colorectal and Gynecologic Cancer with Lynch Syndrome.
Increase risk of other Cancers with Lynch Syndrome

Risk of Cancer (%)

- Gastric: 13%
- Hepatobiliary: 1%
- Ureter/Renal Pelvis: 1%
- Small Bowel: 1%
- Brain/CNS: 1%
- Pancreatic: 1%
- Sebaceous Adenoma: 1%

Lynch Syndrome vs. General Population

Increase risk of Second Cancer with Lynch Syndrome

- Within 10 years: Lynch Syndrome 30.0%, General Population 3.5%
- Within 15 years: Lynch Syndrome 50.0%, General Population 5.0%

Cancer 1993;36:388-93.
Who To Test
Patients With Cancer

- Colorectal or endometrial cancer before age 50
- Two or more lynch syndrome cancers at any age
- Lynch syndrome Cancer and one or more relatives with Lynch syndrome Cancer
- Lynch syndrome mutation in the family
- MSI-High Histology in Colorectal cancer under age 60
  - Medullary growth pattern, Crohn’s like lymphocytic reaction, signet ring, tumor infiltrating lymphocytes, mucinous
- MSI/IHC tumor test results
Patients without Cancer

- Family history of two or more Lynch cancers, one before age 50
- Family history of three or more Lynch cancers at any age
- Family history of Lynch mutation
MSI vs. MSI-High histology

- Microsatellite Instability (MSI)
  - PCR based test on tumor tissue
  - Specific order
  - If high, then likely mismatch repair dysfunction which suggests Lynch syndrome

- MSI-High histology
  - Specific histologic features that suggest MSI would show as high
  - Suggestive of Lynch syndrome
  - Automatic on pathology report

- Neither are genetic tests for Lynch mutation, only on tumor tissue

- Absence of MSI or MSI-high histology does not exclude genetic mutation
Management options

• Increased Surveillance
• Surgery
Colorectal Cancer

• Surveillance
  – Colonoscopy every 1-2 years
  – Lynch cancer usually right sided
  – Cancer risk reduction over 50%
  – General population Adenoma to cancer in 10 years, Lynch syndrome takes **1-3 years**

• Surgical Options
  – Colectomy with ileorectal anastomosis for cancer or more then one advanced adenoma
  – Hemicolecctomy with annual colonoscopy
Gynecologic Cancer

• **Surveillance**
  – Annual Transvaginal ultrasound starting age 30-35
  – Annual endometrial aspiration starting age 30-35
  – CA-125 testing

• **Surgical Options**
  – Hysterectomy and bilateral salpingo-oophorectomy after child bearing years
Other Cancers

- Gastric and small bowel cancer consider EGD and capsule endoscopy yearly starting age 30-35
- Urothelial cancer consider annual urinalysis
- CNS cancer advise annual physical exam
- Pancreatic Cancer no specific recommendations
Possible Results

- Positive for deleterious mutation
  - Lynch mutation present
- Negative for deleterious Mutation
  - No mutation present
- Polymorphism
  - Mutation present but not associated with increased cancer risk
- Genetic Variant of Unknown Significance
  - Mutation present but not enough data to determine if cancer risk is increased
Familial Adenomatous Polyposis
Important Facts

• About 30% of adults will have adenoma or precancerous polyp
• APC and MYH are associated gene mutations
• Causes about 1% of colon cancer
• About 85% of FAP caused by APC mutation
• About 15% of polyposis syndrome from MYH
• 3 significant syndromes
  – Familial Adenomatous Polyposis (FAP)
  – Attenuated FAP
  – MYH Associated Polyposis (MAP)
Adenomatous polyposis syndromes

Familial and Attenuated

Familial Adenomatous Polyposis Syndrome

- APC gene
- Autosomal dominant
- Hundreds of polyps in FAP
- Less than 100 polyps in AFAP
- Colorectal cancer risk $\geq 80\%$ by age 70

MYH associated polyposis

- MYH gene
- Autosomal recessive
- 0-1000 polyps
- Colorectal cancer risk $\geq 80\%$ by age 70

FAP causes hundreds of polyps, Attenuated FAP usually less than 100
Importance of Testing

Colorectal Cancer by age 70

- General Population: 2%
- AFAP and MAP: 80%
- FAP: 99%

Risk of Cancer (%)
Risk Factors

- 10 or more adenomatous polyps cumulative, personally or in family
- Colorectal cancer and adenomas
- Positive mutation in family
Possible Results

- Positive for deleterious mutation
  - Mutation present
- Negative for deleterious Mutation
  - No mutation present
- Polymorphism
  - Mutation present but not associated with increased cancer risk
- Genetic Variant of Unknown Significance
  - Mutation present but not enough data to determine if cancer risk is increased
Treatment options

- Yearly colonoscopy if FAP
- Possible colectomy for severe polyposis
- Possible chemoprevention with COX-2 inhibitors or Aspirin
Hereditary Melanoma

- p16 mutation
- Up to 76% melanoma risk and 17% pancreatic cancer risk
- Risk factors
  - Two or more melanomas in a family
  - Positive p16 mutation in family
  - At least one pancreatic cancer and one melanoma
- If positive needs aggressive and frequent skin exams
- Possible pancreatic screening such as CT, EUS, or research protocols, unclear guidelines
Li-Fraumeni Syndrome (LFS)

- Autosomal Dominant
- Affects 1/20,000
- TP53 mutation, CHEK2 mutation
- 50% risk of LFS cancer by age 30
- 49% breast cancer risk by age 60
- 93% lifetime cancer risk
- Average age of diagnosis 21.9 years
- 5%-8% of women with no family history have TP53 mutation

LFS tumors

- Soft tissue sarcoma
- Osteosarcoma
- Brain Tumor
- Premenopausal breast cancer
- Adrenocortical carcinoma
- Leukemia
- Bronchoalveolar lung cancer
Testing Guidelines

- Woman with Breast Cancer before age 35
- Individual with LFS tumor before age 46 and 1st or 2nd degree relative with LFS tumor before age 56
- Individual with multiple tumors of LFS spectrum with first before age 46
- Individual with adrenocortical carcinoma or choroid plexus tumor
- Individuals with family history of TP53 mutation
Treatment options

- No definitive data for specific guidelines
- Increased surveillance
  - Annual MMG alternate with MRI every 6 months
  - Colonoscopy every 2-3 years start age 25
  - Avoid radiation exposure
- Surgical intervention
  - Prophylactic mastectomy
  - Mastectomy advised over lumpectomy
Case Studies
Patient H.G.

- 49 year old unaffected male, Ashkenazi Jewish ancestry

Family history:
- Maternal grandmother breast age 50
- Maternal grandfather throat cancer age 70
- Maternal uncle testicular cancer age 30
- Maternal uncle prostate age 60
- Mother breast age 50
- Father prostate age 30
Testing offered
• BRCA mutation testing

Test Results:
• *BRCA2* mutation (6174delT one of the three common mutations)

My Recommendations
• Manage with male mammogram follow up with oncology and urologist
• Patient discussed results with family members
• Daughter, age 19, tested positive
Patient A.P.

- 66 year old male, Ashkenazi Jewish ancestry
- Colon cancer diagnosed age 31

Family history
- Father colon age 60
- Maternal grandmother breast age 75
Testing offered
- Lynch testing
- BRCA testing

Test Results:
- $MSH2$ positive
- $BRCA$ negative

My Recommendations
Treatment / Surveillance
- Previously had subtotal colectomy, cholecystectomy, followed by oncology, had ca 19-9
Outcome

• Recently diagnosed with Stage 1 pancreatic cancer, status post whipple, XRT and undergoing chemo
• Daughter tested positive for mutation had subtotal colectomy, hysterectomy and cholecystectomy
Patient M.H.

- 59 year old female, Ashkenazi Jewish ancestry

Family history
- Maternal grandmother breast cancer
- Paternal uncle gastric cancer
- Paternal aunt breast cancer age 45
- Paternal cousin breast cancer age 32, BRCA1+
- Paternal cousin ovarian cancer age 40
- Paternal uncle prostate cancer
Testing offered
• BRCA mutation testing
• Lynch mutation

Test Results:
• BRCA1 187delAG (one of the three common mutations)

My Recommendations
Treatment / Surveillance
• M.H. chose bilateral mastectomy, TAH BSO
Outcome

• 32 year old daughter tested
• \textit{BRCA1 Positive}
  – Screening Mammogram done
  – Positive for Stage 1 Breast Cancer
  – Status post double mastectomy
Final Comments

• Genetic testing saves lives
• Genetic testing advised by multiple medical societies
• Testing protected by state and federal Genetic Information Nondiscrimination Act (GINA laws)
• Genetic testing allows for primary prevention of many cancers
• Genetic mutations more common then realized
• Easy to incorporate into practice