HEREDITARY CANCER SYNDROMES: IDENTIFYING THOSE AT RISK

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OBJECTIVES

1) Taking a Cancer Family History

2) Identify patients and/or family members appropriate for hereditary cancer syndrome genetic testing: referral guidelines handout and last 8 slides

3) Learn the cancer risks and management options for HBOC, LYNCH, and other cancer predisposition genes

4) Review various issues associated with genetic testing; insurance, discrimination, result interpretation, role of the genetic counselor
Distribution of Cancer

Hereditary
- Gene mutation is inherited in family
- Significantly increased cancer risk

Familial
- Multiple genes & environmental factors may be involved
- Some increase in cancer risk

Sporadic
- Cancer occurs by chance or related to environmental factors
- General population cancer risk

5-10%

15-20%

70%
Lifetime Cancer Risks for people who have a hereditary cancer

- Breast: up to 87%\(^1\)
- Ovarian: up to 44%\(^1\)
- Colon: up to 99%\(^2\)
- Uterine: up to 71%\(^3\)
- Melanoma: up to 76%\(^4\)
- Pancreatic: up to 80%\(^6\)
- Gastric: up to 36%\(^5\)
- Prostate: up to 44%\(^7\)

Myriad 2015
In some families, a pattern of cancer is obvious; in others, small family size, incomplete family history, inability to document diagnosis or non-specific family histories makes it more difficult to detect a pattern.
Recommended Key Elements for Minimum Adequate Cancer Family History (Table I)

- First degree relatives: siblings, parents, children
- Second degree relatives; grandparents, aunts, uncles
- Both Maternal and Paternal side
- Ethnicity
- For each cancer case in family, establish:
  - Age of cancer diagnosis
  - Type of primary cancer
- Results of any cancer predisposition testing in any relative

**NOTE** family history should be taken at DIAGNOSIS and updated periodically.

Studies show that patient report are most reliable for 1<sup>st</sup> and 2<sup>nd</sup> degree relatives.
| MULTIPLE: | 2 or more: breast/ovarian/ prostate/ pancreatic OR  
|           | 2 or more: colorectal/ uterine/ ovarian/ stomach/ pancreatic/ other cancers (i.e. ureter/renal pelvis, biliary tract, small bowel, brain, sebaceous adenoma) OR  
|           | 2 or more: melanoma/pancreatic |
| YOUNG:    | Breast Cancer  
|           | Colorectal Cancer  
|           | Uterine Cancer  
|           | Any solid tumor (some exceptions: not lung, cervical, testicular) |
| RARE:     | Ovarian cancer  
|           | Breast: male breast or triple negative breast  
|           | Colorectal Cancer with abnormal microsatellite (MSI) or immunohistochemistry (IHC) or MSI associated histology  
|           | Uterine cancer with abnormal MSI/IHC  
|           | 10 or more gastrointestinal polyps  
|           | Other rare cancers: medullary thyroid cancer, retinoblastoma, hepatoblastoma, adrenocortical carcinoma, Pheochromocytoma |
| ETHNICITY | Ashkenazi Jewish with breast/ovarian cancer in family |
Characteristics of Hereditary Cancer

- Unaffected Individual
- Affected Individual

BR. Breast Cancer
OV. Ovarian Cancer
NUMBER Age of Onset

Characteristics of Hereditary Cancer

- Multiple family members with cancer
- Several relatives with same cancer or cancers that tend to cluster together (i.e. breast & ovarian; colon & uterine)
- Family members with more than one primary cancer (bilateral breast cancer, colon & uterine)
- Cancer diagnosed at early ages (<50 years of age)
- Presence of rare tumor types or unusual cancer presentations (male breast cancer)

- ALSO: Ethnicity - where your family has immigrated from (for example Ashkenazi Jewish: founder mutations)
“The primary goal of cancer genetic counseling is to identify individuals and families at increased risk of cancer for the purpose of promoting awareness, early detection and cancer prevention. Genetic counselors are uniquely qualified to increase efficiency in your practice by dealing with both technical and emotional aspects related to increased cancer risk.”

~National Society of Genetic Counselors
THE CANCER GENETIC COUNSELOR

1. Review medical and family history of cancer
2. Discuss genetic testing options: Is person appropriate for testing or someone else in the family?
3. Review medical management options with or without genetic testing
4. Provide psychosocial support and facilitating communication between patients and families
5. Review health insurance coverage for genetic testing and medical management surveillance
6. Discuss risks with genetic testing? Life insurance discrimination; limitations in interpreting variants of unknown clinical significance
BENEFITS OF GENETIC TESTING

A. Estimates one’s lifetime cancer risk
B. Personalized screening recommendations
C. Decision making
   A. Lifestyle changes and choices
   B. Chemoprevention
   C. Surgery
   D. Treatment options for chemotherapy
D. Help other family members to understand their cancer risk
RISKS OF GENETIC TESTING

A. Emotional reactions
B. Confidentiality concerns
C. Fear of genetic discrimination
D. Concern about children and family
E. Does not eliminate other causes of cancer
LIMITATIONS OF GENETIC TESTING

**Indeterminate (Uninformative Negative) Result:**
- No mutations were detected in patient and no mutations have been previously identified in the family

**Inconclusive:** variant of unclear clinical significance (VUS)
- A VUS was detected (we do not know if the alteration found on the gene is a mutation or benign)
- 30% chance in panel testing

**Positive result**
- Cannot predict when, where, or if cancer will occur. Not a 100% chance for cancer in one’s lifetime.

**True Negative**
- Not a carrier of mutation that was previously identified in the family
- Moderate risk cancer gene mutation: can’t rule out cancer risk completely. Are there other modifying factors—both genetic and environmental?
- History of cancer on both sides of the family

✔ Testing minors is not recommended in most cases
INSURANCE

1. Most commercial insurance will cover genetic testing if patient and/or family history meets criteria for BRCA1/2 or Lynch based on NCCN criteria or has a family member with a mutation
   - Most labs only reimburse for 1 to 2 genes on panel (like BRCA1/2)

2. Medicare will only pay for testing in patient with cancer
   - Exception: Invitae will now accept all Medicare patients

3. MaineCare: requires prior-auth or utilize labs that offer assistance

4. Cigna requires genetic counseling by a certified GC as part of testing
INSURANCE CONT.

5. Aetna, Anthem Blue Cross Blue Shield, United require prior-auth
   - Either ordering provider needs to request or labs can assist
   - BC/BS and United are utilization AIM prior-auth service; must be done by ordering provider

6. Labs assist with prior authorization and pre-verification
   - Most notify patients if testing is > $100
     - Patient assistance plans: help with high deductible, co-insurance, or denial
     - If we can get coverage for at least two single genes the lab will still run the panel

7. Patient Pay: depending on income testing could be free or OOP max of $475 with Invitae, or ColorGenomics $150
GENETIC DISCRIMINATION

- GINA 2008: The Genetic Information Nondiscrimination Act (GINA) was signed into law on May 21, 2008 and became fully effective November 21, 2009. GINA prohibits discrimination by health insurance companies and employers based on “genetic information.”
  - Protection for employment and health care insurance
  - Employers with fewer than 15 employees are not required to abide by the employment protections set forth by GINA

- What GINA does not do!
  - GINA does not apply to life, disability, or long-term care insurance
  - Department of Defense and Uniformed Services are bound by different laws and regulations than civilians. Therefore, GINA does not protect members of the United States Armed Services, many service members who receive care through TRICARE (although family members are covered), the Veteran’s Administration, or the Indian Health Service.
CURRENT PRACTICE

1. Offer next generation sequencing panels to most patients eligible for genetic testing (as of May 2014)

2. Turn around time now around 2-4 weeks (depending on lab used)
   - STAT Breast panel for surgical decision making in one week
   - Tumor testing for DNA mismatch repair still gold standard for colon and endometrial cases

3. Gene specific testing still offered and available
   - BRCA1/2, Lynch, single gene, familial mutation, etc.
1994/1995- Myriad Genetic Laboratories and the University of Utah patent the BRCA1 and BRCA2 genes

March 29, 2010- Federal District Court in Manhattan invalidated patents

August 16, 2012- Federal District Court of New York overturned the ruling

June 13, 2013- Supreme Court rules human genes cannot be patented: Opened the market for BRCA1/2 testing

2013- the release of multi-gene panels by Ambry (now many labs)
CASE EXAMPLES

1. HBOC (BRCA1/2)
2. HBOC IN PANEL SETTING
3. LYNCH SYNDROME
4. MULTI-GENE PANEL
Inheritance for Most Hereditary Cancer Syndrome

Autosomal Dominant Segregation, One Parent Affected

- Unaffected Individual
- Affected Individual

1 in 2 chance that the child will be affected (50%)

1 in 2 chance that the child will not be affected (50%)
CASE 1: EXAMPLE OF HBOC

- 40 y.o. woman
- Referred for family history of premenopausal breast cancer in mom
- Family history follows:
CASE 1

- Proceed with Ambry BRCA1/2 with the CancerNext Panel (32 genes): **POSITIVE**

**BRCA1/2 Analyses with CancerNext**

<table>
<thead>
<tr>
<th>RESULTS</th>
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<tbody>
<tr>
<td><strong>BRCA2</strong></td>
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**SUMMARY**
Lifetime Risk for Cancer in Women (BRCA1/2 mutations)

- Breast: ~12%
- Ovarian: 1-2%
- General Population: 20-40%
- BRCA Alteration Carriers: 50-85%

King MC et al 2003
RISK OF SECOND BREAST CANCER (AFTER INITIAL BREAST CANCER DIAGNOSIS) WITH (BRCA1/2 MUTATIONS)

Cancer Risk (%)

- **Within 5 years**
  - General Population: 3-11%
  - BRCA Alteration: 27%

- **By age 70**
  - General Population: 3-11%
  - BRCA Alteration: 64%

Metcalfe et al 2004 JCO
Ford et al 1994 Lancet
LIFETIME RISK OF CANCER FOR MEN
(BRCA1/2 GENE MUTATION)

Cancer Risk (%)

Breast Cancer

Prostate Cancer

<1% 8% 15% 20%

MEDICAL MANAGEMENT: BRCA1/2 CARRIER

**Breast**

- **Screening**
  - Self breast exam start at 18
  - Annual Clinical breast exam at 25
  - Annual Breast MRI (starting at age 25)
  - Annual Mammogram (starting at age 30)
  - Men start SBE in 30s, Clinical breast exams every 1y at 35, consider mammogram

- **Prevention**
  - Preventive bilateral mastectomy
  - Chemoprevention (Tamoxifen)

**Ovary**

- **Prevention**
  - Preventive salpingoophorectomy (removal of ovaries and fallopian tubes) by age 35-40
  - Chemoprevention (birth control pills)

- **Screening**: Limited usefulness! Clinicians discretion…
  - Transvaginal ultrasound
  - CA-125

**Other Cancers**

1. **Prostate**: Screening for men start at age 40
2. **Pancreatic**: Limited screening. Only if family history
3. **Melanoma**: Annual dermatology

NCCN v. 2017
REDUCING CANCER RISKS IN BRCA1/2 CARRIERS

Proactive Cancer Management Reduces the Risks

Preventive Measure

<table>
<thead>
<tr>
<th>Preventive Measure</th>
<th>Breast Cancer Risk Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>53%*</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>≥90%</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>Up to 68%</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>Up to 60%</td>
</tr>
</tbody>
</table>

* In contralateral breast cancer.
CASE 2: EXAMPLE OF HBOC IN A PANEL SETTING

- Newly dx 51 y.o. woman with breast cancer
- Referred for genetic counseling
  - Sister with endometrial cancer has a CHEK2 mutation (My Risk at Myriad)
    - CHEK2 is a moderate risk breast cancer genes
  - Paternal family history of breast and pancreatic cancer
  - ALSO a STK11 VUS (Variant of uncertain significance) found in sister
    - STK11 is seen in Peutz-Jeghers syndrome: breast, pancreatic, Hamartomatous polyps, other cancers

FAMILY HISTORY FOLLOWS:
- Proceed with My Risk Analysis Myriad
  - Not convinced that the CHEK2 mutation explained the family history of breast and pancreatic cancer
  - Unknown if STK11 VUS is pathogenic
  - Stayed with Myriad to keep the family data together
POSITIVE BRCA2 Deleterious Mutation

BRCA2
c.1796_1800del (p.Ser599*)
Heterozygous

High Cancer Risk
This patient has Hereditary Breast and Ovarian Cancer syndrome (HBOC).

DETAILS ABOUT: BRCA2 c.1796_1800del (p.Ser599*): NM_000059.3; (aka: 2024del5)

Functional Significance: Deleterious - Abnormal Protein Production and/or Function
The heterozygous germine BRCA2 mutation c.1796_1800del is predicted to result in the premature truncation of the BRCA2 protein at amino acid position 599 (p.Ser599*).

Clinical Significance: High Cancer Risk
This mutation is associated with increased cancer risk and should be regarded as clinically significant.

ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

<table>
<thead>
<tr>
<th>GENE</th>
<th>VARIANT(S) OF UNCERTAIN SIGNIFICANCE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
</table>
| BRCA2  | c.5636A>G (p.Glu1879Gly) (aka E1879G (5864A>G)) | UNCERTAIN CLINICAL SIGNIFICANCE
There are currently insufficient data to determine if these variants cause increased cancer risk. |
| STK11  | c.1211C>T (p.Ser404Phe)               |                                                    |
1. BRCA2 result significantly alters this patient’s management
   ✓ Opted for bilateral mastectomy
   ✓ TAH/BSO recommended and pancreatic cancer screening in a research trial (Dana Farber)
   ✓ Update for 2017: if she develops metastatic Breast cancer eligible for PARP inhibitor

2. How is CHEK2 mutation modifying the expression of BRCA2 or visa versa in this family?...

3. Single site analysis is not always the most appropriate test
   ✓ Still look at family history
   ✓ We will start to see more and more families/individuals with multiple mutations
4. Impact for the rest of the family

1. Offer to test children and family members at age 18 since BRCA1/2 is adult onset

2. Discuss risk for Fanconi Anemia in parents that are carriers for BRCA2; 25% risk to offspring

3. CHEK2 and BRCA2 mutations to test for in her two other sisters
   - CHEK2 is a moderated risk cancer gene; elevated risk for breast, colon, male breast, and prostate cancer
   - Women with a CHEK2 mutation would still be eligible for high risk breast cancer surveillance
   - Men and women with CHEK2 have elevated risk for colon cancer. Per NCCN guidelines start colonoscopy at age 40, repeat every 5 years.
CASE 3: EXAMPLE OF LYNCH SYNDROME

- 28 year old man
  - Diagnosed with small bowel cancer at age 25
  - Loss of expression of DNA mismatch repair enzyme MSH2 and MSH6

- Family History:
  - Classic Lynch pattern
  - Meets Amsterdam Criteria for Lynch Syndrome
LYNCH EXAMPLE

HNPCC/Lynch Syndrome: Gene Sequence Analysis & Deletion/Duplication Analysis of MSH2

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>MSH2 FULL GENE</th>
<th>Known Mutation(s):</th>
<th>None Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Variants of Unknown Significance:</td>
<td>None Detected</td>
</tr>
<tr>
<td>MSH2 DEL/DUP</td>
<td>Gross Deletion(s)/Duplication(s):</td>
<td>EX3_6del</td>
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- 2011: Ordered only MSH2 gene analysis because the pattern loss of MSH2/MSH6 is often seen is more often due to a germline in MSH2 gene. Would now have include deletion duplication analysis of the EPCAM gene. If negative would have reflexed to MSH6.
- MSH2 associated with increased risk for colon, uterine, ovarian, stomach, small bowel, pancreatic urinary and renal pelvis
- 50% chance for first degree family members to have MSH2 mutation
Cancer risk does vary depending on gene; highest with MLH1 and MSH2. MSH6 and PMS2 are associated with much lower risk for colorectal cancer (10-22%) and endometrial cancer 15% to 26%.
## MEDICAL MANAGEMENT: LYNCH SYNDROME

<table>
<thead>
<tr>
<th>Screening Method</th>
<th>Age to Start Screening</th>
<th>Frequency of Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colon</strong></td>
<td>20-25y or 10y earlier than earliest age of first diagnosis</td>
<td>Every 1-2 year</td>
</tr>
<tr>
<td><strong>Gynecological (Endometrial and Ovarian)</strong></td>
<td>18-21 y</td>
<td>Every 6 months to a year</td>
</tr>
<tr>
<td>Pelvic Ultrasounds</td>
<td>30-35 y or 5-10 y earlier than earliest age of first diagnosis of ovarian cancer in family</td>
<td>Every 6-12 months</td>
</tr>
<tr>
<td>Limited usefulness!!! Transvaginal ultrasound and CA-125 levels and endometrial biopsies</td>
<td></td>
<td>Every year for biopsies</td>
</tr>
<tr>
<td><strong>Stomach and Small Bowel</strong></td>
<td>30-35 y</td>
<td>Every 3-5 years</td>
</tr>
<tr>
<td>Upper Endoscopy (consider capsule endoscopy for small bowel cancer)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Upper Urinary Tract</strong></td>
<td>30-35y</td>
<td>Every year</td>
</tr>
<tr>
<td>Urology visit with urine cytology, urinalysis and cystoscopy</td>
<td></td>
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</tr>
</tbody>
</table>

### Preventative Surgery
- **Endometrial Cancer**: total abdominal hysterectomy (TAH)
- **Ovarian Cancer**: bilateral salpingo-oophorectomy (BSO) upon completion of childbearing

### Chemoprevention
- Research into different drugs for the prevention of colorectal cancer (Aspirin, NSAIDS)

### Treatment
- Use of immunotherapies for cancer
CASE 3 LYNCH SYNDROME INTERPRETATION

- Patient at risk for additional cancer; needs to be followed closely
- Does he want more children?
  - Discuss PGD (preimplantation genetic diagnosis)
- Should we test his son who is 3?
  - Not yet, but consider testing at 15 since patient and his paternal aunt were 25 at time of diagnosis
  - Typically would only offer genetic testing at 18
  - Discuss Genetic Discrimination
- Discuss CMMRD- Constitutional Mismatch Repair Protein Expression
  - Autosomal Recessive: Parents who are carriers for a mutation in the same Lynch syndrome gene have a 25% chance to have a child with CMMRD (high risk for childhood cancers, café au lait macules similar to NF1)
50 y.o. woman referred for genetic counseling
- family history of breast, colon, and pancreatic

- No personal history of cancer.
  - Is she really the best person to test in the family?
  - No close living relatives with cancer
  - She was offered the MyRisk panel
RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

<table>
<thead>
<tr>
<th>GENE</th>
<th>MUTATION</th>
<th>INTERPRETATION</th>
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<tbody>
<tr>
<td>ATM</td>
<td>c.2250G&gt;A (p.Lys750Lys)</td>
<td>High Cancer Risk</td>
</tr>
<tr>
<td></td>
<td>Heterozygous</td>
<td>This patient has ATM-associated Cancer Risk.</td>
</tr>
</tbody>
</table>

DETAILS ABOUT: ATM c.2250G>A (p.Lys750Lys): NM_000051.3

Functional Significance: Deleterious - Abnormal Protein Production and/or Function
The heterozygous germline ATM mutation c.2250G>A is located near the 3' end of exon 13, and it is predicted to result in abnormal mRNA splicing.

Clinical Significance: High Cancer Risk
This mutation in combination with a second ATM mutation has been reported in multiple patients with classic features of the autosomal recessive disorder ataxia-telangiectasia (Stankovic T et al. 1998, Am J. Hum. Genet. 62:334-345; Teraoka SN et al. 1999, Am J. Hum. Genet. 64:1617-1631). This mutation is associated with increased cancer risk and should be regarded as clinically significant.
ATM GENE: A MODERATE PENETRANCE GENE:

**Breast Cancer Risk 17-52%** Per 2017 NCCN guidelines
- At age 40 annual MRI and mammogram every 6 months
- Discuss risk reduction strategies; mastectomy (no firm recommendations for or against at this time)

**Pancreatic Cancer** (elevated risk, exact % not known)
- Consider pancreatic cancer screening (MRCP or EUS), understand screening limitations, enroll in research protocol

**Possible risk for other cancers?** (Unknown at this time; more research) ??Lymphoma, prostate cancer…

**Radio-sensitivity?** No consensus yet on avoiding radiation therapy

**Ataxia Telangiectasia:** autosomal recessive disorder, characterized by progressive difficulty with coordinating movements (ataxia) beginning in early childhood with higher risk for immune deficiencies and leukemia and lymphomas; Important for family members of childbearing age to know carrier status and test partner
MULTI-GENE EXAMPLE INTERPRETATION

- Provides patient with understanding into her family history
- She can now enroll in high risk breast cancer screening (MRI and mammogram every 6 months)
- She has a family history of pancreatic cancer….should she be screening. Discussed limitations.
  - Typically stand by the rule of offering screening to mutation carriers when they have one first degree relative with pancreatic cancer or >2 second degree relatives with pancreatic
- Other issues: Will insurance cover screening and testing family members?
THANK YOU!

Questions?

Email: caryj@newecs.og
REFERENCE SLIDES

REFERRAL BASED ON SYNDROME
**Hereditary Breast and Ovarian Cancer Syndrome (HBOC)**

- Breast cancer by age 45
- Triple negative breast cancer by age 60 (NCCN 2011 guidelines)
- Ovarian cancer by age 50
- Individual & one relative* with breast cancer, both by age 50
- Two or more breast primaries, with first by age 50
- Breast cancer at any age & 2 relatives with breast and/or ovarian cancer
- Breast and ovarian cancer in individual
- Breast cancer by age 50 & relative with ovarian cancer
- Ovarian cancer & one relative with breast cancer by age 50 or 2 relatives with breast cancer at any age
- Ashkenazi Jewish heritage, breast cancer by 50 or ovarian cancer at any age
- Male breast cancer in patient or relative

- Breast or ovarian cancer at any age & 2 relatives with pancreatic cancer
- Pancreatic cancer at any age & 2 relatives with breast and/or ovarian and/or pancreatic cancer
- Confirmed BRCA1 or BRCA2 mutation in family
- Unaffected individual with a first-degree relative (FDR) or second-degree relative (SDR) meeting any of the above criteria
- Individuals with an HBOC-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years
- *First-, second-, and third-degree relatives
**Li-Fraumeni Syndrome**

- Breast cancer by age 30 and BRCA negative, especially if family history of sarcoma, brain tumor, or adrenocortical carcinoma
- Individual diagnosed with a childhood tumor or sarcoma, brain tumor, or adrenocortical carcinoma by age 45 & relative with breast cancer, sarcoma, leukemia, brain tumor, or adrenocortical carcinoma
- Confirmed p53 mutation in family
- Individuals with an LFS-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years
**Cowden Syndrome**

- Breast cancer in individual & one of the following in individual:
  - Endometrial Cancer
  - Non-medullary thyroid cancer
- Breast cancer in individual & family history of the cancers listed above
- Confirmed PTEN mutation in family
- Individuals with a Cowden Syndrome-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years

*Other major criteria for Cowden Syndrome include: macrocephaly, benign skin growths (facial and mucosal), and multiple GI hamartomas/ganglioneuromas. Minor criteria for Cowden Syndrome include: thyroid lesions (i.e. nodules, goiter), mental handicap, autism spectrum disorder, single GI hamartoma/ganglioneuroma, fibrocystic breast disease, lipomas, fibromas, renal cell carcinoma and uterine fibroids.*
**HNPCC/Lynch Syndrome**

- Colorectal cancer by age 50
- Endometrial cancer by age 50
- Adenoma by age 40
- Colorectal or endometrial cancer at any age & FDR with an HNPCC-associated cancer* diagnosed by age 50
- Colorectal or endometrial cancer at any age & 2 or more FDR or SDR with HNPCC-associated cancers* regardless of age
- 2 or more HNPCC-associated cancers* in individual
- IHC for mismatch repair proteins (MLH1, MSH2, MSH6, or PMS2) demonstrating absence of one or more proteins in tumor
- Tumor demonstrates MSI-H
- Confirmed MLH1, MSH2, MSH6, or PMS2 mutation in family

- Unaffected individual with a FDR or SDR meeting any of the above criteria
- Individuals with an HNPCC-associated cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years

* colorectal, endometrial, stomach, ovary, small bowel, pancreas, ureter or renal pelvis, biliary tract

FDR= first degree relative
SDR= second degree relative
**Polyposis Syndromes**

- Refer if: > 10 adenomas in a lifetime

**Hereditary Melanoma**

- Individual with pancreatic cancer and melanoma
- 3 FDRs or SDRs affected with melanoma and/or pancreatic cancer
- Confirmed CDKN2A mutation in family
- Individuals with melanoma or pancreatic cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years

FDR = first degree relative  
SDR = second degree relative
Hereditary Prostate Cancer

• Personal history of:
  • metastatic, early onset, or Gleason 7 or higher prostate cancer
  • prostate cancer plus a family history of breast (male or female), ovarian, pancreatic, and other cancers
  • Multiple primary cancers

• Family history of:
  • 3 or more prostate or other cancers on the same side of the family
  • Early onset (< 50y) uterine, colorectal, breast, or other cancers
  • Male breast or ovarian cancer
**Hereditary Pancreatic Cancer**
- Individual with pancreatic cancer & two close relatives with pancreatic cancer at any age
- Families with at least two FDRs with pancreatic cancer
- Families with at least three FDRs or SDRs with pancreatic cancer
- Individuals with pancreatic cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years *First, second-, and third-degree relatives

**Hereditary Kidney Cancer**
- Multiple generations of kidney cancer
- Bilateral kidney cancer
- Early age of onset
- Individuals with a kidney cancer that have a limited family history, such as a small family or family without many relatives surviving beyond 45 years

FDR= first degree relative  
SDR= second degree relative
**Neuro-oncology automatic referrals:**

- Individual with primary brain/neuroaxis tumor and one FDR with primary brain/neuroaxis tumor
- Two or more CNS or retinal hemangioblastomas
- Single CNS or retinal hemangioblastoma and personal or family history of renal, hepatic, or pancreatic cysts; pheochromocytoma; renal cell carcinoma; endolymphatic sac tumor; cystadenoma of the epididymis/broad ligament; or neuroendocrine tumor of the pancreas
- Bilateral vestibular schwannoma/acoustic neuroma
- Unilateral vestibular schwannoma/acoustic neuroma with personal or family hx of meningioma, schwannoma, glioma, neurofibroma, or juvenile posterior subcapsular lens opacity

**Li-Fraumeni Syndrome**

- Breast cancer by age 30 and BRCA negative, especially if family history of sarcoma, brain tumor, or adrenocortical carcinoma
- Individual diagnosed with a childhood tumor or sarcoma, brain tumor, or adrenocortical carcinoma by age 45 & relative with breast cancer, sarcoma, leukemia, brain tumor, or adrenocortical carcinoma
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