HEREDITARY CANCER SYNDROMES

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Common Genetics Terms

• **Gene**: A hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism.

• **Trait**: A distinguishing feature, a genetically determined characteristic or condition.

• **Locus**: Specific area on a chromosome where the gene is found.

• **Allele**: Versions of a gene.

• **Genotype**: The genetic makeup of an organism.

• **Phenotype**: The physical appearance of an organism.

• **Pleiotropy**: The ability of a gene to affect an organism in many ways.

• **Epistasis**: Gene at one locus influences the expression of a gene at another locus (different gene).

• **Polygenic Inheritance**: Additive effect of 2 or more genes on a phenotypic character.

• **Phenocopy**: The observed result of an environmentally induced, nongenetic alteration of a phenotype to a form that resembles the expression of a known genetic mutation.
Genetic Heterogeneity

• Genetic heterogeneity: A number of similar or identical phenotypes are caused by different genotypes
  • mutations at different loci
    • locus heterogeneity
      • Hearing loss

• may be the result of different mutations at the same locus
  • allelic heterogeneity means that different mutations within a single gene locus (forming multiple alleles of that gene) cause the same phenotypic expression.
  • For example, there are over 1000 known mutant alleles of the CFTR gene that cause cystic fibrosis.
Variation in the Phenotype

- Penetrance
  - the probability that a gene will have ANY phenotypic expression
    - it is an all or none concept
    - if some people with an appropriate genotype fail to express the phenotype, there is reduced penetrance

- Expressivity
  - Severity of the manifestations of the phenotype
  - when phenotypic severity varies among those with identical genotypes, variable expressivity is shown

- Pleiotropy
  - Multiple phenotypic effects of a single gene or gene pair
  - when the effects are not obviously related
Genotype vs. Phenotype

- **Same genotype** (genetic makeup) **different phenotype** (observed features)
  - Pleiotropy (single gene influences multiple phenotypic traits)
    - Ex. MSH6 assoc. w/ colon ca, endometrial ca, ovarian ca, ureter ca, etc.
  - Expressivity (different degrees of presentation)
    - Ex. APC gene mutations– classic vs. attenuated

- **Same phenotype different genotype**
  - Ex. Breast cancer assoc. w/ mutations in BRCA, PTEN, TP53
Goals of Pedigree Analysis

• 1. Determine (suggest) the mode of inheritance: autosomal dominant (AD), autosomal recessive (AR), sex-linked, mitochondrial.

• 2. Determine the probability of inheriting an affected gene for the offspring.
Basic Symbols

- □ Male (unaffected)
- ● Male (affected)
- ○ Female (unaffected)
- ◆ Female (affected)
- △ Unknown sex
- ‹ Dead
- □ □ Mating
- □ ○ Consanguineous mating
- □ □ Offspring
  Arrow points to proband
Modes of Inheritance

• **Autosomal Dominant**: affects both males and females in all generations.
  • Examples: Achondroplasia, Huntington’s disease, Neurofibromatosis types 1 & 2, and many, many more!
Modes of Inheritance

- **Autosomal Recessive**: offspring of 2 carrier parents can be affected. Usually only seen in one generation. Males and females affected and transmit.
  - Consanguinity may be apparent in parents of affected child.
  - Examples: Cystic Fibrosis, PKU, Wilson’s disease, and many more!
Modes of Inheritance

- **X-linked recessive**: only sons of heterozygous mothers (carriers) can be affected, there is no father to son transmission. All daughters of an affected male will be carriers.
  - Examples: Duchenne muscular dystrophy, Hemophilia A and B
  - Females may rarely be affected due to non-random inactivation of X chromosome
Modes of Inheritance

- **X-linked dominant**: Males and females can be affected. All daughters of affected fathers are affected. No male to male transmission.
  
  - Example-
    - Hypophosphatemic rickets (X-linked hypophosphatemic rickets): increased phosphate wasting at proximal tubule (kidney)
Modes of Inheritance

- **Mitochondrial**: Transmission ONLY through the mother. Mitochondria are only inherited from the mother. All offspring of affected mothers are affected.

  - Variable expression due to heteroplasmy
  - The effect a mutation in mtDNA will have on a cell's function will therefore depend on the number of mutant organelles in a cell compared to the number of normal, or "wild type", present. In this respect, each cell is analogous to an organism in which somatic mutation can produce mosaicism. Here the mixture of genotypes is termed heteroplasmy.

*Example of a family tree showing members of a family in which runs an inheritance of a mitochondrial condition (Adapted from: Greenwood Genetic Centre (1995): Counseling Aids for geneticists. Greenwood Genetic Centre, USA)*
General Principles

- Causes of cancer
- Inheritance Patterns
- Importance of diagnosing a genetic disorder
- Cancer genetic risk assessment
Cancer

- **Familial cancer** ~ 15-20%
  - More cases of a specific type(s) of cancer within a family than expected, but no specific pattern of inheritance
  - Age of onset variable
  - May result from chance clustering of sporadic cases
  - May result from common genetic background (low penetrance gene), similar environment and/or lifestyle factors

- **Hereditary cancer** ~ 5-10%
  - Early diagnosis
  - Bilateral cancers
  - Multiple primaries in an individual
  - Multiple affected family members
  - Spanning a number of generations
  - Rare cancers (ovarian cancer, male breast cancer)

- **Sporadic cancer** ~ 75-80%
  - Typical age of onset (older age)
  - Even if there is more than one case in the family, there is no particular pattern of inheritance
• ~5-10% of all cancers (with some exceptions)

• High risk of multiple primaries

• Occur at younger age

• Multiple family members affected

• Early identification would benefit from preventive care options
Genetic Cancer Risk Assessment Component and Activities

• Document patient and family cancer history
• Assess psychosocial and interpersonal dynamics
• Discuss basic principles of cancer genetics
• Assess/interpret personal and family medical history to establish differential diagnosis
• Assess mutation probabilities/empiric risk
• Physical examination
• Develop genetic testing strategies
• Facilitate informed consent when testing is pursued
• Disclose/interpret test results
• Develop personalized risk management plan
• Case administration and management
Obtaining a Family History

• 4 generations – list all maternal and paternal relatives, whether or not they have had cancer
  • Limited family structure (<2 females over age 45 on one side of the family) for HBOC
• Age at cancer diagnosis
• Pathology
• Age at death/cause of death
• History of oophorectomy or hysterectomy, CRC polyps-including number and pathology
• Ancestry
Development of Hereditary Cancer

In hereditary cancer, one damaged gene is inherited.
(Some) Hereditary Cancer Syndromes

- Hereditary Breast and Ovarian Cancer Syndrome (BRCA1 and BRCA2)
- HNPCC/Lynch Syndrome (MMR genes – MLH1, MSH2, MSH6, PMS2) and EPCAM
- FAP, AFAP and MAP (APC and MYH)
- Malignant melanoma (p16, CDK4)
- Hereditary Diffuse Gastric Cancer (CDH1)
- Paraganglioma Syndromes (SDHB,C,D)
- Von Hippel Lindau (VHL)
- Cowden Syndrome (PTEN)
- Neurofibromatosis type 1 and type 2 (NF1 and NF2)
- Juvenile Polyposis (BMPR1A, SMAD4, LKB1)
- Li-Fraumeni Syndrome (TP53)
## Hereditary syndromes associated with breast cancer
*(most common)*

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Associated cancers/ disease characteristics</th>
<th>Inheritance mode</th>
<th>Lifetime breast cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
<td>Breast (M, F) Ovarian, prostate, pancreas, melanoma</td>
<td>AD</td>
<td>Up to 84%</td>
</tr>
<tr>
<td>Li Fraumeni</td>
<td>TP53</td>
<td>Breast, sarcomas, brain tumors, leukemia, adrenocortical tumors</td>
<td>AD</td>
<td>~60%</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>PTEN</td>
<td>Breast, thyroid, endometrial, Macrocephaly, lipomas, hamartomas</td>
<td>AD</td>
<td>25-50%</td>
</tr>
<tr>
<td>Hereditary diffuse gastric cancer</td>
<td>CDH1</td>
<td>Diffuse gastric cancer, lobular breast cancer</td>
<td>AD</td>
<td>39% (lobular breast cancer)</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>Breast, pancreas, GI polyps, Sex cord tumors</td>
<td>AD</td>
<td>29% (by age 65)</td>
</tr>
</tbody>
</table>

| Ataxia                              | ATM        |                                                                                 | AD              | 15%                         |
Hereditary Breast and Ovarian Syndrome (HBOC)
# BRCA 1 and 2 genes mutation penetrance

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Inherited Risk</th>
<th>General Population Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast - female</td>
<td>45 - 84%*</td>
<td>11-12%</td>
</tr>
<tr>
<td>- male</td>
<td>up to 8%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ovarian and ovarian related</td>
<td>11 - 62%</td>
<td>1.5-2%</td>
</tr>
<tr>
<td>Prostate</td>
<td>20%</td>
<td>16.2%</td>
</tr>
<tr>
<td>There is also an increased incidence of melanoma, pancreatic and/or colon cancer in some families.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Women who have already had breast cancer have up to a 20% risk to develop a new primary breast cancer within 5 years of their initial diagnosis, and up to a 60% risk in their lifetime.*
Models used to calculate breast cancer risks

• **Claus Model** - Age specific risk estimates for breast cancer, considers maternal and paternal history, age at onset, first and second degree relatives (excludes some relatives).

• **Gail Model** - Estimates the chance that a woman of specific age would develop breast cancer, includes age at menarche, childbirth, # of prior biopsies, and first degree relatives. Excludes paternal relatives, non-first degree relatives. Adapted to consider atypical hyperplasia.


Models used to calculate likelihood of BRCA1 or BRCA2 mutation

- **BRCAPRO** - computer model, uses pedigree to calculate risk based on several different models.
- **Myriad Model/Tables** - use family history and personal history to estimate risk of mutation in BRCA1 or BRCA2.
- **BOADICEA** (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) – University of Cambridge computer model to assess risk of BRCA1/2 mutation.

Role of BRCA1&2 genes

• Tumor suppressor genes
• Primarily executing the DNA double-strand break repair by homologous recombination
Function of BRCA in DNA damage repair

RAD51

BRCA

γH2AX

DNA damage with double stranded break

Repair via homologous recombination

Loss of functional BRCA proteins and implications for DNA repair
• Early age onset of Breast cancer (BC) (≤ 50)
• Triple negative (ER/PR/HER2)
• Two breast cancer primaries in the individual (synchronous or metachronous)
• BC + one or more of the following cancers: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestation, leukemia/lymphoma
• BC +
  • ≥ 1 (first, second or third degree relative) with BC ≤ 50
  • ≥ 1 (first, second or third degree relative) with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age
  • ≥ 2 (first, second or third degree relative) with BC and/or pancreatic cancer at any age
• Male BC
• Ovarian/fallopian tube/primary peritoneal cancer regardless of age
Criteria for referral for genetic risk evaluation -

**Unaffected individual**

- ≥ 2 BC primaries from the same side of the family
- ≥ 1 OC (ovarian cancer) primary from the same side of the family
- BC + one or more of the following cancers: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestation, leukemia/lymphoma
- Known familial mutation in a breast cancer susceptibility gene
- High risk population (e.g. Ashkenazi Jewish)
- Male breast cancer
BRCA1 & 2 founder mutations

Ashkenazi Jewish population (most common):

• BRCA1 185del AG
• BRCA1 5382ins C
• BRCA2 6174del T

~ 1/40 Ashkenazi Jews are BRCA1/2 mutation carriers (1:400 to 1:800 in general population)

http://www.ncbi.nlm.nih.gov/books/NBK1247/
BRCA1/2 gene testing options

• Comprehensive BRAC Analysis Testing:
  - Full examination of the most common changes of BRCA1 and BRCA2 genes.
  - For people who do not have any known gene mutations in the family.

• Single Site BRAC Analysis:
  - For people who already know a BRCA1 or BRCA2 gene mutation is in the family.

• Multisite 3 BRAC Analysis:
  - Assess for the three most common BRCA1 and BRCA2 gene mutations in individuals of Ashkenazi Jewish ancestry.

• BRAC Analysis Large Rearrangement Test (BART):
  - There are some much less common gene mutations that can only be found with this test.

Possible test results

Positive Result

Increased Cancer Risk
Medical management based on recommendations for people who have the BRCA1 or BRCA2 gene mutations

A gene mutation has been previously identified in the family (Single Site Analysis)

No Increased Cancer Risk
Medical management based on general population cancer screening recommendations

No gene mutation has been previously identified in the family (Comprehensive Analysis)

Chance of HBOC Significantly Reduced
Medical management based on personal and family history of cancer

Negative Result

Uncertain Variant

Cancer Risk Not Fully Defined
Medical management based on personal and family history of cancer

Management of BRCA Carriers

Increased surveillance
- Breast cancer, ovarian cancer, prostate cancer, melanoma and pancreatic cancer

Chemoprevention
- Tamoxifen (for breast cancer)

Prophylactic surgery
- Mastectomy, salpingo-oophorectomy
Power of a negative test result in a HBOC family

A. Our patient was tested and no mutation found
   • Increased risk for breast cancer based on family history
     1. Annual CBE and mammogram
     2. Annual breast MRI
     3. Consider tamoxifen
   • Increased risk for ovarian cancer based on family history
     1. Screening for ovarian cancer
     2. Consider prophylactic bilateral salpingo-oophorectomy

B. Mutation identified in pt’s relative and our pt tests negative for the familial mutation
   • Pt. now at the general population risk to develop breast and ovarian cancer
     1. Annual CBE and annual mammogram
     2. No screening for ovarian cancer
New investigational therapy: PARP inhibitors

• Two genes are said to be in a **synthetic lethal relationship** if a mutation in either gene alone is not lethal but mutations in both cause the death of a cell.
• Inhibition of PARP[poly(adenosine-diphosphate-ribose) polymerase] appears to selectively kill cells which lack functional BRCA.
PARP function

DNA damage with single stranded break

Poly ADP-ribose polymerase (PARP)

DNA damage repaired base pair excision

DNA damage with single stranded break

Poly ADP-ribose polymerase (PARP)

No repair. Becomes double stranded break

The role of PARP in DNA repair and connections to other proteins where there is evidence for synthetic lethality in cancer treatment. Wang X et al 2010
PARP Inhibitors

• There are currently a number of ongoing clinical studies in *BRCA1/2* mutation carriers utilizing various PARP inhibitors both as single agents and in combination with chemotherapy.

• Phase III studies are needed
Li-Fraumeni Syndrome

• Initially described by Frederick Li and Joseph Fraumeni as syndrome associated with sarcomas and other diverse tumors.

• Associated cancer include:
  ○ soft-tissue sarcoma,
  ○ osteosarcoma,
  ○ early-onset breast cancer,
  ○ brain tumors,
  ○ adrenocortical carcinoma,
  ○ and leukemias, primarily acute leukemia.

• Inherited in an autosomal dominant manner.
• Gene mutations: TP53 (tumor suppressor gene)
Cowden syndrome

- An autosomal dominantly inherited hamartoma syndrome with an incidence of at least 1/200,000 (probably an underestimate)
- Pathognomonic cutaneous feature is the trichilemmoma, a benign tumor derived from outer-root sheath epithelium of a hair follicle
- Variable expression
- Associated with inherited alterations in the gene, PTEN gene (Tumor suppressor)
- The KLLN gene on chromosome 10q23.31 shares the same transcription site as the PTEN gene, but is transcribed in the opposite direction.
- Among 123 patients with a clinical diagnosis of Cowden or Cowden-like syndrome without germline PTEN or SDHB/D mutations, Bennett et al. (2010) found that 45 (37%) had germline hypermethylation and epigenetic inactivation of the KLLN promoter

Cancer Risks Associated with Cowden Syndrome:
- Female Breast Cancer 25%-50% lifetime risk (vs ~11% in general pop.) Average age of diagnosis may be around age 38-46
- Thyroid Carcinoma: 3%-10% lifetime risk (vs 1% in general population) Non-medullary
- Endometrial Cancer 5-10%
Cowden syndrome- Mucocutaneous features

(A) Acral keratotic lesions of the feet (case 1),
(B) Acral keratotic lesions of the dorsal aspect of hands (case 1),
(C) Papillomas on hypertrophic gingival mucosa (case 3),
(D) Pinkish papules of the nose (case 4).

Trichilemmoma

[Image of skin lesion]

Hereditary Diffuse Gastric Cancer (HDGC)

CDH1 gene – only gene known to be associated w/ HDGC; however accounts for only 1/3 of hereditary diffuse gastric cancers a poorly differentiated adenocarcinoma that infiltrates into the stomach wall causing thickening of the wall (*linitis plastica*) without forming a distinct mass.

Diffuse gastric cancer is also referred to as signet ring carcinoma or isolated cell-type carcinoma.

CDH1 mutations confer:

- Increased risk for diffuse gastric cancer
  - 67% lifetime risk for men
  - 83% lifetime risk for women
- Increased risk for lobular breast cancer (39% lifetime risk)
- Majority of cancers diagnosed before age 40
Peutz-Jeghers Syndrome
Clinical Features

- Benign growths (polyps) in small intestine (stomach/bowel)
- Abdominal pain and internal bleeding
- Breast, testicular, pancreatic cancers
- Dark-brown or dark-blue spots on lips, gums, inside mouth, around mouth, eyes, nostrils (mucocutaneous macules)
Peutz-Jeghers Syndrome - Diagnosis

- Gastrointestinal polyps and pigmented spots
- Endoscopy detects polyps
- Polyps have distinct shape and histological composition
- DNA test available for asymptomatic individuals
- In individuals with a clinical diagnosis of PJS, molecular genetic testing of *STK11 (LKB1)* reveals disease-causing mutations in nearly all individuals who have a positive family history and approximately 90% of individuals who have no family history of PJS.
Colorectal Cancer Genetics

- Sporadic
- Rare CRC syndromes
- HNPCC (2-5%)
- FAP (1%)
- Familial

from Burt, RW. Inheritance and Genetic Testing for Colon Cancer
Lynch syndrome (LS)/Hereditary non-polyposis colorectal cancer

- Germline mutations in one of four mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*).
- *MLH1* and *MSH2* germline mutations account for approximately 90%;
- *MSH6* mutations ~7%-10%; and
- *PMS2* mutations in fewer than 5%.
- Germline deletions in *EPCAM* (not a mismatch repair gene) inactivate *MSH2* in about 1% of individuals with Lynch syndrome.

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>General Population Risk</th>
<th>Lynch Syndrome (<em>MLH1</em> and <em>MSH2</em> heterozygotes)</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>52%-82%</td>
<td>44-61 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>25%-60%</td>
<td>48-62 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>6%-13%</td>
<td>56 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>4%-12%</td>
<td>42.5 years</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>1.4%-4%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>1%-4%</td>
<td>~55 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>3%-6%</td>
<td>49 years</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1%-3%</td>
<td>~50 years</td>
</tr>
<tr>
<td>Sebaceous neoplasms</td>
<td>&lt;1%</td>
<td>1%-9%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Aarnio et al [1999], Vasen et al [2002], American Cancer Society [2002], Hampel et al [2005], Ponti et al [2006], South et al [2008], Watson et al [2008], barrow et al [2009], Barrow et al [2009], Stoffel et al [2009]
Lynch syndrome- MMR genes

The DNA mismatch repair (MMR) mechanism in humans.

*Current Genomics, 2009, Vol. 10, No. 2*
Amsterdam Criteria used to diagnose Lynch syndrome (3-2-1)

Amsterdam Criteria

- **Three** or more family members, one of whom is a first-degree relative of the other two, with a confirmed diagnosis of colorectal cancer
- **Two** successive affected generations
- **One** or more colon cancers diagnosed before age 50 years
- FAP (Familial Adenomatous Polyposis) excluded

Amsterdam II Criteria

- **Three** or more family members, one of whom is a first-degree relative of the other two, with HNPCC-related cancers **

Bethesda Guidelines - used to screen (criteria for microsatellite instability testing)

Colorectal cancer

- Under age 50
- With a synchronous or metachronous HNPCC tumor
- Under age 60 with histology consistent with HNPCC
  - tumor infiltrating lymphocytes, Crohn-like reaction, mucinous/signet ring differentiation, medullary growth pattern
- With a first-degree relative who has an HNPCC tumor <50
- With 2 first or second-degree relatives with HNPCC tumor

Pedigree of a Lynch syndrome family
Lynch syndrome testing (colorectal cancer)

**INDICATIONS FOR TESTING**
- Tumors from individuals should be tested for microsatellite instability in the following situations (based on Revised Bethesda Guidelines for testing colorectal tumors for microsatellite instability):
  - Colorectal cancer diagnosed in an individual <50 years of age
  - Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors (colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain tumors; sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome, and carcinoma of the small bowel), regardless of age
  - Colorectal cancer with MSI-H histology (presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in an individual <50 years of age
  - Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one cancer diagnosed at <50 years
  - Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age
  - Patients diagnosed with Muir-Torre syndrome or Turcot Syndrome (especially glioblastoma brain tumor)
  - Family members of individuals with a known mismatch repair gene mutation

**Consider Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC)**

**ORDER**
- Microsatellite Instability by:
  - Mismatch Repair by IHC

- Stable as per IHC but high clinical suspicion of Lynch syndrome exists

- ORDER
  - HNPCC/Lynch Syndrome, Microsatellite Instability by PCR

- Abnormal staining for MLH1 and PMS2

- Test for BRAF V600E mutation
  - ORDER
    - BRAF codon 600 Mutation Detection with Reflex to MLH1 Promoter Methylation

- Genetic mutation testing for Lynch syndrome
  - Recommend HNPCC/Lynch Syndrome (MSH2) Sequencing and Deletion/Duplication as first test

- Genetic mutation testing for Lynch syndrome
  - Recommend HNPCC/Lynch Syndrome (MSH6) Sequencing and Deletion/Duplication as first test

- Genetic mutation testing for Lynch syndrome
  - Recommend HNPCC/Lynch Syndrome (PMS2) Sequencing and Deletion/Duplication as first test

- Probable sporadic colorectal cancer

- Genetic mutation testing for Lynch syndrome
  - Recommend HNPCC/Lynch Syndrome (MLH1) Sequencing and Deletion/Duplication as first test

- *Note: Targeted testing for a mutation previously identified in a family member is also available

- Recommend Familial Mutation, Targeted Sequencing

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www.arupconsult.com
**Lynch syndrome**

Microsatellite instability testing is used to identify tumors caused by defective mismatch repair by comparing the number of nucleotide repeats in a panel of microsatellite markers in normal tissue with the number from tumor tissue from the same individual.

Microsatellite stability (MSS) is present if the same number of repeats is present in each marker in both the tumor and the normal tissue.

Microsatellite instability (MSI) is present if the number of repeats in the tumor and the normal tissue differs.

---

Microsatellite replication

<table>
<thead>
<tr>
<th>Normal</th>
<th>Abnormal (Mismatch repair defect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCACACACACACCT</td>
<td>GCACACACACCT</td>
</tr>
<tr>
<td>CGTGTGTTGTTGGA</td>
<td>C A A C</td>
</tr>
<tr>
<td>GCACACACACACCT</td>
<td>GCAC AC ACCT</td>
</tr>
<tr>
<td>CGTGTGTTGTTGGA</td>
<td>CGTGTGTTGGA</td>
</tr>
<tr>
<td>GCACACACACACCT</td>
<td>CGTGTGTTGGA</td>
</tr>
</tbody>
</table>

Adapted from Gruber SB, Kohlmann W. The genetics of hereditary nonpolyposis colorectal cancer. J Nat Comp Cancer Net. 2003;1:137-44.

Microsatellite Instability testing

• Must have tumor and normal tissue (or normal control – blood sample)
• Most effective when combined with clinical information
• Studies of Lynch syndrome-associated adenomas suggest a slightly lower rate of MSI compared to invasive cancers, with approximately 80% of adenomas being MSI-high
• Approximately 20%-30% of endometrial cancers exhibit MSI, and as with colon cancers the majority are the result of somatic MLH1 promoter methylation

• **MSI-high** if more than two (or >30%) of the markers show instability
• **MSI-low** if one (or <30%) of the markers show instability
• **MSI-stable** if 0 (or 0%) of the markers show instability

Immunohistochemistry (IHC)

• Stain archived tumor tissue for MMR proteins
• Missing protein indicates which gene to sequence
  • MLH1 and PMS2
  • MSH2 and MSH6
• MLH1 can be lost by methylation or by somatic mutations
Management of Lynch syndrome

- Increased surveillance
  - Colorectal, endometrial, ovarian, urinary tract
- Prophylactic surgery
  - Colorectal, endometrial, ovarian

- Does surveillance help??
  - Detection of CRC at an earlier stage, to a 63% reduction of the risk of CRC and to a significant reduction of the mortality associated with CRC

Colon Polyposis Syndromes

- Familial Adenomatous Polyposis (FAP)
  - Hundreds of polyps, earlier age of onset
  - ~20% de novo rate
  - Gardner and Turcot variants
  - APC gene
  - AD inheritance
- Attenuated FAP (AFAP)
  - 10 or more polyps, later age of onset
  - APC gene
  - AD inheritance
- MYH-associated Polyposis (MAP)
  - 10 or more polyps
  - MYH gene
  - Autosomal recessive!
FAP

• Mutation in APC gene (a tumor suppressor)
• Autosomal dominant (AD), nearly 100% penetrant
• 20-25 % new mutation rate
• Patients develop 100s – 1000s of colon polyps, some of which become malignant

Also at risk for:
• CHRPE (Congenital Hypertrophy of the Retinal Pigment Epithelium )
• Epidermoid cysts
• Abnormal dentition
• Desmoid tumors
• Malignant tumors (hepatoblastoma, CNS tumors, thyroid cancer)
• Attenuated form (AFAP) with typically <100 polyps
# FAP/AFAP and MAP-associated cancers

<table>
<thead>
<tr>
<th>FAP/AFAP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colorectal</td>
<td>• Colorectal</td>
</tr>
<tr>
<td>• 70% AFAP -100% FAP</td>
<td>• Extra colonic</td>
</tr>
<tr>
<td>• Small bowel</td>
<td>• Similar to FAP/AFAP?</td>
</tr>
<tr>
<td>• 4-12%</td>
<td>• Risk of CRC in a carrier does not seem to be significantly increased (although increased compared with general population)</td>
</tr>
<tr>
<td>• Pancreas, thyroid, CNS, liver (hepatoblastoma), bile duct</td>
<td>• Less than 5%</td>
</tr>
</tbody>
</table>
Management of Colon Polyposis (FAP/AFAP/)

- Increased screening
  - Colorectal, duodenum, stomach, thyroid
  - Hepatoblastoma (<5 years of age)
- Prophylactic surgery
  - Colorectal
Multiple Endocrine Neoplasia Type 1

- MEN1

  - Pituitary tumors
  - Parathyroid tumors
  - Endocrine tumors of the gastro-entero-pancreatic tract
    - gastrinoma, insulinoma, glucagonoma
  - 90% symptomatic by mid-20s
  - 10% new mutation rate

endocrine.niddk.nih.gov/pubs/men1/images/men.gif
Multiple Endocrine Neoplasia Type 2

• MEN2A
  • Medullary thyroid cancer -- occur in ~95% of cases
    • Average onset by age 15-20
  • Pheochromocytoma -- occur in ~50% of cases
  • Parathyroid disease -- occur in ~20-30% of cases

• MEN2B
  • Medullary thyroid cancer -- occur in 100% of cases
    • Average onset in early-childhood
  • Pheochromocytoma – occur in ~50% of cases
  • Mucosal neuromas
  • Marfanoid body habitus

• FMTC
  • Medullary thyroid cancer -- occur in 100% of cases
    • Average onset in middle-adulthood
MEN 2 syndrome pedigree

Benefits and Limitations of Testing

Benefits

• Offers personalized hereditary cancer risk assessment
• Can bring information to help make medical management decisions to reduce cancer risk
• Important information for family members
• Reduced anxiety and stress

Limitations

• Testing does not detect all causes of hereditary cancer
• A negative result is most helpful when there is a known mutation in the family
Genetic test results

Possible Genetic Test Results

- **Positive Result**
  - A mutation has been previously identified in the family (Single Site Analysis)
  - **Increased Cancer Risk**
    - Medical management based on recommendations for mutation carriers

- **Negative Result**
  - **No Increased Cancer Risk**
    - Medical management based on general population cancer screening recommendations
  - No mutation has been previously identified in the family (Comprehensive Analysis)
  - **Cancer Risk Not Fully Defined**
    - Medical management based on personal and family history of cancer

- **Uncertain Variant**
  - **Cancer Risk Not Fully Defined**
    - Medical management based on personal and family history of cancer

Issues in Genetic Counseling/Testing

- Blood sample (or other tissue sample)
- Non-directive counseling
- Informed consent
  - Positive, negative, variant of uncertain significance
- Insurance Discrimination/Genetic Privacy Laws
  - HIPAA, State Laws Governing Genetic Discrimination, Genetic Information Non-Discrimination Act (GINA)
- Minors
- Uninformative negative test result
- Family implications
Some individuals want to know about prenatal diagnosis.

- As hereditary cancer syndromes are not uniformly lethal, and the manifestation is in adulthood, prenatal diagnosis with a view to terminate pregnancy is not generally recommended.

- For Autosomal Dominant syndromes patients should be counseled that there is a 50% chance that the fetus does not carry the genetic mutation, and that inheriting the defective gene does not mean that cancer will definitely develop.

- As medical knowledge advances, we expect new preventive surveillance and treatment options may become available to the next generation and may significantly reduce cancer risk or improve cancer cure rates.

- Other considerations include PGD-IVF, gamete donation, and adoption.
DNA BANKING

If genetic testing is not possible (e.g. not covered by insurance) or not informative, DNA banking is a relatively simple and inexpensive procedure (~$100) that can save a sample of the affected person’s DNA for future testing.
Pharmacogenetics

- Irinotecan is approved worldwide for the treatment of metastatic colorectal cancer
- Some UGT1A1 gene polymorphisms predispose to irinotecan toxicity
- Genotyping can identify those at high risk for toxicity and who may be better treated with a different agent
"You’re lucky nobody was injured. Your base pairs are out of alignment and that has your reading frames all messed up."
QUESTIONS?