Genetic Testing and Counseling for Inherited Cancer Syndromes

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Proportion of inherited cancers

- 5-7% breast ca
- 5-7% of colon ca
- 15-20% ovarian ca
- 30% fallopian ca
- 5% endometrial ca

Increased cancer risk associated with >100 single gene and chromosome disorders

Objectives

- Identify personal, family history and pathology clues for possible inherited cancer conditions
- Review some of the highly penetrant inherited cancer syndromes
- Briefly review common genetic counseling issues

Sources

- National Society of Genetic Counselors, Practice Guidelines (www.nsgc.org)
- American College of Medical Genetics & Genomics, Practice Guidelines (www.acmg.net)
- American Society of Clinical Oncology
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines
- GeneReviews/GeneTests (www.genetests.org)
Referral indications guideline

A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

Hampel H, Bennett RL, Buchanan A, Pearlman R, Wiesner GL

Genetic Testing is Complex

More than just a saliva or blood test!

- Multiple genes
- Somatic vs germline
- Gene variants of unknown clinical significance (VUS or VOUS)
  - 5-10% or higher in many ethnic groups
- Multiple labs, not all the same
  - Costs of tests
  - Methods of testing
  - Rates of VUS

Genetic Testing is Complex

- Test person with greatest likelihood of testing positive (affected)
- Whole family becomes “patient”
- Options aside from genetic testing

Genetic testing MUST be interpreted in context of family hx.

- Not all mutations detected
- Can be phenocopy
  May initiate ca, screening or preventive surgery based on family hx. alone
If only one opportunity to see pt for genetic counseling, prefer BEFORE testing
“Genetic consultation offers new, objective, and scientific knowledge from outside the person, but it arouses within the person old, subjective and irrational knowledge of personal griefs, angers, and confusions about the connections between family and illness.”
Andree Lehmann (1997)

Common genetic counseling issues
- Parental guilt
- Survivor guilt
- Non-compliance with screening
- Cancer worry
- Not sharing test results with relatives
- Grief, shame, regret
- Altered sense of self

Goals of Cancer Genetic Counseling & Testing
- Age of initiation of cancer screening
- More intensive screening
- Encourage healthy lifestyle choices
- Chemoprevention
- Prophylactic/preventive surgery
- Counseling to promote informed choices and adaptation to the condition
  - Empowerment, clarity, relief
**Resources at SCCA/UWMC**

**UWMC Genetic Medicine Clinic** 206-598-4030
- 6 genetic counselors/6 med geneticists
- UW Genetics Laboratory testing (BROCA, COLOSEQ)

**SCCA Prevention Clinics** 206-288-6990
- Multidisciplinary model
- GI Cancer Prevention
- Breast-Ovarian Cancer Prevention
- Prostate
- Colon Cancer Specialty Clinic

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**Matrix for analysis**

- Pathology
- Family history
- Health & Demographics
- Genetic testing

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**Pedigree**

- Mutation carrier
- Affected with trait
- Personally examined/records reviewed

Bennett RL et al. American Journal of Human Genetics, 1995

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**Standardized nomenclature**


**Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors**

Bennett RL, French KS, Resta RG, Doyle DL
Most cancer susceptibility genes are Dominant with incomplete penetrance

*Penetrance is often incomplete
*May appear to “skip” generations
*Individuals inherit altered cancer susceptibility gene, not cancer

Ideally, Begin Testing With an Affected Person

If a mutation is found in an affected person, testing will be more informative for other family members

Pedigree

- Two generations up and two down
- Ask about non-biological relatives contributing to risk
- Ask about relatives without ca., too
- Ethnicity of all four grandparents

Potential environmental occupational/toxins
Family hx. signposts
- Cancer in paired organs
- Cancer at young age
  - Premenopausal breast cancer
  - CRC < 50
  - Endometrial < 60
  - Prostate < 60
  - Childhood cancers
- Metachronous/synchronous ca.
- Unusual dermatological findings
- Multiple relatives on same side of family (3)

Claus model and risk for breast ca

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<th>30-39</th>
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<td>79</td>
<td>17%</td>
<td>13%</td>
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<table>
<thead>
<tr>
<th>Age mother &amp; aunt</th>
<th>29 y</th>
<th>1.8%</th>
<th>1.4%</th>
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<tr>
<td>Dtr:</td>
<td>49</td>
<td>15%</td>
<td>12%</td>
<td>7.5%</td>
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<td>79</td>
<td>44%</td>
<td>35%</td>
<td>25%</td>
<td>15%</td>
<td>11%</td>
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</table>

Red Flags of Family History
- Multiple primary cancers
- Unusual cancers
  - Lung ca in non-smoker
  - Sarcoma
  - Adrenal cortical (< 18 possible TP53/Li-Fraumeni)
  - Pheochromocytoma (25% genetic)
- Clusters of cancers
  - Breast-ovarian (e.g., BRCA1/BRCA2)
  - Colon-endometrial (Lynch)

Bennett, 2010 Practical Guide to Genetic Family History
Targeted Medical Systems

- Eye tumors/blindness
- Skin changes or birthmarks
- Lumps and bumps
- Intellectual disability
- Dysmorphic features
  - Macrocephaly (>98 percentile)
    - Cowden syndrome
    - Biallelic Lynch
    - Neurofibromatosis 1

Family history is dynamic

Update family history
Maybe useful to readdress genetic counseling/testing

CRC genetic referral

- Individuals that meet Amsterdam criteria
- Any CRC or endometrial ca <50
- 2 Lynch associated ca
  - including synchronous/metachronous CRC
- Signet-ring cell CRC <45
- Adenomas >10
- CRC with MSI-H, < 60y
Lynch syndrome
(HNPCC/hereditary non-polyposis colon cancer)

Mismatch repair genes
- MLH1 ~60%
- MSH2 ~38%
- Ashkenazi founder mutations A636P
- MSH6 <2%
- PMS2 <1%
- TACSTD1/EPCAM

Carcinoma of colon & Lynch
- Mean age colon ca. 44 y
- Risk: males ~80%, females ~40% (varies by gene)
- Pathology
  - Proximal
  - Mucinous
  - Signet ring or cribriform histology
  - Diploid tumors (on flow cytometry)
  - Tumor infiltrating lymphocytes
  - Absence of staining by IHC

Immunohistochemistry for Lynch
on colon or endometrial

- MLH1 Could be somatic (BRAF)
- MLH1/PMS2 Germline MLH1
- PMS2 Germline PMS2
- MSH2 Germline MSH2 or EPCAM
- MSH2/MSH6 Germline MSH2 or EPCAM
- MSH6 Germline MSH6

Sebaceous neoplasm often sporadic unless multiple, at young age.
Personal or family history of Lynch type tumors.
**Lynch-adenomas**
- Proximal
- Usually single or less than 10
- Villous
- High grade dysplasia
- Proclivity for malignant degeneration
- Use of IHC not standard

**Lynch-Other cancers**
- Endometrial (high ca. risk, 40%-60%)
  - Some laboratory experience with MSI/IHC
- Stomach (11%-19%)
- Small bowel (1-4%)
- Pancreas
- Hepato-biliary (2-7%)
- Upper urologic (o bladder) (4-5%)
  - Transitional cancer of the ureters
- Brain (Turcot syndrome-glioblastoma)
- Keratocanthomas (Muir-Torre)

**Ovarian cancer-Lynch**
- Lifetime risk ~10%
- Earlier age
  - Mean age 43 y
  - 85% by age 50 y
- Epithelial
  - Slight excess endometrioid
- Not typically borderline
- MSI/IHC not validated at this time

**Constitutional mismatch repair deficiency (CMMR-D)**
- Biallelic Lynch (autosomal recessive)
  - MLH1, MSH2, MSH6, PMS2
- Childhood cancers (median age at dx. 4 y)
  - colon
  - brain
  - leukemia
  - macrocephaly
  - café au lait spots
- Consanguineous parents
Familial Adenomatous polyposis (FAP) (APC)

Tumor suppressor gene at 5q
- Attenuated form mutations 5'; FAP 3'
- Adenomas >100 with FAP,
  - 5-10 (often flat) with attenuated APC
- Risk of CRC ~100% FAP by age 39; ~80% AFAP age 50
- Other cancers FAP: periampullary carcinoma, papillary thyroid ca (cribiform morular variant), brain tumors (medulloblastoma), small bowel cancer (4-12%)
- CHRPE (FAP)
- Desmoid tumors
- Osteomas

Greater than 10 adenomatous polyps: APC testing

MYH Polyposis (MUTYH)

Autosomal recessive
- 20-500 polyps
- Pan-colonic cancer/polyps
- Onset of polyps 40s-50s y
- Average age cancer ~50 (similar to AFAP)
- Lifetime risk of colon cancer, ~80%
- Other cancers?

New kids on the block (polyp)

Polymerase proofreading associated polyposis (PPAP)
- POLD1, POLE
- 10-100 adenomas
- Risk of CRC increased, but how high?
- Endometrial cancer risk
- Similar phenotype to Lynch syndrome

Juvenile polyposis syndrome

SMAD4 (20%) BMPRIA (20%)
- Juvenile type hamartomatous polyps throughout GI
  - Usually >5
  - Smooth histological appearance with predominant stroma, dilated cystic glands and lack of smooth muscle core
- SMAD4 can also have symptoms of HHT (hereditary hemorrhagic telangiectasia)
Overlap with polyp types

Hereditary Breast Cancer

**BRCA1 & BRCA2**

Hereditary Breast Ovarian Cancer Syndrome (HBOC)

- Majority of hereditary breast cancer
  - single male breast ca., likelihood mutation 7-14%
- At least 15% of ovarian/fallopian/primary peritoneal ca.
  - REGARDLESS of family hx.
  - 30% likelihood of mutation if Ashkenazi

**HBOC**

- Over 1,000 mutations in each gene
- Founder mutations
  - Ashkenazi
    - BRCA1 187delAG, 5385 insC; BRCA2 6174 delT
  - Icelandic
  - Dutch
- Most identified by gene sequencing
  - ~5-10% gene rearrangements (BART)
  - Seen in African and Native Americans, Hispanic

**BRCA1**

risk to age 70 of breast ca 45-85%, male ~2-4%
risk to age 70 ovarian ca 20-45%

Breast cancer-triple negative (11-28% mut +)

- Medullary most common
- ER-/PR-
- High nuclear grade
- Her2/neu -
- Less likely to observe DCIS by itself or associated with invasive cancer
- Basaloid cell type-microarray
- P53 overexpression

Ovarian cancer

- Epithelial
- Mostly high grade, serous
- Not borderline
- Not mucinous

Prophylactic BSO:

Occult fallopian/ovarian ca seen in ~10%
### BRCA2

**Breast cancer**
- Risk 50-85%, male 7%
- No typical phenotype
- ER/PR profiles similar to sporadic (most positive)

**Ovarian cancer**
- 15-25%
- Epithelial
- High grade, serous
- Not usually borderline
- Not mucinous

**Prophylactic BSO:**
Occult fallopian/ovarian ca seen in ~10%

### Associated cancers

**BRCA1 & BRCA2**
- Prostate cancer (associated with BRCA2)
- Pancreas (associated with both, rare)
- Gallbladder/bile duct (BRCA2)
- Stomach (BRCA2)
- Melanoma (BRCA2, including ocular)

NOT: colon ca, lymphoma, uterine ca

### PALB2 (“BRCA3”)

- ~ double risk of female breast cancer
  - Similar to BRCA2
- ~40% triple negative
- Male breast cancer
- Pancreatic cancer
- Ovarian cancer (consider BSO at age 50)

May account for 2.4% of familial breast ca

### Li-Fraumeni syndrome

**Germline TP53 mutations**
- 1/20,000
- “SBLA”: Sarcoma (bone, soft tissue); Breast (often premenopausal, not male); Brain, Lung, Leukemia (acute); Adrenocortical
- “Guardian of genome”
  - Control cell cycle & apoptosis
- High cancer risk
  - 50% cancer risk by age 30, 90% cancer risk by age 60
  - Risk of multiple primary cancers (colon ca included)
    - Risk of 2nd ca ~57%
  - Childhood cancers
  - Choroid plexus tumor
PTEN Hamartoma Tumor syndrome (Cowden) syndrome
Tumor suppressor gene, cell cycle control and survival
- Breast cancer (~25%-50%, average age 38-46 y)
- Thyroid cancer (~5-10%)
  - follicular/papillary (not medullary)
- Thyroid goiter
- Endometrial cancer (~5-10% possibly as high as 28%, 30s-40s)
- Lipomas
- Vascular malformations
- Macrocephaly (58 cm women/60 cm men)
- Lhermitte-Duclos disease (dysplastic gangliocytoma of cerebellum in adult)
- GI hamartomas or ganglioneuromas (~90%)
- Renal cell ca., 35%
- Colon ca. 9% (mid 30s)
- Autism spectrum disorders 10-20% with macrocephaly

Other genes & breast cancer clues

<table>
<thead>
<tr>
<th>Breast ca &lt; age 35</th>
<th>Multiple primary ca</th>
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<tbody>
<tr>
<td><em>CHEK2</em></td>
<td><em>ATM</em></td>
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<tr>
<td><em>ATM</em></td>
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<td>Male breast cancer</td>
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<tr>
<td><em>NBN</em></td>
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Autosomal dominant

*STK11* gene on chromosome 19

GI hamartomas

Characteristic pigmentation

93% overall cancer risk by age 65 years

Cancers include colon, breast, pancreas, stomach, ovaries, and others
Ovarian cancer genes

Beyond BRCA1 and BRCA2

- RAD51C (not breast)
  - Finnish founder
- RAD51D
  - Finnish founder
- NBN
- PALB2
- MRE11
- CHEK2
- BRIP1
  - Icelandic founder
  - 6X risk

Known genes but not always thought of
- TP53 (Li-Fraumeni)
- Lynch

Recent association
- CHEK1

Unlikely association
- RAD51

Consider referral for possible Hereditary Diffuse Gastric Ca

- >2 cases of gastric cancer at least one <45
- >3 cases of gastric cancer at any age
- Diffuse gastric cancer < age 45
- Diffuse gastric cancer and lobular breast cancer
  in same individual
  - Same individual OR
  - Two first degree relatives

CDH1 & CTNN1A

Renal Cell Cancers

- Von Hippel Lindau (VHL)
- Birt-Hogg-Dube (BHD)
- Tuberous sclerosis complex (TSC)
- Hereditary leiomyomatosis & RCC
- Cowden syndrome
- Peutz-Jeghers
- Lynch syndrome
- Familial clear cell RCC
- Hereditary papillary RCC

Von Hippel Lindau VHL

Multiple tumors-great variability

- Clear cell RCC (25%-70%)
- **Retinal angiomas, multiple (60-80%)**
- **Cerebellar hemangioblastomas (56%-80%)**
- Spinal cord hemangioblastoma (14%-20%)
- Pheochromocytoma (risk associated with mutation)
- Pancreatic cysts, islet cell/neuroendocrine tumors
- Epididymal cystadenoma
- Broad ligament cystadenoma
- Endolymphatic sac tumors
  - 20% are new mutations in the family
**Birt-Hogg-Dubé Syndrome**

- Rare syndrome characterized by
  - Chromophobe renal cancer (and other histologies)
  - Fibrofolliculoma
  - Spontaneous pneumothorax
  - Autosomal dominant
  - Gene on chromosome 17p11.2

**Tuberous Sclerosis: Malignant Complications**

- Subependymal giant cell astrocytoma
- Malignant angiomyolipoma of the kidney
- Renal cell carcinoma

*These neoplasms are usually associated with significant morbidity and mortality.*

**Tuberous Sclerosis: Clinical Features**

- Ash leaf spot
- Forehead plaque and facial angiofibroma

**Hereditary leiomyomatosis & RCC (HLRCC)**

- Renal cell ca (62%)
- Skin nodules (leiomyomata)
- Uterine leiomyomas
- Uterine leiomyosarcomas
- Uterine fibroids (leiomyomas)
- Uterine leiomyosarcoma
Familial pancreatic cancer

Consider referral

- 2 pancreatic cancer in first degree relatives
- Single pancreatic ca & Ashkenazi Jewish heritage
- Single pt. with pancreatic cancer <age 50
- Pancreatic ca any age with two close relatives with breast and/or ovarian, and/or primary peritoneal, and/or pancreatic ca at any age

Familial pancreatic cancer

*BRC*2 and probably also *BRCA*1

- In Ashkenazi, likelihood of mutation ~5.5%-31%

*CDKN2A*

- Rare if no cases of melanoma in family

*Lynch syndrome*

*PALB2*

- 0.9%-3.7% if pancreatic ca and one 1st degree relative
**Pheochromocytoma-25% inherited**

**Familial paraganglioma-pheochromocytoma syndrome (AD)**

Familial cases 70% detection rate/sporadic 8-17%

Catecholamine-secreting tumors (from neural crest cells)

SDH- Succinate dehydrogenase complex/mitochondrial complex II

- **SDHB** (most common)
  - often malignant, extra-adrenal, renal cell ca, GIST
  - Founder mutation, Netherlands p. Asp92Tyr, p. Leu139Pro

- **SDHD**
  - head & neck, maternal imprinting effect-inherit from father, GIST

- **SDHC**
  - papillary thyroid ca, GIST

- **SDHAF2 (G78R)**
  - rare, early onset, maternal imprinting effect-inherit from father

**Other autosomal dominant causes**

- TMEM127 (isolated pheo or rarely pgl)
- Von Hippel Lindau
- MEN2 (RET)
- Neurofibromatosis 1 (rare complication)

**Testing Minors**

Usually not considered for cancer syndromes that occur in adults

Concerns that might cause psychological harm or even physical harm

Age of consent 18 y

**Future of genetic testing**

**Next-generation sequencing**

- Reduce cost
- Test for multiple genes at same time
  - Large gene panels/targeted panels
- Still have issues of uncertain results
- More genes on panels that we have poor “natural history” data on
  - Whole exomes
- Caution before testing unaffected person as first person tested
Option

DNA Banking

Key Points

- Most cancer is not inherited
- Careful family hx. 1st step in diagnosis
- Cancer more likely inherited when not following “usual patterns,” (e.g. early onset, synchronous, multiple affected, rare cancers)
- Identify genetic “mutation” 1st in relative with cancer before testing healthy persons
- Tumor pathology essential, but few pathognomonic
- Genetic counseling should be offered with genetic testing, not just afterwards