Learning Objectives

• Formulate focused family history questions and document a comprehensive family history.
• Establish the capacity to use family history and genetic information to tier patient risk.
• Determine how to access current information and resources for genetic testing.
• Apply counseling skills to the risk assessment, evaluation, and management of patients in the primary care setting.
• Review clinical management materials for specific genetic conditions.
• Explore the importance of genetics for all patients

AAP – General FH Elements

• Any relative told they have (indicate who, what):
  • Structural or sensory birth defects
  • Cancer (<50 yrs, specify type)
  • Carrier of genetic condition
  • Clotting, bleeding, or blood disorder
  • DD, ID, ASD, LD, received special education services
  • Early, sudden, unexplained, or unexpected death (< 50 yrs, give details)
  • Heart attack (<55 yrs in men, <65 yrs in women)
  • Known genetic condition
  • Multiple miscarriages/stillbirths
  • Seizures
Recognizing family risk

- Family history of known genetic disorder
- Multiple affected family members with same or related disorders
- Earlier age at onset of disease than expected Breast, ovarian, endometrial cancer < 50 yrs (premenopausal)
- Colon and prostate cancer < 50 yrs
- Stroke and noninsulin-dependent diabetes < 50 yrs
- Dementia < 60 yrs
- Coronary artery disease < 55 yrs males, < 65 yrs in females
- Sudden cardiac death in a person who seemed healthy
- Multifocal or bilateral occurrence in paired organs
- Ethnic predisposition to certain genetic disorders

What are you doing about FH in your own family and pediatric work?

Image courtesy of https://familyhistory.hhs.gov/fhh-web/home.action
Introduction to Genetics

- Genetics is the study of biologic heredity
  - Gene: basic unit of heredity

- Genomics is the study of the entire human genome, & their interactions
  - Genome: DNA representing all the genes for a species

Breast-ovarian cancer susceptibility genes

**BRCA1**: chromosome 17, cloned in 1994

**BRCA2**: chromosome 13, cloned in 1995

Lifetime risk of breast cancer is **45-87%**

Lifetime risk of ovarian cancer:
- **BRCA1**: 40%
- **BRCA2**: 20%
Hereditary Cancer Risk Assessment

Persons may be at elevated risk for certain cancers based on personal history, lifestyle, family history.

Hereditary Cancer Risk Assessment

Gail Model
(http://bcra.nci.nih.gov/brc/start.htm)

Claus Model

Autosomal Dominant Inheritance of Early-Onset Breast Cancer

Implications for Risk Prediction

Elizabeth B. Claus, Ph.D., Neil Risch, Ph.D., and W. Douglas Thompson, Ph.D.

CANCER February 2, 1994, Volume 73, No. 3
Multi-Gene Testing Options

Patients who are eligible for genetic testing can have all cancer related genes tested for initially.

Now this can be done upfront along with BRCA testing, with less cost, less time and more answers…

Next Generation Sequencing

sequence multiple genes simultaneously

Comparing Sequencing Technology

- Sanger Sequencing
  - Historical "gold standard"
  - 2 reads per base pair (forward and Reverse)
- Next Generation Sequencing
  - Massively parallel sequencing
  - 100s – 10000s of reads per base pair

Hereditary Cancer Risk Assessment

- Risk assessment based on personal and/or family history of disease
  - Ex.
    - Breast & ovarian cancer - BRCA
    - Colon & endometrial cancer – Lynch Syndrome
    - Breast, thyroid, & endometrial cancer – Cowden Syndrome
- Formulate an evaluation and management plan
Other well-defined syndromes associated with increased breast cancer risk

- **CDH1**
  - Hereditary Diffuse Gastric Cancer
- **PTEN**
  - Cowden syndrome
- **TP53**
  - Li-Fraumeni syndrome

### Hereditary Diffuse Gastric Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer(s)</th>
<th>Additional Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDH1</td>
<td>Breast</td>
<td>Hereditary Diffuse Gastric Cancer</td>
</tr>
<tr>
<td></td>
<td>Gastric</td>
<td>- Diffuse gastric cancer</td>
</tr>
<tr>
<td></td>
<td>Colorectum</td>
<td>- Lobular breast cancer</td>
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<tr>
<td></td>
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<td>- Signet ring carcinoma</td>
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</tbody>
</table>

- High risk breast screening
- Screening endoscopies
- Consider prophylactic gastrectomy

### Cowden syndrome

- High risk breast screening
- Thyroid and colon screening

### PTEN

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</tr>
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<tbody>
<tr>
<td>PTEN</td>
<td>Breast</td>
<td>PTEN Hamartoma Tumor syndrome (PHPT5)</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
<td>Cowden syndrome (CS)</td>
</tr>
<tr>
<td></td>
<td>Endometrium</td>
<td>- Mucocutaneous lesions (trichilemmomas, acral keratosi, papilomatous papules)</td>
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<tr>
<td></td>
<td>Colorectum</td>
<td>- Macrocephaly</td>
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<tr>
<td></td>
<td>Kidney</td>
<td>- Adult Lhermitte-Duclos disease</td>
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<tr>
<td></td>
<td></td>
<td>- GI hamartomas or ganglioneuromas</td>
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<tr>
<td></td>
<td></td>
<td>- Benign breast, thyroid, and uleus lesions</td>
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<tr>
<td></td>
<td></td>
<td>- Nonmedullary thyroid cancer</td>
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</tbody>
</table>
Li-Fraumeni syndrome

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<tr>
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<th>Cancer(s)</th>
<th>Additional Characteristics</th>
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</thead>
<tbody>
<tr>
<td>TP53</td>
<td>Breast, Sarcoma, Brain, Adrenocortical, Leukemias</td>
<td>Li-Fraumeni syndrome (LFS) - Soft tissue and osteosarcomas - Colorectal and many other cancers - Childhood onset cancers - Increased radiation sensitivity - Risk for multiple primary tumors</td>
</tr>
</tbody>
</table>

Personalized care

If we can understand cancer genetics, we can:

- Identify who will benefit from high-risk intervention
- Individualize screening based on mutation status and family history
- Target therapy specifically to the genetic type of cancer
  - PARP inhibitors in BRCA carriers
  - Avoid radiation in TP53 carriers

Precision Oncology—Emerging Model of Cancer Treatment

Tumor tissue routinely acquired for molecular diagnostics

All actionable mutations assessed

Therapy selected based on molecular characteristics
New Era

Era of genetic medicine has begun

• Will challenge long held models of medical practice

• Clinical care binary
  • Diagnosis – Treatment

Barriers to Integration

Fragmentation of our health care system.

Health care delivery systems and incentive structures are focused on sick care, not disease prevention or avoiding adverse effects.

Complexity of the lab results.

Lack of computational decision support.

Personalized Medicine
Preemptive Clinical Pharmacogenetics

Develop process to perform pharmacogenetic testing and use results in routine clinical care

Codeine
Metabolized by an enzyme that is genetically regulated called CYP2D6

\[
\text{Codeine} \rightarrow \text{liver} \rightarrow \text{Morphine (analgesic activity)} \rightarrow \text{CYP2D6}
\]

Nearly 90% of general population OK, but 10% has inactive copies = codeine has no analgesic effect

We have known this for greater than 25 years yet CYP2D6 is not considered when prescribing could have dead prodrug or be dangerously activated

CYP2D6

Migrate pharmacogenetics tests from laboratory to routine patient care

CYP2D6 - responsible for the metabolism of many commonly prescribed drugs –
Analgesics, antidepressants, beta-blockers, anti-psychotics

30% of Asians and individuals of Asian descent are intermediate metabolizers
Factor V Leiden

Identified in 1993, genetic mutations have been found to cause a hereditary prothrombin condition associated with deep venous thrombosis (DVT).

Mutations for Factor V Leiden occur in about 5% of whites and are absent in Asians and Blacks.

Heterozygotes have 4 to 10 times and homozygotes have 50 to 100 times the risk of DVT of the general population.

DVT has the potential to cause pulmonary emboli and death. The incidence of DVT is increased with use of oral contraceptives. The two risk factors for DVT, oral contraceptives and Factor V Leiden mutation, interact.

Factor V Leiden

In women without the genetic mutation in Factor V Leiden, incidence of DVT rises from 0.8/10,000 women per year among those not on oral contraceptives to 3.0/10,000 women per year for those taking the pill.

The baseline incidence of DVT in heterozygotes with a Factor V Leiden mutation is 5.7/10,000 women per year, rising to 28.5/10,000 women per year among those taking oral contraceptives.

Resources

American Cancer Society
Facing Our Risk of Cancer Empowered (FORCE)
facingsourrisk.org

GeneTests:
http://www.genetests.org

International Society of Nurses in Genetics:
http://www.isong.org

National Comprehensive Cancer Network:
http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf