Learning Objectives

1. Describe differences between sporadic and hereditary cancer and heart disease

2. Evaluate personal/family history to identify risk of hereditary cancer and heart disease

3. List differences between genetic testing options and explain what testing may best suit a patient
Common disease

- Disease that affects a large percentage of the population
  - More than 1/1000
  - Responsible for the majority of morbidity, mortality, and health care costs in the US

Top two leading causes of death in the US

- Heart disease: 690,882
- Cancer: 598,932

Source: JAMA
Common diseases are multifactorial

- Most likely caused by genes (nature) AND environment (nurture)
- Need the “perfect mix” of various components
  - Multiple genes and environmental factors
Common disease and genetics

- “It runs in the family”
- Goal is to be able to evaluate the family history to identify who is at risk for hereditary vs. multifactorial vs. environmental causes of disease
- Common diseases are more common in some families than in others
- Do not follow dominant or recessive inheritance patterns
Cancer: a disease of cell overgrowth

- Cancer is a common disease
  - More than 1.9 million new diagnoses in 2020
- 80% of all cancers diagnosed in people 55yo or older
- Lifetime cancer risks
  - Men: 40%
    - Highest risk is prostate cancer: 1 in 9
  - Women: 38%
    - Highest risk is breast cancer: 1 in 8

Source: American Society of Cancer
What causes cancer?

- Accumulation of mutations
  - Can lead to cancer

![Diagram showing the process of cancer development](image)

*Figure 11.18B*
How do mutations cause cancer?

Lots of good genes work to prevent cancer!

- **TP53**: Prevents the growth of damaged cells!
- **MLH**: Helps repair mutations in DNA

Mutations accumulate and cells start to grow uncontrollably, leading to cancer.
Mutations in the cell increase with age

Cancer increases with age
Most cancer occurs randomly (sporadic)

- **Sporadic**
  - Happens by chance in 1-2 relatives
  - Older age of onset

- **Familial**
  - Clustering of cancer
  - May be due to genes and/or environment

- **Hereditary**
  - Clustering of cancer
  - Due to genetic mutations
  - Younger age of onset
  - Passed on from parent to child
SOMATIC VS GERMLINE MUTATION

SOMATIC MUTATION
• Every cancer has many somatic mutations.
• A somatic mutation is a change in the gene that arose in the tumor and is confined to the tumor.
• Most cancer is sporadic (i.e., it happened by chance).

GERMLINE MUTATION
• A germline mutation is a change in the gene that was inherited and therefore causes an increased risk for cancer.
• This is also known as hereditary cancer.
• Only around 10% of cancer is hereditary.
HEREDITARY CANCER

Younger age of onset
When to suspect hereditary cancer in a family?

1. **CANCER AT AN EARLY AGE**
   - At an age younger than average

2. **CERTAIN RARE CANCERS**
   - Such as male breast cancer, sarcoma etc.

3. **MULTIPLE CANCERS**
   - Multiple individuals within the family may have cancer. Or one individual may have multiple cancers
HEREDITARY CANCER SYNDROMES
**Breast and Ovarian Cancer**

**Risk factors:**
- Gender
- Age – 2/3 diagnosed after age 50
- Early menarche, late menopause, nulliparity/first live birth >30
- Radiation exposure (previous cancer diagnosis)
- Post menopausal hormone replacement therapy
- Family history
- Genetic Predisposition
- Alcohol use
- High fat diet/ Obesity
- Ethnicity (Ashkenazi Jewish)
Hereditary breast and ovarian cancer syndrome

- Increased susceptibility to breast and ovarian cancer
- Autosomal dominant
- BRBreast CAncer (BRCA) gene mutations
BRCA1 and BRCA2

<table>
<thead>
<tr>
<th>Chromosome location</th>
<th>BRCA1</th>
<th>BRCA2</th>
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</table>

**Function of BRCA1 and BRCA2:** Tumor suppressor, DNA repair

**Types of mutations:** Single nucleotide change, deletion, duplication, etc.
What does BRCA1/BRCA2 do??

Double-strand break in DNA
What happens when BRCA is mutated?
Why do we want to know about genetic risks?

Can influence management and screening if person is positive for mutation!

- Breast
- Monthly self-breast exams
- Early clinical surveillance
  - Annual mammograms and breast MRI
  - **Men:** Prostate screening – Digital rectal exam and PSA blood levels starting at 45
- **Ovarian**
  - No proven methodology
  - Annually or semiannually, starting at 30-35
    - Transvaginal ultrasound
Prevention (surgical)

Prophylactic Mastectomy
- Removes most but not all breast tissue
- Significantly reduces breast cancer risk in women with a family history (90-95%)

Prophylactic bilateral salpingo-oopherectomy
- Having ovaries and fallopian tubes removed
- Recommended age: 35-40, can do 40-45 with BRCA2
- 85-95% reduction in gynecologic cancer risk

Prevention (chemical)

Tamoxifen
50% reduction in breast cancer incidence in high risk women

Oral contraceptives
Reduce risk of ovarian cancer in the general population
Many genes increase the risk of breast cancer.
A single gene can increase the risk of many cancers!
Colon cancer
Risk factors

- **Age**
- **Personal history of polyps**
- **Inflammatory bowel disease**
- **Family history of CRC**
- **Hereditary colon cancer syndrome**
- **Lifestyle factors**
  - Obesity, lack of physical activity, smoking, alcohol consumption, diet
- Lynch syndrome, up to 4%
- Familial adenomatous polyposis (FAP), up to 1%
- MUTYH-associated polyposis (MAP), up to 1%
- Other rare syndromes, up to 4%
Lynch syndrome

Increased susceptibility to colon and uterine cancer

Caused by mutations in DNA mismatch repair (MMR) genes

*MLH1, MSH2, MSH6, PMS2, EPCAM*

Almost 90% of mutations are found in *MLH1* and *MSH2*
CANCER RISKS ASSOCIATED WITH LYNCH SYNDROME

GENES ASSOCIATED WITH LYNCH SYNDROME
- MLH1
- MSH2
- MSH6
- PMS2
- EPCAM

CANCERS KNOWN TO HAVE ELEVATED RISKS WITH LYNCH SYNDROME

COLORECTAL CANCER
ENDOMETRIAL CANCER
OVARIAN CANCER
GASTRIC CANCER
SMALL BOWEL CANCER
URETER/RENAL PELVIS CANCER
PANCREATIC CANCER
HEPATOBILIARY TRACT CANCER
CENTRAL NERVOUS SYSTEM CANCER
SEBACEOUS NEOPLASMS
PROSTATE CANCER

% RISK TO AGE 70

- MLH1, MSH2, and EPCAM
- MSH6
- PMS2
- Elevated risk with MLH1, MSH2, MSH6, PMS2, and EPCAM (specific number unknown)
Management and screening

Colorectal cancer
- Colonoscopy every 1-2 years beginning at age 20-25
- Want to catch and remove polyps!

Endometrial cancer
- Screening via biopsy every 1-2 years
- Hysterectomy is also a risk reducing option

Surveillance reduces risk of colorectal cancer

% of subjects with CRC

No surveillance
Surveillance

Years of follow-up

Adapted from Jarvinen HJ et al. Gastroenterology. 2000;118:829-834. Reprinted with permission from Elsevier Inc.
When to suspect Lynch syndrome?

- **Three** or more relatives with Lynch-associated cancer (Colon, endometrial, small bowel, ureter, renal pelvis)
- **Two** generations affected
- **One** diagnosis before age 50
Familial Adenomatous Polyposis (FAP)

- Colon cancer predisposition syndrome
- Gene: APC, autosomal dominant
- Polyps burden: 100-1000 adenomatous polyps
- Average age of developing polyps: 16y
- Mean age of colon cancer diagnosis: 37y
- Risk of developing colorectal cancer without treatment: 100%
FAP management

- Surgery: Goal to take out entire colon and entire rectum and replace with small intestine
  - Intense surgery with significant side effects for the patient, but only way to prevent colon cancer
SOME CASE EXAMPLES!
When to suspect hereditary breast cancer in a family?

1. **Cancer at an Early Age**
   At an age younger than average

2. **Certain Rare Cancers**
   Such as male breast cancer, sarcoma etc.

3. **Multiple Cancers**
   Multiple individuals within the family may have cancer. Or one individual may have multiple cancers.
Likely low risk

- Mom diagnosed over age 50
- Lung cancer not considered hereditary
- Prostate cancer is fairly common in older men
Family History #2

- **High risk**
  - 1st degree relative (sister) with 2 primary cancers at young age
  - **Maternal side:**
    - Multiple relatives with colon cancer
  - **Paternal side**
    - Breast and ovarian cancer on same side of the family
    - Prostate cancer in child of a female with breast cancer
HEART DISEASE
Coronary heart disease

- Most common form of heart disease – leading cause of death in the US
- Arteries supplying blood to the heart narrow or harden from build up of plaque
- Decrease in blood flow can lead to heart attack
Causes of coronary heart disease

**Environmental Risk Factors**
- Diet
- Exercise
- High cholesterol
- Smoking
- Obesity
- Diabetes

**Genetic**
- Estimated heritability is 40-60%
- GWAS: found many genetic regions are associated with increased risk
  - We don’t know how!
- Many genes of small effect (over 60 identified)
An exception: Familial hypercholesterolemia

- Monogenic (one gene) disorder that elevates cholesterol
  - Mutations in LDLR gene is most common cause
  - Autosomal dominant
- Increases risk of coronary artery disease and heart attacks
- Affects 1 in 250 people
- Treatment: Statins or cholesterol lowering drugs
Besides coronary heart disease, there are many genetic heart conditions!

- Familial dilated cardiomyopathy
- Familial hypercholesterolemia and other hereditary dyslipidemias
- Hypertrophic cardiomyopathy
- Long QT syndrome
- Noncompaction cardiomyopathy
- Restrictive cardiomyopathy
- Sudden cardiac arrest/death
- Inherited Cardiovascular Connective Tissue Disease (Marfan Syndrome, Vascular Ehlers Danlos Syndrome, aortopathies, etc.)
Cardiomyopathies

- Cardiomyopathy=heart muscle disease
- Diseases of the myocardium
  - Enlarged and dilated, thickened &/or stiffened
- Some causes of cardiomyopathy:
  - Genetics
  - Viral infection
  - Metabolic disorder
Dilated cardiomyopathy

- Heart muscle becomes thin and heart can’t squeeze efficiently
- **20 to 50** percent of individuals with DCM have a familial form
- Mostly autosomal dominant
- TTN gene most commonly mutated
  - TTN encodes largest protein in the human body!
  - Functions as a molecular spring that helps muscle elasticity
Hypertrophic cardiomyopathy

- Heart muscle is thickened (hypertrophic).
- Most common inherited heart disorder: 1/500
- Arrhythmia especially during exercise
- Can cause sudden cardiac death
- Largely genetic,
  - 40 to 70 percent chance that an underlying genetic cause will be identified
- Autosomal dominant
What to look for in a medical history?

- Fatigue
- Shortness of breath on exercise
- Arrhythmia/ pacemaker
- Muscle Weakness or dystrophy
- Syncope/fainting
- Sudden cardiac arrest/death
GENETIC TESTING
Types of testing!

Single gene testing
- BRCA1/BRCA2
- APC (Familial adenomatous polyposis)

Panel testing:
- Breast cancer panel: BRCA1, BRCA2, ATM, P53
- Lynch syndrome panel: MLH1, MLH2, MSH6, PMS2
- Cardiomyopathies, conduction defects

Comprehensive panels
- Large panels with known inherited causes of cancer, heart disease

An example of the genes on a comprehensive cancer panel from Ambry genetics

<table>
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<tr>
<th>GENE(S)</th>
<th>BREAST</th>
<th>OVARIAN</th>
<th>COLORECTAL</th>
<th>UTERINE</th>
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Many labs offer genetic testing!

Ambry
Invitae
Myriad
GeneDx
BluePrint Genetics
Centogene
Fulgent Genetics
LabCorp
...and many more!!!
<table>
<thead>
<tr>
<th>Case Study</th>
<th>Genetic Testing Needed</th>
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<tbody>
<tr>
<td>A 25 year old male with family Hx of colon cancer but no personal history. Is planning on having kids with his wife and wants to know all the information that is available.</td>
<td>Colon cancer gene panel or comprehensive cancer panel</td>
</tr>
<tr>
<td>Highly anxious 35 year old female who has just been diagnosed with breast cancer. She wants to make surgical decisions based on her genetic information. Tells you that she is overwhelmed and can't sleep at night because of all the uncertainty in life.</td>
<td>Breast cancer gene panel</td>
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<tr>
<td>A father dies from sudden cardiac arrest. His autopsy shows hypertrophic cardiomyopathy and genetic testing finds a mutation in the MYH7 gene. His children want to get tested to know if they're at risk</td>
<td>Single gene / mutation testing of MYH7</td>
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</table>
Main Takeaways

1. Common diseases are multifactorial
2. Most cancer occurs randomly with increasing age
3. Some genetic mutations can significantly increase cancer or heart disease risk! (ie. BRCA mutations)

   Signs of genetic syndrome? Early age of diagnosis, multiple family members, rare cancers

4. Genetic testing can help patients understand their risk of disease and improve their clinical management!
Questions?