Outline

- Genetics underlies all cancers
- “Somatic” or “tumor” genetics
- “Germline” or “inherited” genetics
- Personal impact of genetics in gynecologic cancer
Genes are the “instruction books” for our bodies

www.cancer.gov
Cancer is the result of accumulated mutations in genes

- Some genes contain instructions that can prevent cancer
  - Tumor suppressor genes, oncogenes

- Mutation = “spelling mistake” in a gene that interferes with the gene’s normal instruction

- Current terminology is “pathogenic variant” – there are many normal variations of genes. A pathogenic variant is associated with disease
Cancer is the result of accumulated mutations in genes

Tumor mutations:
Understanding the specific genes involved in each cancer can improve treatment
Some families have an inherited mutation

Inherited mutations:
Do not cause cancer but do increase susceptibility to cancer

Understanding specific mutations can improve prevention and treatment
Somatic vs. Germline Mutations

- All cancers are the result of the accumulation of **somatic (tumor) mutations**
  - Accumulated during a person’s lifetime
  - Present in an **isolated** group of cells
  - Tests: UCSF500, FoundationOne, Guardant

- Some people have **germline (inherited) mutations**
  - Inherited from a parent & present from conception
  - Present in every cell of the body
Cancer genomes are complex and generate huge amounts of data.

One person’s genetic code is the equivalent of 1.5 billion characters of text, or...

10,714,286 tweets
A classic presentation of pancreatic cancer?

A classic presentation of pancreatic cancer?

A classic presentation of pancreatic cancer?

A new diagnosis drives platinum treatment

...and a dramatic cancer regression.
Could computational genomics have influenced this case?
Single gene vs. whole genome sequencing
When a technology outperforms Moore’s Law we should pay attention
<table>
<thead>
<tr>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL1, AKT1, AKT2, AKT3, ALK, APC, AR, ARAF, ARFRP1, ARID1A, ARID2, ASXL1, ATM, ATR, ATRX, AURKA, AURKB, AXL, BAP1, BARD1, BCL2, BCL2L2, BCL6, BCOR, BCO1, BCO1L1, BLM, BRAF, BRCA1, BRCA2</td>
</tr>
</tbody>
</table>
Cross cancer comparison

![Bar chart showing alteration frequency across different cancer types, with specific details about amplification, homozygous deletion, mutation, and multiple alterations.](chart.png)
Our patient’s genomic fingerprint
Imagine if we hear hoof beats and can distinguish between zebras and horses.
The promise of molecular profiling

Sample patient cells
from healthy tissue

Healthy DNA

Analyse DNA
from samples

Cancer DNA

Look for faults in
cancer DNA

Study many people
with the same cancer type to find
shared DNA faults to group patients

Within a decade, it will be possible to better tailor treatment
- Develop gene tests to routinely group patients
- Find new drugs that target specific groups better
Germline Mutations and Inherited Cancer Risk

- What is inherited cancer risk?
- Genetic testing for inherited risk
- Caring for high-risk populations
Inherited mutations are (not so) rare

- 75% Sporadic (average risk)
- 10-15% Familial (moderate risk)
- 5-10% Hereditary (high risk)

- Ovarian cancer – 20%
- Endometrial (uterine) cancer – 5%
- Uterine sarcoma – unknown
- Cervical cancer – minimal inherited factors
Inherited risk for cancer

- (NOT SO) rare...
- BUT have great impact
  - Risk of cancer can be high e.g. 40% ovarian cancer risk with BRCA1 mutation
  - Multiple primary cancers are common
- Opportunity for PREVENTION

An Ounce of prevention is Worth a Pound of cure
- Benjamin Franklin -
Genetic Counseling: Risk assessment and follow-up

Risk Classification

- Average
- Moderate ("Familial")
- High/Genetic

Intervention

- Standard prevention and screening
- Personalized prevention and screening
- Genetic evaluation with personalized prevention and screening

Family Hx
Some people have a mutation in the gene

Actually… some people have a pathogenic variant in the gene
Some families have an inherited mutation

Inherited mutation:
• Early age at onset
• Multiple primaries
• Incomplete penetrance
• Dominant inheritance

Stanford Healthcare
Inheritance of Hereditary Cancer

http://www.in.gov/isdh/24477.htm
Summary: Signs of Hereditary Cancer

- Early age of diagnosis
- Family history of the *same* or *related* types of cancer
  - eg. breast and ovarian; colon and endometrial
- Multiple primary cancers
- Rare cancers eg. Male breast, fallopian tube
- Ancestry eg. Ashkenazi Jewish and BRCA1 and BRCA2
- Risk models exist for some major syndromes
  - eg. BRCAPRO
Genetic Testing for Inherited Mutations

- Testing done on healthy tissue - usually blood or saliva
- For healthy people, as well as those with cancer
- An inherited mutation is not a diagnosis of cancer
- Information can be used for early detection, prevention, and treatment of cancer
- Information can affect relatives
Genetic Tests: Caveat Emptor

- There are many types of genetic tests
- Tests vary in quality and scope
- Even among tests of high quality
  - Different tests for different needs
  - Results can be complex
Hereditary Breast and Ovarian Cancer

The numbers are shifting quickly, as we see results from genetic testing panels!

Proportions of patients with primary ovarian, fallopian tube, or peritoneal cancers with germ-line loss-of-function mutations in BRCA1 (red); BRCA2 (blue); BARD1, BRIP1, CHEK2, MRE11, NBN, PALB2, RAD50, or RAD51C (green); MSH6 (purple); or p53 (yellow).

Walsh T et al. PNAS 2011;108:18032-18037
Multi-Gene Panels: Evolving Policy

- UCSF offers multi-gene tests in most cases

- With increasing information, increasing complexity
  - Variants of unknown significance (VUSs)
  - Genes linked to moderate risk
  - Genes linked to unknown risk
Complex Genetic Test Results

- Uninformative Tests
  - no mutation with a strong family history
  - variant of unknown significance
    - Rare sequence changes where there is insufficient or conflicting information – cannot be classified as pathogenic or benign
    - There could still be increased risk of cancer in these families!

- Even when a mutation is found,
  - information about that gene may be preliminary
  - Risks may appear low, making recommendations unclear
Caring for high-risk populations: Hereditary Breast and Ovarian Cancer

Korea

Dx 55
d. 56

Dx 42
Died 82

Dx 36
38 yrs

Dx 70

68

Ruth
45

Dx 37

Ruth
45

Mexico

Key

- Breast CA
- Ovarian CA
Cancers Risks with BRCA1 or BRCA2 mutation

breast cancer
(up to 80%)
Second primary
(up to 50%)

male breast cancer
(5-10%)

ovarian cancer
(up to 50% BRCA1;
up to 25% BRCA2)

Other cancers: prostate, pancreas, melanoma, etc.
Lynch Syndrome

Caused by mutations in mismatch repair genes: MLH1, MSH2, MSH6, PMS2, EPCAM

Cancer risks: Colon, endometrial, ovarian, urinary tract, other
Caring for High-Risk Populations

- Increased screening
  - Breast MRI, colonoscopy

- Risk-reducing medications
  - Tamoxifen, Oral Contraceptives

- Risk-reducing surgeries
  - Mastectomy reduces breast cancer by 90%
  - Hysterectomy prevents endometrial cancer
  - Salpingo-oophorectomy reduces ovarian cancer by 90%; can also reduce breast cancer risk!
Hereditary cancer is rare

Identifying inherited risk can improve early detection, prevention, and treatment of cancer

Early-onset cancer, multiple primaries, family history, and ancestry can suggest inherited risk

Genetic testing with multi-gene tests provides the most information. Tests vary widely in quality and scope.

Genetic counseling will help patients and providers manage complex genetic information
UCSF Cancer Genetics
415-885-7779

- Founded in 1996
- Team of genetic counselors, physicians, researchers
- Database of thousands of individuals with strong family histories or germline mutations
- Provide cancer risk assessment, genetic testing, assistance in coordinating follow-up, including support resources and involvement in clinical trials
- New dedicated clinic and research program for families with inherited mutations
  - 415-353-9797
Resources

- Gene Reviews
- National Comprehensive Cancer Network (NCCN)
- UCSF Cancer Genetics and Prevention Program
- UCSF Center for BRCA Research
  - Brca.ucsf.edu
- Kintalk
  - www.kintalk.org
Resources for Family History

- Surgeon General’s Family Health History Initiative: