Genetic Testing for Women: Roadmap to Health Care, or Too Much Information?
Laura McKay, DNP, CNM, FNP-BC
South University, Savannah GA

Objectives
- The participant will be able to:
- Differentiate between genetics and genomics.
- Compare direct to consumer genetic testing and clinical genetic testing.
- Describe the components of a thorough genetic history.
- Describe appropriate candidates for cancer genetics testing, prenatal genetics testing, and pharmacogenetics testing.
- Discuss ethical dilemma associated with genetic testing.

Normal Chromosomes
How do genes express themselves?

What is genetic testing?
- The study of general mechanisms of heredity and variation in inherited traits
- Analyzes the functioning and composition of the single gene
- More specific to one person, and one disease process

Beery and Workman (2012)

Types of genetic testing
- Diagnostic testing: done to rule in, or rule out, a specific disease
- Predictive testing: done to predict risk of developing a specific type of inherited disorder
- Carrier testing: done to determine if a person is a carrier of an inherited disorder, often to make decisions about whether to have biological children
- Prenatal testing: done to determine if the fetus in an existing pregnancy is at risk for a genetic disorder
- Preimplantation genetic diagnosis: done in conjunction with in vitro fertilization in order to implant only unaffected embryos
Methods of genetic testing

- DNA sequencing - analysis of the bases in a stretch of DNA. Polymerase chain reaction (PCR) is used to amplify the DNA for examination.
- Cytogenetic testing - evaluation of whole chromosomes for variations in structure or number.
- Fluorescent In Situ Hybridization (FISH) - uses a string of fluorescently labeled DNA bases that are complementary to the bases in an area of interest to determine specific chromosome translocations, deletions, microdeletions, or duplications.
- Genome-Wide Association Studies - used to look for genetic markers of disease in the genomes of large numbers of people.

What is genomic testing?

- The study of the function of all nucleotide sequences present within the entire genome of a species, including gene and non-gene DNA.
- Addresses all genes and their interrelationships in order to identify their combined influence on the growth and development of the organism.

Let’s talk about the human genome...

- A genome is all the genes that make up an organism.
- Genes are made up of DNA.
- DNA is made up of long strands of Adenine, Cytosine, Thymine, and Guanine or A, C, T, and G.
- The genome is the code that tells cells what to do, or how to behave.
- The first human genome was sequenced in 2003, a project that took more than two decades for scientists and researchers around the world to complete.
Direct to Consumer Testing

- Several companies offer DTC genetic testing for a range of disorders from single gene testing to multifactorial disease
- Most do not offer any type of genetic counseling
- Cost ranges from a few hundred to several thousand dollars
- There is no federal oversight regulating these companies
- Statements from the American College of Medical Genetics (AMCG) and the American Society of Human Genetics (ASHG) warn against use of these tests without appropriately trained genetic counselors

The best risk assessment is still a good history

- Ancestry - the work of Darwin and Mendel helped us to understand heritability of traits.
- We now know that ancestry increases risk for specific diseases (i.e., people of Ashkenazi Jewish descent are more likely to develop Tay-Sachs disease)
Family History

- A thorough family history can reveal risk for diabetes, heart disease, cancers, and many others

Personal History

- Childhood diseases
- Immunizations
- Onset of puberty
- Use of hormonal contraception or other hormones
- Obstetric history
- Chronic diseases
Cancer genetic testing

Reasons we might perform testing:

- To understand causes of cancer in a family
- To perform surveillance and prevention of other cancers
- To allow for options for family planning

Cancer development

Hereditary breast and ovarian cancer syndrome (HBOC): BRCA1 and BRCA2

- Prevalence in the general population: ~1 in 400
- Prevalence in the Ashkenazi Jewish population: ~1 in 40

Consider testing when history includes one of the following:

- Ovarian cancer at any age
- Breast cancer at or before age 50
- Triple negative breast cancer at or before age 60
- Two primary breast cancers in the same person or on the same side of family
- Breast and ovarian cancer in the same person
- ≥3 relatives with breast, ovarian, pancreatic cancer and/or aggressive prostate cancer on the same side of family
- Ashkenazi Jewish Ancestry and a personal or family history of breast, ovarian or pancreatic cancer
- Male breast cancer
**BRCA mutation cancer risks**

<table>
<thead>
<tr>
<th>General Population</th>
<th>BRCA1 or BRCA2 mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>12%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>0.3%</td>
</tr>
<tr>
<td>Prostate</td>
<td>15-18%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Increased risk for a second primary breast cancer
Reports of increased risk for melanoma

**BRCA Risk By Age**

**Lynch syndrome: MLH1, MSH2, MSH6, PMS2, EPCAM**

Consider when history includes one of the following:

- Colon cancer before age 50
- Uterine cancer before age 50
- ≥ 2 Lynch cancers in the same person
- ≥ 2 relatives with a Lynch cancer, one <50 years old
- ≥ 3 relatives with a Lynch cancer at any age
- Abnormal MSI and/or IHC tumor test result
  - Performed on colon and uterine tumors
Lynch syndrome cancer risks

<table>
<thead>
<tr>
<th></th>
<th>General Population Risk</th>
<th>Lynch syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>5.5%</td>
<td>40-80%</td>
</tr>
<tr>
<td>Uterine</td>
<td>2.7%</td>
<td>25-60%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>1-13%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.6%</td>
<td>1-24%</td>
</tr>
</tbody>
</table>

Also at increased risk:
- Small intestine, biliary system (pancreas, liver, bile duct), brain, skin, and urinary tract (kidneys, ureters, bladder, urethra)

Lynch Cancer Risk By Age

Types of results from cancer genetic testing

- **Negative:** no mutation detected
  - Base cancer risks on family history

- **Positive:** mutation detected that causes an increased risk for cancer
  - Follow management guidelines for care
  - Offer genetic testing to other family members

- **Variant of uncertain significance (VUS):**
  - Change identified, but not enough evidence to determine if disease causing or benign
  - Identified in ~10% of tests
  - Cannot test family members. Exception: Family Studies Programs
  - VUS will be reclassified over time
Prenatal genetic testing

Prenatal or preconceptual carrier screening:
- Used to detect risk for an inherited disease to be passed on to a child
- May be done prior to conception or during pregnancy

Maternal serum screening for aneuploidy:
- Screening done during pregnancy to test for risk specific to the outcome of that pregnancy

Carrier Frequencies Based on Ethnic Origin

<table>
<thead>
<tr>
<th>Population</th>
<th>Condition</th>
<th>Carrier Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>Sickle Cell</td>
<td>1 in 10</td>
</tr>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>1 in 65</td>
</tr>
<tr>
<td></td>
<td>Beta-Thalassemia</td>
<td>1 in 75</td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>Sickle cell</td>
<td>1 in 15</td>
</tr>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>1 in 25 – 1 in 20</td>
</tr>
<tr>
<td></td>
<td>Tay-Sachs disease</td>
<td>1 in 20</td>
</tr>
<tr>
<td></td>
<td>Gaucher disease</td>
<td>1 in 40</td>
</tr>
<tr>
<td>Asian</td>
<td>Alpha-Thalassemia</td>
<td>1 in 20</td>
</tr>
<tr>
<td></td>
<td>Beta-Thalassemia</td>
<td>1 in 50</td>
</tr>
<tr>
<td>European American</td>
<td>Cystic Fibrosis</td>
<td>1 in 20 – 1 in 20</td>
</tr>
<tr>
<td>French Canadian, Cajun</td>
<td>Tay Sache disease</td>
<td>1 in 30</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Cystic Fibrosis</td>
<td>1 in 46</td>
</tr>
<tr>
<td></td>
<td>Beta-Thalassemia</td>
<td>1 in 46 - 1 in 50</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>Beta-Thalassemia</td>
<td>1 in 29</td>
</tr>
<tr>
<td></td>
<td>Sickle Cell</td>
<td>1 in 60</td>
</tr>
<tr>
<td></td>
<td>Cystic Fibrosis</td>
<td>1 in 29</td>
</tr>
</tbody>
</table>

Prenatal or preconceptual carrier screening:
- Used to detect risk for an inherited disease to be passed on to a child
- May be done prior to conception or during pregnancy

Maternal serum screening for aneuploidy:
- Screening done during pregnancy to test for risk specific to the outcome of that pregnancy
### Common Serum Screening Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>When</th>
<th>How</th>
<th>What For?</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple Screen</td>
<td>15-22 weeks</td>
<td>Serum</td>
<td>Trisomy 18, trisomy 21, spina bifida</td>
<td>73% sensitive, 9% false positive rate</td>
</tr>
<tr>
<td>Quad Screen</td>
<td>15-22 weeks</td>
<td>Serum</td>
<td>Trisomy 18, Trisomy 21 Spina Bifida</td>
<td>81% sensitive, 5% false positive rate</td>
</tr>
<tr>
<td>First Trimester Screen</td>
<td>10 4/7-13 6/7 weeks</td>
<td>Ultrasound + Serum</td>
<td>Trisomy 21, trisomy 18, trisomy 13</td>
<td>82-87% sensitive, 5% false positive rate</td>
</tr>
<tr>
<td>Sequential Screen</td>
<td>10 4/7-13 6/7 weeks</td>
<td>Ultrasound + serum</td>
<td>Trisomy 21, Trisomy 18, Spina Bifida</td>
<td>95% sensitive, 5% false positive rate</td>
</tr>
</tbody>
</table>

### What are trisomies?

- Humans have 23 pairs of chromosomes, which are strands of DNA and proteins that carry genetic information. A trisomy is a chromosomal condition that occurs when there are three copies of a particular chromosome instead of the expected two.

### Trisomy 13: Patau Syndrome

- **Trisomy 13** is due to an extra copy of chromosome 13. Trisomy 13 causes Patau syndrome, which is associated with a high rate of miscarriage. Infants born with trisomy 13 usually have severe congenital heart defects and other medical conditions. Survival beyond the first year is rare. It is estimated that trisomy 13 is present in approximately 1 out of every 16,000 newborns.
Trisomy 18: Edwards Syndrome

- **Trisomy 18** is due to an extra copy of chromosome 18. Trisomy 18 causes Edwards syndrome and is associated with a high rate of miscarriage. Infants born with Edwards syndrome may have various medical conditions and a shortened lifespan. It is estimated that Edwards syndrome is present in approximately 1 out of every 5,000 newborns.

Trisomy 21 Down Syndrome

- **Trisomy 21** is due to an extra copy of chromosome 21 and is the most common trisomy at the time of birth. Trisomy 21 causes Down syndrome, which is associated with mild to moderate intellectual disabilities and may also lead to digestive issues and congenital heart defects. It is estimated that Down syndrome is present in 1 out of every 700 newborns.

Other aneuploidy and microdeletion syndromes

- 22q deletion syndrome (DiGeorge)
- 5p (Cri-du-chat syndrome)
- 15q (Prader-Willi/Angelman syndromes)
- 1p36 deletion syndrome
- 4p (Wolf-Hirschhorn syndrome)
- 8q (Langer-Giedion syndrome)
- 11q (Jacobsen syndrome)
- Trisomy 16
- Trisomy 22
Noninvasive Prenatal Testing

- Detects fetal DNA in maternal serum
- Can be collected as early as 9-10 weeks
- 92-99% accuracy, depending on the disorder being reported
- Most labs can run the test on multiple gestation pregnancies, IVF pregnancies and others where serum screening or invasive testing may not be recommended

ACOG’s Stance on Prenatal Screening & Diagnosis

- All women should be offered aneuploidy screening before 20 weeks, regardless of maternal age
- All women should have the option of invasive testing regardless of age
- Primary provider should be able to discuss the detection rates, false positive rates, disadvantages & limitations

ACOG Practice Bulletin #77: Screening for Fetal Chromosomal Abnormalities

PHARMACOGENOMICS AND PERSONALIZED MEDICINE
Pharmacogenomics defined

- AMCP (Academy of Managed Care Pharmacy) defines pharmacogenomics as the intersection of pharmacology and genetics which studies how an individual’s inherited variations in genes affects the body’s response to medications and may be used to predict future response to therapy.


Personalized Medicine Defined

- President’s Council of Advisors on Science and Technology defines Personalized Medicine as “the tailoring of medical treatment to the specific characteristics of each patient. [I]t does not literally mean the creation of drugs or medical devices that are unique to a patient. Rather, it involves the ability to classify individuals into subpopulations that are uniquely or disproportionately susceptible to a particular disease or responsive to a specific treatment.”¹
- The National Cancer Institute defines Personalized Medicine as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”²

¹ President’s Council of Advisors on Science and Technology. Priorities for Personalized Medicine. President’s Council of Advisors on Science and Technology, 2008.


Associated Definitions

- Genomics – The study of the entire set of genetic instructions found in a cell (DNA)
- Pharmacogenomics (PGx) – is a branch of pharmacology concerned with using DNA and amino acid sequence data to inform drug development and testing
- Pharmacogenetics (PGt) – The study or clinical testing of genetic variation that assists in individual patients differentiation response to drugs

Changing the Medical Diagnostic Paradigm

Potential Benefits of Personalized Medicine

- Shift the emphasis in medicine from reaction to prevention
- Predict susceptibility to disease, improve disease detection, preempt disease progression
- Customize disease-prevention strategies
- Prescribe more effective drugs and avoid prescribing drugs with predictable side effects
- Increase patient adherence to treatment by targeting the right patient with the right drug
- Improve quality of life
- Reduce the time, cost, and failure rate of pharmaceutical clinical trials
- Relieve drugs that failed in clinical trials or were withdrawn from the market
- Control health care cost by avoiding unnecessary costs where drug is proven ineffective

Limitations of Personalized Medicine

- Reimbursement pathway of testing not established
- Ethical issues with genetic testing and data sharing
- Integration of pharmacogenomics, personalized medicine, and the payer and regulatory environment is still ongoing
- Clinician are generally not educated concerning available tests, associated drugs, and outcomes
- The response to a medication may be a result of the interactions of multiple genes

ETHICAL ISSUES IN GENETIC TESTING

Case Study #1
Rachel comes from a family with a history of breast cancer on her mother's side. Rachel's mother died of breast cancer when she was very young. Rachel has two sisters, Lisa and Kristin. Rachel has remained close to Lisa, but she no longer has a relationship with Kristin. At a routine check-up, Rachel is told about the availability of genetic testing for identifying a predisposition to breast cancer. Her doctor recommends the test to Rachel, given her family history. Rachel has the genetic testing done and finds that she has a mutated BRCA1 gene. Her doctor tells her she is at high risk for developing breast and ovarian cancer. Rachel's doctor suggests she ask her sisters to be tested also, so they can take the proper preventative measures. Rachel feels comfortable sharing this information with Lisa, but she has not spoken to Kristin in many years. Rachel tells her doctor that she is not in contact with Kristin and will not make an effort to tell her about BRCA1 and genetic testing. Rachel's doctor feels confident that she can locate Kristin but worries about breaching patient confidentiality if she goes against Rachel's wishes.
If you were Rachel’s provider, what would you do?

- Contact Rachel’s sister. As a provider you have a duty to “do no harm”. By not warning someone of a potential cancer risk, you are inflicting harm.
- Follow Rachel’s wishes. Rachel is your patient, not her sister. Therefore your primary obligation is to Rachel. You cannot risk compromising her privacy by contacting an estranged relative.

Case Study #2

Scott, a 30 year-old male, has a family history of Huntington’s disease. Huntington’s disease causes neural degeneration, and eventually death. Affected individuals may experience mental and behavioral changes including paranoia, hallucinations and dementia, as well as physical symptoms such as difficulty walking and jerky movements. The disease has a late onset, which means symptoms don’t show up until about 35-40 years of age. Most people live about 20 years after symptoms become apparent. Scott decides to be tested for the genetic mutation that causes Huntington’s disease and finds out that he has it and will eventually get the disease.

Meanwhile, Scott’s wife, Catherine, discovers she is pregnant. Together they decide that they should get genetic testing done to determine if their unborn child inherited the mutation and will also get Huntington’s disease in adulthood. They will continue with the pregnancy regardless of the results. Although there is no medical intervention possible to stop the disease, they feel strongly that they want to know about their child’s future. At their next obstetric appointment, they inform their doctor of their wishes. The doctor hesitates because the parents are requesting information about a disease that will not affect their child until adulthood. At stake is the unborn child’s autonomy. Perhaps the child will NOT want to know if Huntington’s will strike in the future. But, by requesting the information during pregnancy, the parents are predicting their child’s future. Perhaps the child will want to know about Huntington’s in the future and will know how to offer appropriate emotional and psychological support.

If you were Scott and Catherine’s provider, what would you decide?

- Test the unborn child. The parents are your patients and are ultimately responsible for their child’s well-being. You must respect their wishes.
- Do not test the unborn child. Since there are no preventative measures available for Huntington’s disease, it should be up to the affected individual (the unborn child), and no one else, to decide.
Case Study # 3

Sandra is a 42-year-old woman who has come for an annual exam. You have performed routine health maintenance, including a pelvic examination with Pap test and a clinician breast exam; a DT booster has been ordered. The patient is a non-smoker; drinks minimal alcohol, and has no known family history of breast, colorectal or ovarian cancer. Her father has heart disease at age 70 and she reports no other family history of concern. She notes that her brother is an alcoholic. Her exam is normal.

Prior to the visit, you received a phone call from the patient’s brother, asking you to work Sandra up for Charcot-Marie-Tooth disease (CMT). The brother states that he is worried about his sister because he has seen her stumble many times and thinks she has the disease, which also affects him and their father. He has tried to talk with his sister about it and she has refused to discuss it. He does not want you to mention that he has called. He also asks you to inform him of the patient’s status so that he can take whatever measures are necessary to ensure that she is protected from complications of her neurological disease.

You know that CMT is an autosomal dominant disorder resulting in peripheral neuropathy. Thus, the brother’s history (if reliable) would indicate that Sandra has a 50% risk to inherit the condition.

If you were Sandra’s provider, what would you do?

- Disclose to Sandra that her brother called and expressed concern about her physical condition, and recommend that she be tested.
- Tell Sandra’s brother that you cannot acknowledge that Sandra is a patient, and do not discuss it with her even though you know she may be at risk.