Genetics and Personalized Medicine in Primary Care

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Genomic Medicine

“an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use.

(National Human Genome Research Institute)
What Role Will Primary Care Play in the World of Genomic Medicine?
Treating individuals with genetic disorders

Evaluating the genetics of all individuals
Genetic Tests Can Help to:

- Diagnose Your Disease
- Pinpoint Genetic Factors That Caused Your Disease
- Predict How Severe Your Disease Might Be
- Choose the Best Medicine and Correct Dose
- Discover Genetic Factors That Increase Your Disease Risk
- Find Genetic Factors That Could Be Passed to Your Children
- Screen Newborns for Certain Treatable Conditions
Genetic Workforce

Traditionally, medical geneticists and genetic counselors are at the center of genetic services. However, they alone cannot absorb the entire workload of genomic medicine. Currently 3500 certified genetic counselors and 600 board certified medical geneticists.

1 geneticist for every 600,000 people in the U.S.

Instead, it is likely that primary care providers will assume prominent roles at the front lines of genomic medicine.
Genetic Workforce - Medical Geneticists and Genetic Counselors
Do we need to become a Geneticist?

No

Just like all other aspects of primary care, we can become competent to manage a large majority of genetic concerns.
Medicine Today
Reactive, population-based, one-size-fits-all model of care

Personalized Medicine
Predictive, preventive, patient-centric model of care
Education!
Practice!
Shared Journey with our Patients!
Types of Genetic Testing and Methodology
<table>
<thead>
<tr>
<th>Test Category</th>
<th>Population Tested</th>
<th>Recessive Example:</th>
<th>X linked Example:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population Screening</td>
<td>All members of population even without signs or symptoms</td>
<td>Newborn screening</td>
<td>N/A</td>
</tr>
<tr>
<td>Diagnostic Testing</td>
<td>Individuals suspected of having a genetic condition based on signs or symptoms</td>
<td>• Newborn with meconium ileus &lt;br&gt; • Adult man with infertility &lt;br&gt; • Individual with recurrent pancreatitis</td>
<td>• Boy with mental retardation &lt;br&gt; • Women with premature ovarian insufficiency</td>
</tr>
<tr>
<td>Predictive Testing</td>
<td>Asymptomatic individuals at risk for a disease (based on family history)</td>
<td>Mostly Autosomal Dominant-Huntington's, BRCA</td>
<td>Adult man with nephew who has fragile X syndrome</td>
</tr>
<tr>
<td>Carrier Testing</td>
<td>Individuals at increased risk of carrying recessive or X-linked mutation</td>
<td>Parents with a child with CF</td>
<td>Women whose brother has Fragile X syndrome</td>
</tr>
<tr>
<td>Prenatal Testing</td>
<td>Fetus or embryo at risk of a genetic condition</td>
<td>Fetal echogenic bowel</td>
<td></td>
</tr>
</tbody>
</table>
Testing Technologies

Whole Genome Copy number changes:

- Karyotype
- Microarray
- NIPT

Targeted Copy Number changes:

- MLPA (multiplex PCR)
- FISH
- NGS

Targeted Genotyping
Noninvasive Prenatal Testing (NIPT)

Non invasive DNA testing from free circulating fetal DNA in maternal serum.

Compare maternal and fetal DNA and identify multiple specific chromosomal abnormalities.
SNP Arrays
5 min Break
Four Pillars of Genetics in Primary Care
Prenatal
Prenatal Genetics

Preconception testing
  carrier testing done prior to conception
  family hx
  ethnic predisposition
  Everyone? See new guidelines

Prenatal testing
  testing for genetic changes in the fetus
  when there is high risk
  AMA
  family hx

Preimplantation testing
  testing done on IVF embryos prior to implantation
Information about genetic carrier screening should now be provided to every pregnant woman.

Patients may decline any and all screening.

Carrier screening and counseling ideally should be done before pregnancy.

If an individual is found to be a carrier for a specific condition, then the reproductive partner should be offered testing.

Prenatal diagnosis and advanced reproductive technologies to decrease the risk of an affected offspring should be discussed.

If both partners are found to be carriers of a genetic condition, genetic counseling should be offered.

Relatives are at risk and the patient should be encouraged to inform relatives.

It is important to obtain the family history of the patient and partner as a screening tool for inherited risk including:

Ethnic background

Known consanguinity

Positive family hx of known genetic conditions
Carrier screening generally should be only performed once in a person’s lifetime and results documented in the health record.

However, additional mutations may be included in newer screening panels.

Prenatal carrier screening does not replace newborn screening, nor does newborn screening replace the potential value of prenatal carrier screening.

The cost of individual carrier screening may be higher than commercial screening panels.
Carrier Screening in the Age of Genomic Medicine

Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening. Each health care provider should develop a standard approach that is consistently offered and discussed with each patient.

Couples with consanguinity should be offered genetic counseling to discuss increased risk of recessive conditions in their offspring.

Carrier screening will not identify all individuals who are at risk of the screened conditions. Patients should be counseled regarding residual risk with any test result.

If a carrier couple is identified before pregnancy, genetic counseling is encouraged so that reproductive options (eg, donor gametes, preimplantation genetic diagnosis, and prenatal diagnosis) can be discussed.
Given the multitude of conditions that can be included in expanded carrier screening panels, the disorders selected for inclusion should meet several consensus-determined criteria:

- Have a carrier frequency of 1 in 100 or greater
- Have a well-defined phenotype
- Have a detrimental effect on the quality of life
- Cause cognitive or physical impairment
- Require surgical or medical intervention or have an early onset in life
- Provide antenatal opportunities for intervention to improve perinatal outcomes
- Provide changes to delivery management to optimize newborn and infant outcomes

Carrier panels should not include disease of primarily adult onset.
Spinal Muscular Atrophy

Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.

In patients with a family history of SMA, molecular testing reports of the affected individual and carrier testing of the related parent should be reviewed, if possible before testing, if the reports are not available, SMN1 deletion testing should be recommended for the low-risk partner.
Cystic Fibrosis:

Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.

Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.

For a person with a family history of CF, attempt should be made to obtain any previous mutation analysis if available.
Hemoglobinopathies:

A complete blood count with red blood cell indices should be performed in all women who are currently pregnant to assess not only their risk of anemia but also to allow assessment for risk of hemoglobinopathy. Ideally, this should be offered before pregnancy.

A hemoglobin electrophoresis should be performed in addition to a complete blood count if there is suspicion of hemoglobinopathy based on ethnicity or MCV.
Fragile X syndrome:

Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant.

If a woman has unexplained ovarian insufficiency or failure or and elevated FSH before 40 years, fragile X carrier screening is recommended to determine whether she has a \textit{FMR1} premutation.

Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers.
Tay-Sachs Disease:

Screening for Tay-Sachs disease should be offered when considering pregnancy or during pregnancy if either member of a couple is of Ashkenazi Jewish, French-Canadian, or Cajun descent. Those with a family history also should be offered screening.

When one member of a couple is at high risk by ethnicity or family history, but the other partner is not, the high risk partner should be offered screening first.

If disease screening is done as part of a pan-ethnic expanded carrier screening, it is important to recognize the limitations of the mutations screened in detecting carriers in the general population.
Testing Labs:

Local via Quest

In house UPMC

Direct to Consumer and Direct to Physician test kits
Ethnic Specific:

Ashkenazi:

JScreen (Emory University)-expanded testing with results/co ordered via patient and provider

Dor Yeshorim- less diseases screened, no results, only result is compatibility
<table>
<thead>
<tr>
<th>Disease</th>
<th>Carrier Frequency</th>
<th>Detection Rate</th>
<th>Residual Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloom syndrome</td>
<td>1 in 100</td>
<td>99%</td>
<td>1 in 9,901</td>
<td>Causes poor growth and immune system dysregulation. People with this disease usually die from cancer before age 30.</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>1 in 41</td>
<td>98%</td>
<td>1 in 2,001</td>
<td>Causes brain and nervous system degeneration. People with this disease usually die in early childhood.</td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
<td>1 in 75</td>
<td>99%</td>
<td>1 in 7,401</td>
<td>Causes bone marrow failure in young children. The bone marrow is unable to produce platelets (blood cells that stop bleeding) or megakaryocytes (large bone marrow cells that make platelets) so the blood is unable to clot and bleeding occurs. Some types of this condition cause abnormalities of the neurological and skeletal systems, heart defects, and delayed development.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1 in 24</td>
<td>99%</td>
<td>1 in 2,301</td>
<td>Chronic disorder that may cause pneumonia, diarrhea, poor growth, and infant mortality. Some people are only mildly affected, but individuals with severe disease may die in childhood. The average life span is 37 years.</td>
</tr>
<tr>
<td>Dihydroxyoic acid dehydrogenase deficiency</td>
<td>1 in 96</td>
<td>&gt;95%</td>
<td>1 in 1,901</td>
<td>Causes the buildup of amino acids in tissue to toxic levels. Characterized by poor feeding, vomiting, lethargy, low muscle tone, and developmental delay. Can be fatal if untreated.</td>
</tr>
<tr>
<td>Familial dysautonomia</td>
<td>1 in 31</td>
<td>&gt;99%</td>
<td>1 in 3,001</td>
<td>Causes muscular weakness and, sometimes, abnormalities of the heart, kidneys, or limbs. Some individuals have learning disabilities or intellectual disability. It is associated with poor development, progressive degeneration and a high mortality rate.</td>
</tr>
<tr>
<td>Familial hyperinsulminism</td>
<td>1 in 52</td>
<td>97%</td>
<td>1 in 1,701</td>
<td>Causes severe insulin resistance. Onset of the disease can happen during infancy or during the first years of life. If left untreated, it may cause irreversible neurological damage or death.</td>
</tr>
<tr>
<td>Fanconi anemia type C</td>
<td>1 in 89</td>
<td>99%</td>
<td>1 in 8,801</td>
<td>Causes anemia, short stature and, sometimes, abnormalities of the heart, kidneys, or limbs. Some individuals have learning disabilities or intellectual disability. It is associated with a high rate of cancer, especially leukemia.</td>
</tr>
<tr>
<td>Gaucher disease</td>
<td>1 in 18</td>
<td>95%</td>
<td>1 in 341</td>
<td>Causes fatigue, enlarged liver and spleen, bleeding, bone pain and fractures. The most common form is treatable by enzyme replacement therapy. In the most severe form, the brain and nervous system are also affected.</td>
</tr>
<tr>
<td>Glycogen storage disease type Ia</td>
<td>1 in 71</td>
<td>99%</td>
<td>1 in 7,001</td>
<td>Causes severe low blood sugar, enlarged liver, delayed growth and bloating. Treatment consists of a strict diet and continuous tube feedings of glucose.</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>1 in 110</td>
<td>&gt;95%</td>
<td>1 in 2,181</td>
<td>Causes a brain malformation that affects balance and coordination. Symptoms include weakness, loss of muscular control and developmental delay.</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>1 in 81</td>
<td>99%</td>
<td>1 in 8,001</td>
<td>Causes a characteristic odor of the urine due to accumulation of amino acids in the blood. If untreated it can cause intellectual disability, physical disabilities, seizures, and death.</td>
</tr>
<tr>
<td>Mucolipidosis type IV</td>
<td>1 in 127</td>
<td>95%</td>
<td>1 in 2,521</td>
<td>Affects the brain and nervous system. Symptoms begin in the first year of life, resulting in intellectual and physical disabilities, and impaired vision.</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>1 in 108</td>
<td>&gt;99%</td>
<td>1 in 10,701</td>
<td>Characterized by weakness and poor muscle tone, particularly in the face, neck and limbs. The most severe form can cause death in the first years of life, due to respiratory failure.</td>
</tr>
<tr>
<td>Niemann-Pick disease type A/B</td>
<td>1 in 90</td>
<td>97%</td>
<td>1 in 2,968</td>
<td>Causes poor growth, an enlarged liver or spleen, mental and physical deterioration, and repeated lung infections. Neurologic deficits are generally noted after the first few months, and progressive deterioration follows.</td>
</tr>
<tr>
<td>Spinal muscular atrophy (SMA)</td>
<td>1 in 41</td>
<td>90%</td>
<td>1 in 350*</td>
<td>Affects the muscles involved in breathing, swallowing, crawling and walking. The most common form may cause death by two years of age.</td>
</tr>
<tr>
<td>Tay-Sachs disease</td>
<td>1 in 31</td>
<td>99%</td>
<td>1 in 3,001</td>
<td>Causes deterioration in both mental and physical abilities. Children with this disease usually die by age five. A less common form affects adults.</td>
</tr>
<tr>
<td>Usher syndrome type IF</td>
<td>1 in 141</td>
<td>75%</td>
<td>1 in 561</td>
<td>Causes profound deafness at birth, severe balance problems, and visual impairment which progresses over time.</td>
</tr>
<tr>
<td>Usher syndrome type III</td>
<td>1 in 107</td>
<td>98%</td>
<td>1 in 5,301</td>
<td>Causes progressive hearing and vision loss. Individuals are usually completely blind by adulthood and hearing loss is moderate to severe.</td>
</tr>
<tr>
<td>Walker-Warburg syndrome</td>
<td>1 in 120</td>
<td>&gt;95%</td>
<td>1 in 2,381</td>
<td>A form of congenital muscular dystrophy that causes developmental delay, muscle weakness, feeding difficulties, seizures and blindness. Life expectancy is typically less than three years.</td>
</tr>
</tbody>
</table>

*When 2 copies of the SMN1 gene are detected with no history of disease. If 2 copies of SMN1 are detected with no prior history of disease, residual risk is 1 in 6200.
Cancer Genetic Risk Assessment
Genetic Cancer Risk Assessment

5-10% of all cancers are due to an inherited cancer syndrome.

There are more than 50 types of hereditary cancer syndromes.

Important risk reduction opportunities.
<table>
<thead>
<tr>
<th>Syndrome:</th>
<th>Genes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Retinoblastoma</td>
<td><em>Rb1</em></td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td><em>TP53</em> (p53)</td>
</tr>
<tr>
<td>Familial Adenomatous Polyposis</td>
<td><em>APC</em></td>
</tr>
<tr>
<td>Hereditary Nonpolyposis colon cancer (HNPCC) (Lynch Syndrome)</td>
<td><em>MLH1, MSH2, MSH6, PMS1, PMS2</em></td>
</tr>
<tr>
<td>Wilm’s Tumor</td>
<td><em>WT1</em></td>
</tr>
<tr>
<td>Breast and Ovarian Cancer</td>
<td><em>BRCA1, BRCA2</em></td>
</tr>
<tr>
<td>Von Hippel-Lindau</td>
<td><em>VHL</em></td>
</tr>
<tr>
<td>Cowden Syndrome</td>
<td><em>PTEN</em></td>
</tr>
<tr>
<td>Cancer Type</td>
<td>General Population (No Mutation)</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>12%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1-2%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>0.10%</td>
</tr>
<tr>
<td>Prostate</td>
<td>15% (N. Europe Origin)</td>
</tr>
<tr>
<td></td>
<td>18% (African American)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>0.50%</td>
</tr>
</tbody>
</table>
LYNCH SYNDROME LIFETIME CANCER RISKS (%)*

*Recent publications suggest lower risks for MSH6 & PMS2 mutation carriers.
What is BRCA1 & BRCA2?
US Preventative Task Force Recommendation Statement

2013 statement: Primary care providers screen women at risk with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes.

Women with a positive screening result should receive genetic counseling and genetic testing if indicated.
Hereditary Breast and Ovarian Cancer

- Familial, 15-20%
- Hereditary, 5-10%
  
  BRCA1 and BRCA2 are the most common causes of hereditary breast and hereditary ovarian cancer

- Sporadic, 70-80%
Breast Cancer

12% of women in general population develop breast cancer during their lives (Howlader et al., 2010).

55-65% of women who inherit a harmful *BRCA1* and 45% *BRCA2* will develop breast cancer by age 70 (Antoniou et al., 2003, Chen et al., 2007).
Ovarian Cancer:

1.4% of women in the general population will develop ovarian cancer during their lives (Howlader et al., 2010).

39% of women who inherit a harmful BRCA1 and 11-17% of BRCA2 will develop ovarian cancer by age 70 (Antoniou et al., 2003, Chen et al., 2007).
**BRCA1 and BRCA2**

Tumor suppressor proteins which repair DNA Damage.

If the gene mutated, then DNA damage is not properly repaired and cells accumulate new DNA mutations leading to cancer.

BRCA related cancers tend to occur at younger ages than sporadic cancer.

Associated cancers include:

- Breast
- Ovarian
One Hit vs Two Hit Hypothesis

Two-Hit Hypothesis

- No cancer
- Cancer

- Germline mutation
- Somatic mutation

If first hit is a germline mutation, second somatic mutation more likely to enable cancer
BRCA Inheritance

One can inherit a BRCA mutation from either parent.

Each child from a parent who carries the mutation has a 50% chance of inheriting the mutation.
Who Is At Risk?

Everyone of our patients needs to be screened for their genetic cancer risk. Recommend integrating into annual wellness exam or annual gyn exam.
<table>
<thead>
<tr>
<th>Tool</th>
<th>Factors Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ontario family history assessment tool (FHAT) (Gilpin et al., 2000)</td>
<td>Breast and ovarian cancer in first-, second-, third-degree relatives: age of onset (decade); bilateral breast cancer; prostate cancer; and colon cancer</td>
</tr>
<tr>
<td>Referral screening tool (RST) now the breast cancer genetics referral screening tool (B-RST) (Bellcross et al., 2009,2010)</td>
<td>Breast and ovarian cancer in first- and second-degree relatives, breast cancer age less than or equal to 50 or greater than 50 years old; ovarian cancer, diagnosis of both breast and ovarian cancer; bilateral breast cancer, male breast cancer and Ashkenazi Jewish ancestry</td>
</tr>
<tr>
<td>Manchester Scoring System (Evans et al., 2004)</td>
<td>Age of onset for breast cancer (decades), male breast cancer, ovarian cancer and prostate cancer, and presence of pancreatic cancer</td>
</tr>
<tr>
<td>Pedigree assessment tool (PAT) (Hoskins et al., 2006)</td>
<td>Breast cancer (age less than 50 or greater than or equal to 50 years old), ovarian cancer at any age, male breast cancer, and Ashkenazi Jewish ancestry.</td>
</tr>
<tr>
<td>FHS-7 (Ashton-Prolla, 2009)</td>
<td>First-degree relatives with breast or ovarian cancer, male breast cancer, breast and ovarian cancer, breast cancer less than 50 years of age, 2 or more relatives with breast or ovarian cancer or bother, and colon cancer</td>
</tr>
</tbody>
</table>
## Red Flags for Genetic Risk Assessment

<table>
<thead>
<tr>
<th>Red Flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple primary cancers in a single individual (colorectal and endometrial cancer)</td>
</tr>
<tr>
<td>Multifocal tumors or bilateral cancers in paired organs (multifocal renal cancer)</td>
</tr>
<tr>
<td>Several relatives with the same or related cancers (breast and ovarian, colon, and endometrial)</td>
</tr>
<tr>
<td>Autosomal dominant pattern of cancer (cancers occurring in multiple generations of a family)</td>
</tr>
<tr>
<td>Presence of rare cancers (adrenocortical carcinoma and retinoblastoma)</td>
</tr>
<tr>
<td>Unusual presentation of cancer (male breast cancer)</td>
</tr>
<tr>
<td>Presence of other nonmalignant features (colon polyps)</td>
</tr>
<tr>
<td>Uncommon tumor histology (medullary thyroid carcinoma)</td>
</tr>
<tr>
<td>Certain ethnicities (Ashkenazi Jewish)</td>
</tr>
</tbody>
</table>

(Lewis, 2014)
Why are Ashkenazi More at Risk?

Founder mutations around 3000 years ago
Approximately 1/40 people of Ashkenazi
Jewish descent is a carrier for a BRCA
mutation compared to 1/500 in the average
population.

3 Common Ashkenazi mutations
BRCA1 185delAG =1%
BRCA1 5382insC = 0.15%
BRCA2 6174delT = 1.5%

Ethnic specific mutations have been identified
in Norwegian, Dutch, Icelandic, African
American, Hispanics, Asians and non-
Hispanic Whites.
Classic Pedigree

Classic BRCA1 Pedigree

- Breast, dx 42
- Ovarian, dx 49
- Breast, dx 38
- Ovarian, dx 53
Primary Elements of Cancer Genetic Counseling:

Collection of personal medical and family history

Cancer risk assessment

Discussion of possible genetic testing and its implications both to the patient and their family

Informed consent to ensure the individual understands the benefits, risks, and limitations of genetic testing

Coordination of genetic testing

Disclosure of genetic test results and recommendations for further testing, surveillance and risk reduction strategies
Who to Test?

If a family member who has cancer is alive and willing to be tested, they have the highest likelihood of possessing a BRCA mutation.

If a mutation is identified in that person, then other family members should consider counseling and testing.

Since there is no risk reduction strategy that is done in children and the likelihood of developing a BRCA related cancer is low, testing is not recommended in children.
What Genetic Testing is Available?

Single site testing for families with a known hereditary mutation.

Complete BRCA1/2 screening.

Larger cancer risk comprehensive testing panels.

Many commercial companies:

  - Quest
  - In house UPMC
  - Myriad
  - Ambry
Counseling Considerations Before Testing

the appropriateness of genetic testing
the medical implications of a positive or a negative test result
the possibility that a test result might not be informative
the psychological risks and benefits of genetic test results
the risk of passing a mutation to children
explanation of the specific test that might be used and the technical accuracy of the test
Cost $$

Ranges from several hundred to several thousand
Some insurance companies cover it certain criteria are met
Medicaid coverage is state by state
Medicare coverage is criteria based
  a. NCCN guidelines
  b. Must be affected individual
Free testing sometimes available for uninsured individuals
The genetic test result indicates whether a clinically actionable mutation is identified from the 25 genes analyzed.

If positive, the genetic mutation is detailed with appropriate nomenclature, and its clinical and functional significance.

Presence of genetic variants of uncertain significance (VUS) that are not currently considered clinically actionable, are reported.
Positive Test Result

A person has inherited a known harmful mutation in BRCA1 or BRCA2 and therefore has an increased risk of developing certain cancers. A positive test does not determine if an individual will develop cancer or when.

Many people who inherit a BRCA mutation, never develop breast or ovarian cancer. The individual will have a 50% chance of passing on the mutation to each of their children. The siblings of the positive individual each have a 50% chance of having inherited the mutation as well.
Negative Test Result

If a first or second degree relative of the tested person is known to carry a harmful BRCA mutation, a negative test result is clear: the person who does not carry the mutation is a “true negative” for that mutation. They have the same risk of cancer as someone in the general population and cannot pass it on to their children.

If the tested person has a family history suggestive of a BRCA mutation but no mutation is identified in the family, a negative result is not informative. New mutations are being discovered every year, and have not yet identified all harmful mutations, thus the lack of identified mutation, does not mean the patient does not have an inherited cancer causing mutation.

Other mutations in non BRCA genes can also increase the risk of cancer and are not detected by all tests.
Variant of Uncertain Significance

identification of a genetic variation not previously associated with cancer. Up to 10% of testing can yield a VUS. Can take several years to reclassify VUS as significant or not significant.
Risk Management

Enhanced Screening:
start screening at a younger age, or more frequent screening
Clinical breast exams beginning at age 25-35
Mammogram every year beginning at age 25
- consider minimizing radiation (due to compromised DNA break repair)
annual MRI consideration
No effective ovarian cancer screening
- transvaginal u/s and CA-125 not proven to detect tumors early enough to reduce the risk of dying from ovarian cancer
- no clear consensus guidelines for breast and prostate screening in men with BRCA mutations
Prophylactic Surgery

Remove as much of the “at risk” tissue as possible
  bilateral prophylactic mastectomy reduces risk of breast cancer
  bilateral prophylactic salpingo-oophorectomy reduces risk of ovarian cancer (80% risk reduction) and reduces risk of breast cancer (50% risk reduction) in premenopausal women by reducing amount of circulating hormones.
no evidence for mastectomy in males
Chemoprevention

The use of drugs, vitamins or other agents to reduce the risk or delay the recurrence of cancer

Tamoxifen/Raloxifene may reduce risk of developing breast cancer (not adequately studied)

Oral contraceptives may lower the risk of ovarian cancer in women with harmful BRCA mutations (needs additional studies)
Benefits of Testing

Negative results can provide a sense of relief, and reduce costly checkups, tests and preventative surgeries. Positive results can bring relief from uncertainty, allow patients to make informed decisions about their future and take steps to reduce their cancer risk.
Risks of Testing

Knowledge of results may have a harmful effect on a person’s emotions, social relationships, finances and medical choices. Positive results may cause anxiety, depression, anger. They may have difficulty making choices about preventative surgeries, marriage, child bearing, or informing other at risk family members. Negative test results within a family can cause survivor guilt. Violations of privacy and confidentiality are possible which could lead to discrimination in relation to employment, or insurance. Inaccurate results could lead to false sense of security or cause potential emotional harm and medical cost.
Family Affair

genetic test results affect multiple family members
“duty to warn” (Offit et al., 2004)
Psychosocial Assessment

anticipated reaction to results and coping strategies
timing and readiness for testing
family dynamics and relationships
preparing for result disclosure
Questions/Break

15 min
Pharmacogenomics
Pharmacogenomics

SNP’s which affect drug metabolism - causing patient to patient variation
Medications often don’t work for people

- Depression: 38%
- Asthma: 40%
- Cardiac Arrhythmias: 40%
- Diabetes: 43%
- Migraine: 48%
- Arthritis: 50%
- Osteoporosis: 52%
- Alzheimer’s: 70%
- Cancer: 75%

% of patients for whom drugs are ineffective

FDA. Paving the way for personalized medicine. 10/2013.
Figure 3: Relative importance of polymorphisms in human cytochrome P450 enzymes involved in drug metabolism
Population

- Metabolize Fast
- Metabolize Normally
- Metabolize Slowly
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype</th>
<th>Clinical Implications</th>
</tr>
</thead>
</table>
| Ultrarapid metabolizer    | Gene duplication so more active alleles present, or specific mutations that increase activity | Prodrugs: more effect, more risk of toxicity  
Active drugs: less or no effect |
| Extensive metabolizer     | 2 normally functioning alleles                                            | Expected effects and toxicities                                |
| Intermediate metabolizer  | 1 normal and 1 poor functioning allele, or 2 moderate functioning alleles | Normal to different metabolism, more like poor metabolizer if different |
| Poor metabolizer          | 2 poor-functioning or nonfunctional alleles                               | Prodrugs: less or no effect  
Active drugs: more effect, more risk of toxicity |
PGx Case

54 yo male admitted with STEMI
Angio with Stent
post-procedure A-fib with RVR
Cardiology recommending discharge on:
  ASA 81 mg
  Clopidogrel 75 mg
  Metoprolol 50 mg
  Simvastatin 40 mg
  Lisinopril 10 mg
  Warfarin (start 10 mg, continue with 7.5 mg daily initiation protocol)
Warfarin

Very narrow therapeutic window
Subtherapeutic: risk of thrombosis
Supratherapeutic: risk of bleed
Dedicated anticoagulation clinics only therapeutic 60% of the time
Pharmacogenomic Guided Dosing

Ability to decrease out of range INRs
Improve time in therapeutic range
decrease thromboembolic and bleeding events
Clopidogrel

Goal: to prevent thrombotic events associated with cardiovascular disease
large inter-individual variability of response
Current FDA guidelines is to consider testing in those who have had poor therapeutic success
this is reactionary
ideally we want to prevent the negative outcomes before they occur
Clopidogrel (inactive) → Oxidation by cytochromes → No platelet inhibition

2-oxo-clopidogrel (inactive) → Hydrolytic cleavage by PON1 esterase → Platelet inhibition

Thiol metabolite (active) → Prevention of stent thrombosis

Stent thrombosis:
- Heart
- Coronary artery located on the surface of the heart
- Compressed plaque
- Stent thrombus
- Widened artery
- Thrombus
- Compressed plaque
Simvastatin

Goal: Cholesterol lowering for CV risk reduction

Muscle toxicity:
  - myalgia
  - myopathy
  - rhabdomyolysis

Severe reactions are rare, but even myalgia leads to patient discontinuation of medication
Rapid Turn Around Genotyping

CYP2C19*1*1
CYP2C9*2*2
SLCO1B1 rs4149056 CC
VKORC1 -1629 AA
Interpretation

CYP2C19*1*1 (normal metabolizer of clopidogrel)
CYP2C9*2*2 (50-70% reduced clearance of warfarin)
SLCO1B1 rs4149056 CC (reduced hepatic uptake of simvastatin)
VKORC1 -1629 AA (50% reduced expression of vitamin K 2,3 epoxide reductase)
Conclusion

CYP2C19*1*1 (Ok to proceed with clopidogrel with standard safety profile – no increased risk of cardiac adverse events due to clopidogrel metabolism)
CYP2C9*2*2 (recommend reduce dosing protocol of Warfarin due to poor clearance of drug)
SLCO1B1 rs4149056 CC (High myopathy risk from simvastatin: recommendation for low dose or alternative statin)
VKORC1 -1629 AA (recommend reduce dosing protocol of Warfarin due to decreased target expression)
Pharmacogenomic integration provided risk reduction for ADR in three medications.
Reduce risk of stent restenosis
Reduce risk of elevated life threatening INR
Reduce risk of statin induced myopathy and possible therapeutic failure if patient stopped statin therapy due to side effects
FDA Boxed Warning on Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.

- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.

- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.

- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

PLAVIX (clopidogrel bisulfate) tablets PI.
PreCISE-Rx

UPMC Cath lab testing Clopidogrel metabolism on cath lab patients.

30% of patients don’t metabolize Clopidogrel appropriately

Leading to a 10% complication rate.

“Increasingly we are able to pinpoint gene variations and other factors that affect how patients metabolize drugs, allowing us to more precisely target the right drug for the right patient,” explained Philip Empey, Pharm.D., Ph.D., assistant professor of pharmacy and therapeutics at the University of Pittsburgh School of Pharmacy, and the leader of this program.
Over 100 drugs currently on list with pharmacogenomic warnings.
Genetics of Complex Chronic Disease
Genetics of Chronic Disease

Enhance Preventative Approach  Facilitate Tailored Disease Management
Personalized Health Success Plan
Family History
Pedigree Taking
The three-generation pedigree provides a pictorial representation of diseases within a family.

Most efficient way to assess hereditary influences on disease.
The family history is useful in stratifying a patient’s risk for rare single-gene disorders and more common diseases with multiple genetic and environmental contributions.
Can be obtained by the provider

15-30 min

On paper

Electronic tools

(in my opinion still take too long)

Goal: done automatically by EHR
Can be generated by the patient with various online tools


What information to obtain?

- Current age of individual
- Chronic conditions
- Cancers
- Pregnancy loss if relevant
- Age of onset of diagnosis
- Age and cause of death for deceased family members
- Consanguinity

Increased risk for autosomal recessive disease
Family Health History

Information should be reviewed and updated annually for new family medical information

The farther the degree of relatedness, the less accurate the reported information

Absence of disease is reported accurately 90% of the time

Correct reporting of breast and colon cancer 82-95% of the time
<table>
<thead>
<tr>
<th>Element</th>
<th>Example(s)</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relatives</td>
<td>Parents, siblings, children</td>
<td>50% genetically identical</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>Grandparents, aunts, uncles, nephews, nieces</td>
<td>25% genetically identical</td>
</tr>
<tr>
<td>Third-degree relatives (in certain cases)</td>
<td>Great-grandparents, great-aunts, and great-uncles, cousins</td>
<td>Important in family histories of pregnancy complications or miscarriage, rare-diseases, x-linked and recessive conditions</td>
</tr>
<tr>
<td>Age at diagnosis of relevant conditions</td>
<td>diagnosis of breast cancer at age 43 years</td>
<td>early onset of disease suggests a genetic condition</td>
</tr>
<tr>
<td>Other medical diagnosis</td>
<td>In 1 or more relatives on the same side of the family: colon cancer diagnosis at age 53 years, endometrial cancer at age 55 years, ovarian cancer at age 47 years, Hypertension</td>
<td>Multiple similar or related diagnoses in 1 or more relatives on the same side of the family suggests a genetic contribution (this example suggestive of Lynch syndrome)</td>
</tr>
<tr>
<td>Behavioral risk factors</td>
<td>cigarette smoking</td>
<td>might explain occurrence or early onset of some diseases (eg, lung cancer, myocardial infarction)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Early age at death</td>
<td>died at age 25 years due to motor vehicle crash</td>
<td>possible missing data for a disease with typical onset after age of death</td>
</tr>
<tr>
<td>Current age</td>
<td>31 years</td>
<td>Might be too young to have manifested the condition of interest</td>
</tr>
<tr>
<td>Ancestry/ethnicity</td>
<td>Northern European, Mediterranean, Ashkenazi Jewish</td>
<td>Some diseases or specific mutations are more common in certain ancestral or ethnic groups (eg, cystic fibrosis in Northern Europeans, beta-thalassemia in those of Mediterranean ancestry, specific BRCA1 and BRCA2 mutations in Ashkenazi Jews)</td>
</tr>
<tr>
<td>Paucity of family members</td>
<td>lack of information about or small family sizes</td>
<td>Lead to false reassurance as there are not enough family members to provide adequate inheritance patterns for interpretation</td>
</tr>
</tbody>
</table>
Modes of Inheritance: Mendelian

- Autosomal Dominant
- Autosomal Recessive
- X-linked Dominant
- X-linked Recessive
- Y-linked
Modes of Inheritance: Non-Mendelian

Anything not segregating in a Mendelian fashion:

- Imprinting
- Mitochondrial
- Multifactoral
- Sporadic
- Contiguous gene syndromes
- Mosaicism
- Uniparental disomy
Analysis of the Pedigree

Patterns

Vertical patterns

Horizontal patterns

Sex-linked patterns
Autosomal Dominant

Vertical pattern
Multiple generations affected
Males and females equally likely to be affected
See male to male transmission
Each child of an affected individual has a 50% chance to be affected
Every affected child has an affected parent
Autosomal Recessive

Horizontal pattern: single generation affected. Males and females equally likely to be affected.
Parents of affected child are unaffected gene carriers and have a 1 in 4 or 25% recurrence risk.
Unaffected siblings have a 2/3 or 67% chance to be carriers.
Children of affected individuals are obligate carriers.
Special Cases:

To be aware!

Non-penetrance

Not everyone who has a mutation manifests the disease, example BRCA

Variable expressivity

Different family members who inherit the mutation can manifest different degrees of phenotype, example NF

Late onset disorder

Younger generations may look unaffected but simply have not yet manifested disease, example Huntington’s Chorea
# Red Flags for Genetic Risk Assessment

<table>
<thead>
<tr>
<th>Red Flag</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple primary cancers in a single individual (colorectal and endometrial cancer)</td>
<td></td>
</tr>
<tr>
<td>Multifocal tumors or bilateral cancers in paired organs (multifocal renal cancer)</td>
<td></td>
</tr>
<tr>
<td>Several relatives with the same or related cancers (breast and ovarian, colon, and endometrial)</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant pattern of cancer (cancers occurring in multiple generations of a family)</td>
<td></td>
</tr>
<tr>
<td>Presence of rare cancers (adrenocortical carcinoma and retinoblastoma)</td>
<td></td>
</tr>
<tr>
<td>Unusual presentation of cancer (male breast cancer)</td>
<td></td>
</tr>
<tr>
<td>Presence of other nonmalignant features (colon polyps)</td>
<td></td>
</tr>
<tr>
<td>Uncommon tumor histology (medullary thyroid carcinoma)</td>
<td></td>
</tr>
<tr>
<td>Certain ethnicities (Ashkenazi Jewish)</td>
<td></td>
</tr>
</tbody>
</table>

(Lewis, 2014)
Practice
Genetic Counseling Referral
When to Refer to Genetic Counseling?

- Interpret Medical and Family Histories
- Support Patient Decisions
- Educate about Health and Genetics
- Find Medical and Social Resources
- Provide Emotional Support and Counseling

**Genetic Counselor Specialty Areas**

- Prenatal: 35%
- Cancer Genetics: 24%
- Pediatrics: 12%
- Other Specialties: 29%

Results are according to the 2014 NSGC Professional Status Survey.
How To Find A Genetic Counselor?

Contact the Center for Medical Genetics and Genomics
Prenatal/Adult Genetics
Magee-Womens Hospital of UPMC
300 Halket St., Suite 1651
Pittsburgh, PA 15213
Phone: 412-641-4168 or 800-454-8155
Fax: 412-641-1032
Office hours: 8 a.m. to 4:30 p.m., Monday through Friday

Pediatric Genetics
Children's Hospital of Pittsburgh of UPMC
3520 Fifth Ave.
Pittsburgh, PA 15213
Phone: 412-692-5070
Fax: 412-692-6472
Office hours: 8 a.m. to 4:30 p.m., Monday through Friday

Cancer Genetics Program
Magee-Womens Hospital of UPMC
300 Halket St., Suite 1651
Pittsburgh, PA 15213
Phone: 412-641-4168 or 800-454-8156
Fax: 412-641-1132
Office hours: 8 a.m. to 4:30 p.m., Monday through Friday
Remote Online/telephone Genetic Counseling

Genome Medical

Remote based genetic counseling, risk assessment, testing and reporting services
Integration of Genomic Data into the EHR

Future Integrate:

- Family History
- Personal history
- Exposures
- Genetic data
- Research

For Now: Primary Care:

- Integrated patient entered Family Hx which generates Provider RED flags
- System generated Pedigrees
Direct To Consumer Testing
Ancestry Composition tells you what percent of your DNA comes from each of 22 populations worldwide. The analysis includes DNA you received from all of your ancestors, on both sides of your family. The results reflect where your ancestors lived 500 years ago, before ocean-crossing ships and airplanes came on the scene.

- **94.7%** European
  - 24.2% Northern European
  - 13.7% French and German
  - 3.3% Scandinavian
  - 0.6% Finnish
  - 36.9% Nonspecific Northern European
- 4.3% Eastern European
- 0.6% Italian
- 2.3% Nonspecific Southern European
- 2.4% Ashkenazi
- 6.3% Nonspecific European
- **3.7%** East Asian & Native American
- 3.1% Native American
- 0.3% East Asian
- 0.3% Nonspecific East Asian & Native American
- 1.3% Arab
- 1.3% Middle Eastern
- 0.3% Unassigned
Mylynda Massart

- European: 99.7%
- Middle Eastern & North African: 0.2%
- East Asian & Native American: < 0.1%
- Unassigned: < 0.1%

See all 31 tested populations
Genetic Weight

Your genes influence not just your weight, but also the impact of different healthy habits.

Myllynda, your genes predispose you to weigh about 5% less than average.

This predisposition doesn't mean you will definitely weigh less than average. Keep in mind that your lifestyle and environment have a big impact on your weight.

Your reported weight is approximately what your genetic result would predict.

In your health profile you told us you weigh 138 pounds. For reference, a recommended healthy weight range for someone your height is 101-136 pounds, based on CDC guidelines*.

Update your height or weight
How did we calculate your result?

We determined your result by looking at DNA variants associated with weight based on our research. Some variants have a stronger effect on weight than others, which our analysis took into account. Because of this, your proportion of higher to lower weight variants may not exactly align with your overall predisposition. Keep in mind that other variants may also affect your weight. Learn more about how we calculated your result.

What is average?

For a 44-year-old woman who is 5'2" 142 lbs

The average weight for a woman your age who is 5'2" tall is 142 pounds, based on 23andMe participants of European descent. The ancestry we used for your result is based on the information you provided in your settings. European is used as the default for people of mixed ancestry and for those of ancestries for which we do not yet have enough research participants.

You have:

- Variants associated with lower weight: 413
- Variants associated with higher weight: 349

Update your ethnicity settings
Myllynda, you likely do not produce the lactase enzyme.

Likely lactose intolerant

How To Use This Test

This test does not diagnose any health conditions or provide medical advice. Consult with a healthcare professional before making any major lifestyle changes or if you have any other concerns about your results.

Review the Wellness tutorial
See Scientific Details

Intended Uses

- To test for the C/T-13910 variant near the LCT gene.

Limitations

- Does not test for all possible variants related to lactose digestion.
- Does not account for lifestyle or other factors that may affect lactose digestion.

Relevant Populations

- The variant in this report is primarily found in people of non-European descent.
Mylynda, you are likely to be able to smell the asparagus metabolite in your pee.

61% of customers who are genetically similar to you can smell the asparagus metabolite.

<table>
<thead>
<tr>
<th>Your genetic likelihood</th>
<th>European ancestry customers</th>
</tr>
</thead>
<tbody>
<tr>
<td>61% Can smell</td>
<td>67% Can smell</td>
</tr>
<tr>
<td>39% Can't smell</td>
<td>33% Can't smell</td>
</tr>
</tbody>
</table>
Myllynda, 23andMe customers who are genetically similar to you tend to consume 41 mg less caffeine per day than average.
How To Use This Test

This test does not diagnose any health conditions or provide medical advice. Consult with a healthcare professional before making any major lifestyle changes, or if you have concerns about your results.

Intended Uses

- To test for one variant near the CYP1A2 gene and one variant near the AHR gene.

Limitations

- Does not test for all possible variants related to caffeine consumption.
- Does not account for lifestyle or other factors that may affect caffeine consumption.

Relevant Populations

- The variants in this report have been studied primarily in people of European descent. These results may not apply as well to people of other ethnicities.
No mutations were identified.

This means no pathogenic or likely pathogenic genetic variants associated with an increased risk of breast, colorectal, melanoma, ovarian, pancreatic, stomach, or uterine cancers were identified in any of the 30 genes tested.
This result does not eliminate your risk of developing cancer. Inherited mutations explain some cases of cancer, but most are not inherited and can not be explained by a single cause. Some non-genetic factors that can influence cancer risk include environment and lifestyle, as well as family history without a known genetic link. Your healthcare provider can help determine how your screening plan might be influenced by your health history and other factors.

**GENES ANALYZED**

The genes below were analyzed, and no pathogenic or likely pathogenic genetic variants associated with an increased risk of breast, colorectal, melanoma, ovarian, pancreatic, prostate, stomach, or uterine cancers were identified:

*APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4*, CDKN2A(p14ARF), CDKN2A (p16INK4a), CHEK2, EPCAM*, GREM1*, MITF*, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2**, POLD1*, POLE*, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*
Average risk among US women to develop specific cancers by different ages in their lives. Breast and colorectal cancers are highlighted because they are more common.

### Breast Cancer

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>40</td>
<td>&lt;1</td>
</tr>
<tr>
<td>50</td>
<td>1.9</td>
</tr>
<tr>
<td>60</td>
<td>4.0</td>
</tr>
<tr>
<td>70</td>
<td>7.1</td>
</tr>
<tr>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>95</td>
<td>12</td>
</tr>
</tbody>
</table>

### Colorectal Cancer

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>40</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>50</td>
<td>&lt;1</td>
</tr>
<tr>
<td>60</td>
<td>&lt;1</td>
</tr>
<tr>
<td>70</td>
<td>1.6</td>
</tr>
<tr>
<td>80</td>
<td>2.8</td>
</tr>
<tr>
<td>95</td>
<td>4.2</td>
</tr>
</tbody>
</table>

### Other Cancers

<table>
<thead>
<tr>
<th>Type</th>
<th>Age 50</th>
<th>Age 95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine</td>
<td>&lt; 1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>&lt; 1%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>&lt; 0.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>&lt; 1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt; 0.1%</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>
Know Your Screening Guidelines

Below is a summary of screening guidelines from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) established by experts at the National Comprehensive Cancer Network (NCCN) and the American Cancer Society. These guidelines are for women who have the same cancer risk as the average US woman. Your healthcare provider may use the American Cancer Society and NCCN Guidelines® to help create a customized screening plan for you.

**BREAST CANCER**

- **Starting at age 25:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider.

- **Between ages 25-39:** Breast exam by your provider every 1-3 years.

- **Starting at age 40:** Breast exam by your provider and mammogram every year.

**COLORECTAL CANCER**

- **Starting at age 50:** Colonoscopy every 10 years, or stool-based testing (high-sensitivity, guaiac-based, or immunochemical-based) every year, or flexible sigmoidoscopy every 5 years which may include stool-based testing at year three.
A pathogenic mutation was identified in the BRCA1 gene.
Testing positive for a pathogenic mutation in the *BRCA1* gene means your risks of developing breast and ovarian cancer are significantly greater than that of the average US woman. Your risk of pancreatic cancer is also increased by this mutation. This result does **not** mean that you have a diagnosis of cancer or that you will definitely develop cancer in your lifetime. Your actual risk may be different based on other genetic and non-genetic factors.

<table>
<thead>
<tr>
<th>DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENE</td>
</tr>
<tr>
<td><em>BRCA1</em></td>
</tr>
<tr>
<td>Alternate name(s): C61G, chr17.GRCh37:g.41258504A&gt;C</td>
</tr>
<tr>
<td>Transcript: ENST00000357654</td>
</tr>
<tr>
<td>Zygosity: Heterozygous</td>
</tr>
</tbody>
</table>
Risk and Family Information

RISK BY AGE
with a BRCA1 mutation

Risk among US women with a BRCA1 mutation to develop specific cancers by different ages in their life.

**BREAST CANCER**

<table>
<thead>
<tr>
<th>Age</th>
<th>Women with BRCA1 mutation</th>
<th>Average among US women</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>40</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>50</td>
<td>39%</td>
<td>21%</td>
</tr>
<tr>
<td>60</td>
<td>58%</td>
<td>40%</td>
</tr>
<tr>
<td>70</td>
<td>69%</td>
<td>46%</td>
</tr>
<tr>
<td>80</td>
<td>81%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**OVARIAN CANCER**

<table>
<thead>
<tr>
<th>Age</th>
<th>Women with BRCA1 mutation</th>
<th>Average among US women</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>40</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>50</td>
<td>21%</td>
<td>40%</td>
</tr>
<tr>
<td>60</td>
<td>40%</td>
<td>46%</td>
</tr>
<tr>
<td>70</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>80</td>
<td>54%</td>
<td>54%</td>
</tr>
</tbody>
</table>

INCREASED RISK
for other cancers

In addition to increasing a woman’s risk for breast and ovarian cancers, mutations in the BRCA1 gene are known to increase the risk of developing pancreatic cancer.

<table>
<thead>
<tr>
<th>CANCER</th>
<th>RISK BY AGE 80 WITH BRCA1 MUTATION</th>
<th>AVG. US WOMAN²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic³</td>
<td>Elevated (3-5%)</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

_Elevated: Risk is increased, but further research may clarify the exact risk figure._
Consider sharing your results with relatives because:

• This mutation was most likely inherited from either your mother or your father. This would mean that one of your parents has the same mutation, and that your relatives on that side of the family may also have the same mutation. Fathers are just as likely to pass on a mutation as mothers.

• Each of your siblings has a 50% chance of having inherited this mutation. Brothers are just as likely to inherit it as sisters.

• Each of your children has a 50% chance of inheriting the same mutation. Men are just as likely as women to pass the mutation on to their children, and daughters and sons are equally likely to inherit it. Please keep in mind that children are not recommended to be tested for this mutation as it does not impact health or affect medical management in childhood.
• **Starting at age 18:** Breast awareness - Women should be familiar with their breasts and promptly report changes to their healthcare provider. Performing regular breast self exams may help increase breast self awareness, especially when checked at the end of the menstrual cycle.

• **Starting at age 25:** Breast exam by your provider every 6-12 months.

• **Between ages 25-29 or individualized based on family history:** Breast MRI screening (preferred) every year or mammogram if MRI is unavailable.

• **Between ages 30-75:** Mammogram and breast MRI screening every year. Your provider may wish to alternate between these two screenings every 6 months.

• **Between ages 35-40, or after you are finished having children:** NCCN recommends a risk-reducing salpingo-oophorectomy (the surgical removal of the ovaries and fallopian tubes) to lower the risk of developing breast and ovarian cancer. Ideally, this should involve a discussion with a gynecologic oncologist.

• **After age 75:** Your provider may discuss an individualized management plan with you.
Your provider may discuss the option of having a risk-reducing bilateral mastectomy (the surgical removal of both breasts).

Your provider may discuss the use of medications that might reduce the risk of developing breast or ovarian cancer.

While there may be circumstances where ovarian cancer screening with transvaginal ultrasound and a blood test for a protein called CA-125 are helpful, these techniques have not been shown to be effective in detecting early ovarian cancer.

Currently, there are no pancreatic cancer screening guidelines from the NCCN specific to BRCA1 mutation carriers. Please discuss your risk of pancreatic cancer with your healthcare provider.
DID MY GENETIC TESTS COME BACK?

YEAH, SIT DOWN.

IS IT BAD NEWS?
WHAT ARE MY RISK FACTORS?

WE CAN'T BE SURE ABOUT THIS, BUT WE'VE ANALYZED GENES ON SEVERAL OF YOUR CHROMOSOMES, AND IT'S HARD TO AVOID THE CONCLUSION:

AT SOME POINT, YOUR PARENTS HAD SEX.

OH GOD!

STAY CALM! IT'S POSSIBLE IT WAS JUST ONCE!

I... I NEED TO BE ALONE.
Raw Data/3rd Party Interpretation

Promethease: builds a personalized data report based on SNPedia regarding all published data on certain SNPs.

Genetic Genie: looks primarily at methylation and detox pathways

Interpretome: most comprehensive analysis thus far

Genomapp: for complex diseases
Caution!!

Raw data is not validated, there is no quality control or analytical review, NOT CLINICALLY USEFUL

Must individually repeat a CLIA approved test if relevant

What are your patients really looking for when they bring you this data?
Whole Genome/Whole Exome Sequencing
FUN!
Life Uncorked

Vinome brings you the ultimate personalized wine experience! Harnessing the science of taste, we analyze your DNA to match you to wines you will love, then deliver them right to your doorstep.

Vino + Genome = Vinome

GET STARTED
Dinner

Sponsored by: All of US/PA Cares presentation
All of Us/PA Cares
American College of Medical Genetics
Find genetic services

GeneFacts
A point-of-care genetics resource for nongenetics providers
Web site: http://www.genefacts.org

National Center for Biotechnology Information
GeneReviews

National Coalition of Health Professional Education in Genetics
Core principles in family history: collection
Core principles in family history: principles for interpretation
Core principles in family history: tools and downloads
Core competencies for all health care professionals (2007)

National Society of Genetic Counselors
Find a genetic counselor
Web site: http://www.nsgc.org

US Surgeon General
My Family Health Portrait: Family health history tool
Web site: https://familyhistory.hhs.gov/

● Organized by competency
Genetics and Personalized medicine is just beginning to evolve:

We are still learning gene function, the meaning of many variants, how genes interact. As understanding evolves the utility will evolve and the integration into clinical practice.
Discussion:

How would you like to see genetics incorporated into your practice?

What are you excited about?

What do you fear?

What needs to be done to get there?

Return of results:

Would anyone be interested in serving on a panel for return of results?