WE’RE WAY PAST PEAS: USES OF GENETIC INFORMATION TO UNDERSTAND HUMAN HEALTH AND GUIDE HEALTH CARE DECISION MAKING

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Topics for Today

• Basic principles of genetics
• Uses of genetics in health care; genetic testing

• BREAK

• NCBI MedGen portal; other clinical genetics resources.
• Answer practice questions using MedGen
• Genetic health literacy & genetic science literacy
• Genetic consumer health resources
• Direct-to-consumer testing
• Ethics and privacy
• Precision Medicine Initiative

Presentation slides are available at: https://nnlm.gov/pnr/training/presentations
Mendel Discovered Patterns of Inheritance by Studying Physical Traits

Before genes were discovered, Mendel realized that he could make mathematical predictions about the inheritance of physical traits – like flower color.
Mary-Claire King: Way Past Peas!
Some cases of breast cancer clustered in families; must be inherited.

In 1990 demonstrated that a single gene, which she named BRCA1, was responsible for breast and ovarian cancer in many families.

Studied how mutations in BRCA1 lead to breast cancer. (BRCA1 is a tumor suppressor gene.)

Now recommends that all women should be offered genetic testing for BRCA1 and BRCA2 mutations at about age 30 as part of routine medical care. “About half of women who inherit mutations in BRCA1 or BRCA2 have no family history of breast or ovarian cancer and have no idea they are carrying cancer-causing mutations.”

“Most of inherited breast and ovarian cancer can be prevented, if mutation carriers know who they are.”

The Animated Genome

Unlocking Life’s Code video
https://unlockinglifescode.org/media/animations/659#660
Chromosomes are made of DNA
Genes are discrete segments of DNA found on chromosomes.
Humans Receive 23 Chromosomes from Each Parent; Each of Your Cells Contains These 46 Chromosomes*

*Egg and sperm cells only contain one set of 23 chromosomes.
This is Your Genome

- The DNA that contains your 20,000+ genes.
- The DNA that regulates the expression of your genes.
- The DNA of unknown significance.
Each pair of chromosome has the same genes at the same locations, but possibly different alleles (versions).

“F” represents the freckle gene – MC1R on chromosome 16. Freckles are a dominant trait, so if you receive at least one copy of the F allele, you are likely to have freckles.

An allele is one of two or more versions/variants of a gene within a population.
Many Traits Are Multigenic – the Product of Multiple Genes

Eye color is determined by variation at several different genes and the interactions between them.

Brown Eyes
How does a gene affect a physical trait or process?

- Genes encode proteins.
- The DNA sequence dictates the amino acid sequence of the protein.
- Proteins do the work in your body.

Image credit from Harvey Mudd College web page: http://fourier.eng.hmc.edu/bioinformatics/intro/node8.html
Altered genes can lead to altered proteins which can lead to disruptions in normal processes NOT ALWAYS!
CATEGORIES OF DISEASES ATTRIBUTED TO GENES

- Chromosomal Diseases
- Monogenic Diseases
- Multifactorial Diseases
An individual may have a missing chromosome, extra copies of a chromosome, or a portion of a chromosome may be deleted, duplicated, or translocated.

Alteration may be inherited or de novo. Most originate in the egg or sperm.

Examples: Down’s syndrome (extra copy of chromosome 21) or Prader-Willi syndrome (microdeletion from short arm of chromosome 15)

By U.S. Department of Energy Human Genome Program. [Public domain], via Wikimedia Commons
Monogenic Diseases/
Mendelian Diseases

- Single-gene diseases follow the patterns of inheritance that Mendel discovered in his studies of pea plants.
- These rare inherited diseases tend to be caused by mutations in a single gene.
- Examples: cystic fibrosis, sickle-cell anemia, muscular dystrophy, and Huntington’s disease.

Autosomal Recessive Inheritance

Each child inherits one copy of the gene from each parent.

Genetic Science Learning Center, University of Utah, http://learn.genetics.utah.edu
Multifactorial Diseases

- Complex diseases are caused by variation in many genes. They may also be influenced by environmental factors.
- The vast majority of human diseases fall into this category.
- Identifying the genes that contribute to these diseases has been difficult.
- Examples: cardiovascular disease, cancer, diabetes, and a number of birth defects and psychiatric disorders.

Credit: Nature's Scitable website - http://www.nature.com/scitable/topic/genes-and-disease-17
Multifactorial Disease!

"Your weight problem is partly genetic and partly Boston Cream pie."
Type 2 Diabetes: A Multifactorial Disease

According to a 2016 review article by Kaul and Ali

- “Type 2 diabetes (T2D) is a multifactorial anomaly involving 57 genes located on 16 different chromosomes and 136 single nucleotide polymorphisms (SNPs).”

- “Genetic components have their own pathways encompassing insulin secretion, resistance, signaling, and β-cell dysfunction.”

- “Environmental factors include epigenetic changes, nutrition, intrauterine surroundings, and obesity.”

- “In addition, ethnicity plays a role in conferring susceptibility to T2D.”

### Heritability Estimates for Complex Traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>Heritability Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Mineral Density</td>
<td>50-85%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>40-60%</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>25-45%</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>6-15%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>4-15%</td>
</tr>
</tbody>
</table>

Heritability estimate – genetics accounts for what % of a person’s susceptibility to a condition. Complex traits also due to other biological and environmental factors.
How Are Changes in Genetics Affecting Health Care?

- Researchers learn more about genes and variants and disease risk every day.
- Capabilities for precision medicine are increasing.
- Health care providers other than medical geneticists and genetic counselors are dealing with genetic information.
- Clinicians may not have had much (recent) training in genetics.
- Genetic testing is a subject that patients may raise.
- Translating research findings to the clinic – do any of them apply to my patients?
“Despite the growing use of genomic applications in clinical practice, health professional knowledge about genomic information and confidence in using it have not kept pace....

Many health care providers do not have either the knowledge or the tools they need in order to apply genetic information in their day-to-day practices.

This lack of support is contributing to a substantial delay in the translation of genetic research findings, when appropriate, into improvement in patient outcomes within the health care system.”

– Institute of Medicine 2015 report
Four Areas Where Genetics Is Intersecting Health Care

**Diagnostic Testing**

[Image: GTR: GENETIC TESTING REGISTRY]

**Single Nucleotide Polymorphisms**

[Graphic by Diane Rein – modified from Science Magazine, December 21, 2007]

**Tumor Genomic Testing**

[Image: BRAF mutation-positive melanoma cell]

[Image credit: Incyte Pathology blog: https://incytepathology.wordpress.com/2012/04/10/braf/]

**Pharmacogenomics**

(Adapted from Yaffe SJ, Aranda JV: Neonatal and pediatric pharmacology, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)
1. Diagnostic Testing –
Does He Have Alzheimer’s Disease?

Clinicians Don’t Test Everyone.

Practice guidelines recommend testing for 3 genes associated with early onset AD in these 3 populations:

1) symptomatic patients with early onset AD;
2) individuals with a family history of dementia with one or more cases of early onset AD;
3) individuals with a relative affected by a known mutation of \textit{APP}, \textit{PSEN1}, or \textit{PSEN2}.

Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. 2011. PMID:21577118

Beta-amyloid plaques picture: https://www.flickr.com/photos/35049835@N00/16867428955
The Answer to a Genetic Test Is Often Something Other Than Yes or No.

Labs Typically Report an Individual’s Genetic Test Results Using Five Categories

1. Disease-causing mutation found.
2. Mutation found is **likely** disease-causing.
3. Mutation found is **probably** benign and not disease causing.
4. Mutation is known to be benign and does not cause disease.
5. Mutation is a “Variant of **Unknown** Significance” (VUS).
Genetic Test Results Require Interpretation

- Clinicians don’t order genetic tests unless the results are likely to improve patient management.
- Typically Medical Geneticists and Genetic Counselors are the clinicians who are most qualified to order and interpret genetic tests.

Genetic Test Registry
Polymorphism in Nature
2. Genetic Variants – Single Nucleotide Polymorphisms

Over 1,600 SNPs Have Been Identified in the BRCA1 Gene.

Here is one of those SNPs.

Rs55770810

Rs55770810, also known as R1699W, is a SNP in the BRCA1 gene. The more common (C) allele encodes the amino acid arginine (R), while the rare (T) allele encodes a tryptophan (W).

An analysis of sequence variants of unknown clinical significance in the BRCA1 and BRCA2 genes concluded that this SNP was among the top 10 (over both genes) likely to lead to breast cancer, with a calculated odds of over 1,000:1 against this just being a spurious association. Although the clinical importance has not been proven, this may still be of use for genetic counseling [PMID 17924331].

This SNP is also represented on some 23andMe microarrays as 15010082.

https://www.snpedia.com/index.php/Rs55770810

In the BRCA1 gene – which is 193,689 nucleotides long – if this 1 particular nucleotide is a T instead of a C, a person is more likely to get breast cancer.
BRCA1 SNPs –
“You have the breast cancer gene.”

- Approximately 500 of the 1,600+ known BRCA1 variants have been classified as causal.
- What should a person with a BRCA1 variant that is causal expect?
  - Increased risk of developing breast and/or ovarian cancer at an earlier age
  - Lifetime risk of breast cancer is 80 to 90%
  - Lifetime risk of ovarian cancer is 40 to 50%
  - Increased risk of bilateral breast cancer

Credit: OMIM
http://www.omim.org/clinicalSynopsis/604370

Credit SNPedia
https://www.snpedia.com/index.php/BRCA1
Variants of Unknown Significance (VUSs)

Yes! A variant (SNP) is present in a gene. (We don’t typically see that nucleotide in that location.)

No! We don’t know what the clinical significance is. It could be benign, or it could be pathogenic.

A VUS in a lab report really is UNKNOWN.

After more evidence is collected, VUSs can often be categorized as benign or pathogenic.
Clinicians Are Concerned with Clinically Actionable Variants

- If you have a BRCA1 pathogenic variant, clinician may be able to provide:
  - Closer surveillance (MRI in addition to mammogram)
  - Surgery (if warranted)
  - Chemoprevention
  - Genetic Counseling

- Often the significance of a gene variant isn’t known, or there isn’t a helpful clinical way to address a gene variant.
3. Tumor Genomic Testing For Targeted Therapy

1. Researchers study genetic differences between tumor cells and normal cells.
2. Some tumor cells divide rapidly because their BRAF gene is not functioning properly.
3. Drugs are developed to target cells with this particular BRAF mutation.

Melanoma Cell With a BRAF V600 Mutation
Discovering unique therapies that treat an individual’s cancer based on the specific genetic abnormalities of that person’s tumor.

Image credit Cancer.gov: http://www.cancer.gov/research/key-initiatives/precision-medicine
If Your Tumor Cells Have This Mutation, Then We’ll Prescribe This Drug

Some Drugs Are Approved Along With “Companion Diagnostic Tests”

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TAFINLAR safely and effectively. See full prescribing information for TAFINLAR.

TAFINLAR® (dabrafenib) capsules, for oral use
Initial U.S. Approval: 2013

----------------------------------RECENT MAJOR CHANGES----------------------------------
Indications and Usage (1.2) 11/2015
Dosage and Administration (2) 11/2015
Warnings and Precautions (5) 11/2015

----------------------------------INDICATIONS AND USAGE----------------------------------
• TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1, 2.1, 14.1)
• TAFINLAR is indicated, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.2, 2.1, 14.2)

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma. (1.3, 5.2)

----------------------------------DOSAGE AND ADMINISTRATION----------------------------------
• Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. (2.1)
• Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. (2.1)
# Precision Medicine in Oncology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Targeta</th>
<th>Indicationa</th>
<th>Diagnostic Testsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>HER2/Neu Amplificationb</td>
<td>Breast Cancer</td>
<td>Bond Oracle Her2 IHC System</td>
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<tr>
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<td>INFORM HER2 DUAL ISH DNA Probe Cocktail</td>
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<td>INSITE HER-2/NEU KIT</td>
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<td>SPOT-LIGHT HER2 CISH Kit</td>
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<td></td>
<td>PATHWAY ANTI-HER-2/NEU (4B5) Rabbit</td>
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<td></td>
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<td></td>
<td>Monoclonal Primary Antibody</td>
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<td></td>
<td></td>
<td></td>
<td>INFORM HER-2/NEU</td>
</tr>
<tr>
<td>Trastuzumab/Pertuzumab/</td>
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<td>Localized, lymph node-negative breast cancer</td>
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<tr>
<td>Ado-Trastuzumab</td>
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<td>Stage II, lymph node-positive breast cancer</td>
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<tr>
<td>Emtansine</td>
<td></td>
<td>Breast cancer &amp; gastric cancer</td>
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<tr>
<td>Crizotinib</td>
<td>ALK rearrangement</td>
<td>NSCLC</td>
<td>VENTANA ALK (D5F3) CDx Assay</td>
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<tr>
<td>Afatinib</td>
<td>EGFR Exon 19 deletion or L858R</td>
<td>NSCLC</td>
<td>VYSIS ALK Break Apart FISH Probe Kit</td>
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<tr>
<td>Erlotinib</td>
<td>EGFR Expression</td>
<td>NSCLC</td>
<td>therascreen EGFR RQG PCR Kit</td>
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<td>Gefitinib</td>
<td>EGFR T790M</td>
<td>NSCLC</td>
<td>cobas EGFR Mutation Test</td>
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<td>Osimertinib</td>
<td>KRAS Codon 12/13</td>
<td>CRC</td>
<td>therascreen EGFR RQG PCR Kit</td>
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<tr>
<td>Cetuximab/Panitumumab</td>
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<td>DAKO EGFR PharmDx Kit</td>
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<tr>
<td>Dabrafenib/Trametinib</td>
<td>BRAF V600E</td>
<td>Melanoma</td>
<td>THxID BRAF Kit</td>
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<tr>
<td>Vemurafenib</td>
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<td>cobas 4800 BRAF V600 Mutation Test</td>
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<tr>
<td>Pembrolizumab</td>
<td>PD-L1 Expression</td>
<td>NSCLC</td>
<td>PD-L1 IHC 22C3 PharmDx</td>
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<td>Imatinib Mesylate</td>
<td>c-Kit</td>
<td>GIST</td>
<td>DAKO C-kit PharmDx</td>
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<td></td>
<td>KIT D816V</td>
<td>ASM</td>
<td>KIT D816V Mutation Detection by PCR</td>
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<tr>
<td>Olaparib</td>
<td>Germline BRCA1/BRCA2</td>
<td>Ovarian cancer</td>
<td>PDGFRB FISH</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>17p deletion</td>
<td>CLL</td>
<td>BRACAnalysis CDx</td>
</tr>
</tbody>
</table>

4. Pharmacogenomics: Should We Prescribe You a Little, a Lot, or None At All?

**Pharmacogenomics**

**Purpose**: Study how genes affect an individual’s responses to drugs.

**Goal**: Predict who will benefit from a medication, who will not respond at all, and who will experience adverse drug reactions.

(Adapted from Yaffe SJ, Aranda JV: Neonatal and pediatric pharmacology, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)
Plavix (Clopidogrel)

- Anti-platelet drug – inhibits blood clots which can lead to heart attack and stroke.
- Some people have CYP2C19 variants that cause them to metabolize Plavix slowly.
- Slow metabolism of Plavix = increased risk of clotting/adverse events.
- Physicians will prescribe different antiplatelet drugs for these people.
FDA-Approved Drugs with Pharmacogenomic Information in Their Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labeling. The labeling for some, but not all, of the products includes specific actions to be taken based on the biomarker information. Pharmacogenomic information can appear in different sections of the labeling depending on the actions. For more information, please refer to the appropriate labeling guidance.

165 drugs on this FDA list as of October 2016.

Sometimes genetic testing is mandatory for prescribing a drug.

Therapeutic areas include anesthesiology, cardiology, dermatology, endocrinology, gastroenterology, hematology, infectious diseases, and psychiatry. The largest number are oncology drugs.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
Survey of >10,000 US physicians: “Although 98% of all respondents agreed that the genetic profile of a patient could influence drug therapy decision, only 29% had received some pharmacogenomics education during their medical training, and only 10% felt they were adequately trained to apply the knowledge in clinical practice.”

1000 Genomes Project

- Conducted to permit the study of genetic variation in the human population. (Completed 2015.)

- Analyzed 2,504 genomes from 26 populations across 5 continental regions.

- Increased diversity in genetic databases still needed!

Credit Flickr - https://www.flickr.com/photos/trevor-dennis/
Clinical Uses of Genetic Tests

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 Testing image from Genome.gov
https://www.genome.gov/images/content/genetic_testing.jpg
Jean’s Genetic Testing Timeline

Age 1 Day: **newborn testing** for a few serious childhood diseases

Age 30: **carrier testing** (with her partner) before getting pregnant

Age 35: **predictive testing** when sister develops breast cancer at a young age

Age 45: **direct-to-consumer testing** to investigate ancestry

Age 65: **pharmacogenomics testing** when Plavix (anti-platelet drug) was not effective
Repeat Testing May Yield Different Results!

What genes and what variants did you test for?
- Different tests offered for the same conditions.
- Knowledge always changing.

Might not have enough examples in the database to determine associations between specific variants and specific conditions.

Might not have enough examples of people like you in the database.

Possibility of false positive and false negative results.
TAKE A BREAK!
## Selected Genetic Medicine Databases for Clinicians

<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Reviews</td>
<td>Point-of-care information for inherited conditions - diagnosis, management, and genetic counseling information. Peer-reviewed chapters. Search by gene or disorder.</td>
</tr>
<tr>
<td>OMIM</td>
<td>Overviews of Mendelian disorders and genes associated with disease. Can search by symptom.</td>
</tr>
<tr>
<td>ClinVar</td>
<td>Variants found in patient samples along with assertions regarding the variants' clinical significance. Includes level of evidence available.</td>
</tr>
<tr>
<td>PharmGKB</td>
<td>Information on the impact of human genetic variations on drug response. Includes drug dosing guidelines.</td>
</tr>
</tbody>
</table>
# UW Genetic Medicine Guide

[Genetic Medicine Guide](http://guides.lib.uw.edu/hsl/geneticmedicine)

## Genetic Medicine Resources: Starting Points for Clinicians

<table>
<thead>
<tr>
<th>Resource</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGeN</td>
<td>Medical genetics information compiled from GeneReviews, OMIM, ClinVar, Genetic Testing Registry, and PubMed.</td>
</tr>
<tr>
<td>GeneReviews</td>
<td>Search for a gene, genetic disorder, or clinical feature to find summaries of clinical conditions.</td>
</tr>
<tr>
<td>Genetic Testing Registry</td>
<td>Links to practice guidelines.</td>
</tr>
<tr>
<td>PharmGKB</td>
<td>Point-of-care information for inherited conditions - diagnosis, management, and genetic counseling information.</td>
</tr>
<tr>
<td>OMIM (Online Mendelian Inheritance in Man)</td>
<td>Search for symptoms/physical features to find clinical synopses of conditions.</td>
</tr>
<tr>
<td>ClinVar</td>
<td>Variants found in patient samples. Assertions regarding variants' clinical significance.</td>
</tr>
</tbody>
</table>

## Clinical Genetics E-Books

- **Thompson and Thompson: Genetics in Medicine, 8th ed. (2010)** by Robert Nussbaum, Roderic R. McKinnis, Huntington F. Willard
- **Clinical Genomics: Practical Applications in Adult Patient Care** by Michael Murray, Mark W. Babarskis, Monica A. Giovanni
- **Lashley's Essentials of Clinical Genetics in Nursing Practice (2015)** by Huntington Willard
- **Genomic and Personalized Medicine (2013)** by Huntington Willard
- **Emery and Rimoin's Principles and Practice of Medical Genetics, 6th ed. (2013)** by David L. Rimoin

## Key Genetic Medicine Resources

- **Genetic Competency Guidelines & Educational Resources for Clinicians**
  - Genetic Competency Guidelines & Educational Resources

## Medical Genetics Literature in PubMed

Two ways to efficiently identify PubMed references relating to medical genetics:

1. Use the Medical Genetics clinical filter which can be found under "Clinical Queries".
2. Locate a MeSH term that describes the topic you're interested in, and then add the "genetics" subheading. For example: "Cardiomyopathy, Hypertrophic/genetics" (Mesh)

## Pharmacogenomics Resources

- **PharmGKB**: Pharmacogenomics Knowledge Base
  - Curated information on the impact of human genetic variations on drug responses.
  - Drug dosing guidelines.
- **PharmGKB's Level 1A & 1B Clinical Annotations**
  - Clinical variant-drug annotations with the highest level of evidence.
- **FDA Table of Pharmacogenomic Biomarkers in Clinical Genomics (2015)** by Shashikant Kulkarni, John Pfeifer

## GeneTests

- Search by disorder or gene to find available clinical genetic tests.
- NextDx
  - Commercial database of genetic tests.
- Tier Table Database (CDC Office of Public Health Genomics)
  - Ranking of genomic tests and family health history applications by levels of evidence.

**Clinical Genomics (2015)** by Shashikant Kulkarni, John Pfeifer

Provides an overview of the next-generation sequencing (NGS) technologies that are used in clinical diagnostic laboratories. Also focuses on the challenges of diagnostic
Hypertrophy, Left Ventricular

Enlargement of the LEFT VENTRICLE of the heart. This increase in ventricular mass is attributed to sustained abnormal pressure or volume loads and is a contributor to cardiovascular morbidity and mortality.

Year introduced: 1993

PubMed search builder options

Subheadings:

- analysis
- anatomy and histology
- blood
- chemically induced
- classification
- complications
- congenital
- cytology
- diagnosis
- diet therapy
- drug therapy
- economics
- embryology
- enzymology
- epidemiology
- ethnology
- etiology
- genetics
- history
- immunology
- metabolism
- microbiology
- mortality
- nursing
- organization and administration
- parasitology
- pathology
- physiology
- physiopathology
- prevention and control
- psychology
- radiography
- radionuclide imaging
- radiotherapy
- rehabilitation
- statistics and numerical data
- surgery
- therapy
- ultrasonography
- urine
- veterinary
- virology
NCBI’s MedGen Portal


MedGen
Organizes information related to human medical genetics, such as attributes of conditions with a genetic contribution.
MedGen: NCBI Portal to Medical Genetics Content

- Information about human disorders and features or symptoms that have a genetic component.
- Designed for health care professionals and the medical genetics community.
Good Search Strategy Is Following a Link from a PubMed Reference to MedGen

Role of Lung Function Genes in the Development of Asthma.

Abstract
Although our previous GWAS failed to identify SNPs associated with pulmonary function at the level of genomewide significance, it did show that the heritability for FEV1/FVC was 41.6% in a Japanese population, suggesting that the heritability of pulmonary function traits can be explained by the additive effects of multiple common SNPs. In addition, our previous study indicated that pulmonary function genes identified in previous GWASs in non-Japanese populations accounted for 4.3% to 12.9% of the entire estimated heritability of FEV1/FVC in a Japanese population. Therefore, given that many loci with individual weak effects may contribute to asthma risk in this study, we created a quantitative score of genetic load based on 15 SNPs implicated in lower lung function in both Japanese and non-Japanese populations. This genetic risk score (GRS) for lower FEV1/FVC was consistently associated with the onset of asthma (P = 9.8 × 10^{-4}) in 2 independent Japanese populations as well as with the onset of COPD (P = 0.042). Clustering of asthma patients based on GRS levels indicated that an increased GRS may be responsible for the development of a particular phenotype of asthma characterized by early onset, atopy, and severe airflow obstruction.
Exploration of MedGen Together
MedGen Summary – Familial Cancer of Breast

Familial cancer of breast
MedGen UID: 87542 • Concept ID: C0346153 • Neoplastic Process

Synonyms: BARD1-Related Susceptibility to Breast Cancer; BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer; CHEK2-Related Breast Cancer; CHEK2-Related Susceptibility to Breast Cancer

Modes of inheritance: Heterogeneous (HPO)
Autosomal dominant inheritance (HPO)

SNOMED CT: Familial cancer of breast (254843006)

Genes (locations):
AKT1 (14q32.33); ATM (11q22.3); BARD1 (2q35); BRCA1 (17q21.31); BRCA2 (13q13.1); BRIP1 (17q23.2); CASP8 (2q33.1); CDH1 (16q22.1); CHEK2 (22q12.1); ESR1 (6q25.1-25.2); HMIR (5q34); KRAS (12p12.1); NCOA2 (6p25.2); PALB2 (16p12.2); PHB (17q21.33); PIK3CA (3q26.32); PPM1D (17q23.2); RAD51 (15q15.1); RAD54L (1p34.1); RB1CC1 (8q11.23); SLC22A18 (11p15.4); TP53 (17p13.1); TSG101 (1f15p1.1); XRCC3 (14q32.33)

OMIM®
114480

Disease characteristics
Excerpted from the GeneReview: BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer

Hereditary breast and ovarian cancer syndrome (HBOC), caused by a germline pathogenic variant in BRCA1 or BRCA2, is characterized by an increased risk for breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer. The lifetime risk for these cancers in individuals with a pathogenic variant in BRCA1 or BRCA2: 40%-80% for breast cancer, 11%-40% for ovarian cancer, 1%-10% for male breast cancer. Up to 39% for prostate cancer, 1%-7% for pancreatic cancer. Individuals with BRCA2 pathogenic variants may also be at an increased risk for melanoma. Prognosis for BRCA1/2-related cancer depends on the stage at which the cancer is diagnosed; however, studies on survival have revealed conflicting results for individuals with germline BRCA1 or BRCA2 pathogenic variants when compared to controls. [from GeneReviews]

Full text of GeneReview (by section):
Summary | Diagnosis | Clinical Characteristics | Genetically Related (Allelic) Disorders | Differential Diagnosis | Management | Genetic Counseling | Resources | Molecular Genetics | References | Chapter Notes

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Additional descriptions

From OMIM
Breast cancer (referring to mammary carcinoma, not mammary sarcoma) is histopathologically and almost certainly etiologically and genetically heterogeneous. Important genetic factors have been indicated by familial occurrence and bilateral involvement. http://www.omim.org/entry/114480

From GHR
Breast cancer is a disease in which certain cells in the breast become abnormal and multiply uncontrollably to form a tumor. Although breast
Practice Question #1 Using MedGen

Find a data-rich record for Alzheimer Disease. Make a note of the MedGen UID.

- What genes are associated with Alzheimer Disease?
- According to Gene Reviews, what are the causes of Alzheimer Disease?
- Are there practice guidelines for primary care providers on diagnosing Alzheimer Disease? What year were they written?
- BONUS: Does the Genetic Testing Registry include panels of genes for diagnosing Alzheimer Disease?
A physician suspects that her patient doesn’t respond well to clopidogrel.

- Find a MedGen record that addresses this phenomenon.
- What gene is involved in metabolizing clopidogrel?
- When were the most recent practice guidelines for clopidogrel dosing published?
- What percentage of Chinese people are thought to be poor metabolizers of clopidogrel?  
  [Hint: Medical Genetics summaries link]
- Can you find some information that may be helpful for the patient?
- BONUS: What database has detailed information on the effects of gene variants on drug response?  
  [Hint: It’s linked from MedGen record.]
TAKE A BREAK!
The 1000 Genomes Project was undertaken in order to increase the _________ of the genomes represented in public databases.

What term refers to strategies for determining what treatment is right for an INDIVIDUAL rather than what treatment is recommended for a DISEASE?

Clinicians are not concerned about all genetic variants – only those that are ____________.

True or False? GINA (Genetic Information Nondiscrimination Act) protects you from life insurance discrimination.

True or False? A genetic variant may originally be classified as “likely pathogenic” and later classified as “likely benign.”

What resource would you recommend to consumers who wanted to learn more about a genetic condition?

What is a good starting place for finding genetic information for clinicians?