Integrating Genomics in Family Medicine

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- **Disclosure of Relevant Financial Relationships:** The presenter has no financial relationships to disclose.
- **Disclosure of Off-Label and /or Investigative Uses:** The presenter(s) will not discuss off label use and /or investigational use in this presentation.

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Have You Ever …

- Referred a patient for genomic testing?
- Had a patient ask about the benefits of genomic testing?
- Had a patient discuss their genomic test results with you?

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Objectives

- Understand the background of genomics related to Primary Care.
- Discuss the implications of genomics and pharmacogenomics for Primary Care.
- Characterize the clinical activity and attitudes related to genomics in a population of Primary Care clinicians.

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What Is Genomics?

- Study of all genes in an organism including.
  - o Nuclear and extranuclear genes (DNA, mRNA, protein)
  - o Mapping and sequencing of genes
  - o Gene expression under various conditions (e.g. environment, pharma)

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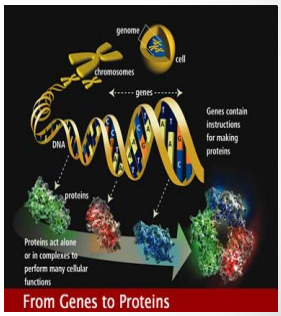
Genome To Proteome

- The genome refers to the complete set of DNA in an organism.
- Any single gene is expressed in a protein.
- The proteome refers to all the proteins in a cell or an organism.
- The interaction of proteins within the proteome and with the environment define the expression of the genome.



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History of the Human Genome Project

- HGP formally started in 1993 and ended in 2003.
- The project goals was to discover the estimated 20,000-25,000 human genes and their component base sequencing (over 3 billion DNA base subunits).

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Principles of Genetics In the Context of Disease

- Genetic variation necessary for survival of our species.
- Maladaptive genetic variation comes to our attention as disease.
- Complex disease is a result of the interaction between the genome and the environment.

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Integrating Genomics

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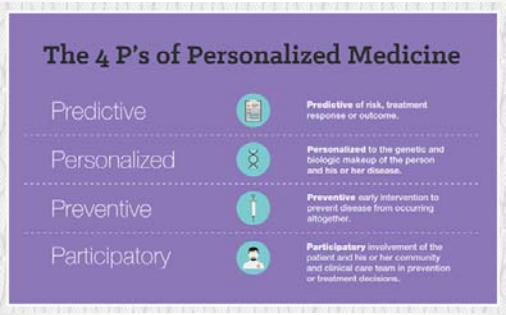
Personalized Medicine

- Personalized Medicine proposes the customization of an individual's healthcare based primarily on his/her genome.
- Personalized Medicine suggests that knowing a patient's genome will allow the patient and his/her doctor to tailor tests and treatments.

The Promise of Personalized Medicine

- Predictive Medicine
  - Genomic markers of disease risk that may allow patients to make choices about lifestyle, environment, and treatment.
- Pharmacogenomics
  - Choosing medications based on genomics to
    - Enhance benefit by matching the medicine to the patient.
    - Reduce adverse events.

The 4 P's of Personalized Medicine



ACCE Framework

- Analytical validity – genomic test results need to be accurate and reliable.
- Clinical validity – reliable results are of consistent clinical significance.
- Clinical utility – there is a clear benefit for intervention based on genomic test results.
- Ethical, legal, and social implications are openly discussed.

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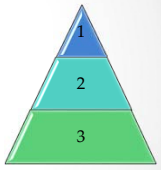
Tiered Approach to Integrating Genomics

- Tier 1 – recommended for clinical use by evidence-based panels and supported by systematic review of evidence.
- Tier 2 – validity and promising evidence of clinical utility, but lack evidence-based recommendations.
- Tier 3 – inadequate validity or utility.



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Single-Gene Disease

- Single-gene disorders tend to present as severe disease that is seen early in life (e.g. cystic fibrosis).
- Inheritance of single-gene disorders is Mendelian.
- Many single-gene disorders are so severe that progeny dies in utero.
- Genetic therapy is typically aimed at treating single-gene disorders.

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Examples of Single-Gene Testing

- Prenatal Testing
  - o Fetal Cells in Maternal Blood (FCMB)
  - o Transcervical retrieval of trophoblasts
  - o Chorionic Villus sampling
  - o Percutaneous Umbilical Blood Sampling (PUBS)
  - o Amniocentesis
- Newborn Screening

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Complex Disease

- Complex disease is much more frequent than single-gene disease.
- Complex disease (cancer, heart disease, diabetes, etc.) are the major contributors to morbidity and mortality in developed and developing countries.
- Complex disease is typically the result of multiple gene products interacting with each other and with the environment.
- Genomics for complex disease are ***probabilistic*** and not ***deterministic***.

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Single-Gene vs. Complex Disease

- A single-gene disorder is usually expressed early in development and, therefore, may have limited prevention and treatment options.
- Complex genetic disease is slow developing, and therefore often amenable to treatment.

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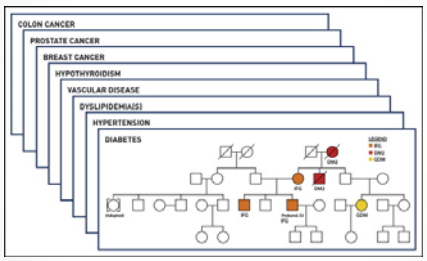
Complex Disease Pedigrees



Disease-specific pedigrees will soon be utilized to optimize risk stratification and assist with appropriate allocation of resources for disease prevention and early discovery. It is necessary that both patients and health care providers have access to these pedigrees because they are dynamic and clinical interpretation changes with time.

Image adapted from The American Journal of Medicine.
Integration of Genomics in Primary Care.
Eric A. Larson MD, Russell A. Wilke MD, PhD. © 2015

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Treating Complex Disease

- Because of its slow development, complex diseases can be treated by
  - Changing the environment (e.g. lifestyle)
  - Early intervention (e.g. early screening, removing a precancerous lesion)
  - Interacting with the body's proteins (e.g. pharmaceuticals)

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Pharmacogenomics

- Pharmacogenomics (PGx) is the study of how individual genetic differences affect drug response.
  - Predict benefit
  - Anticipate adverse reactions
- The ultimate aim of PGx is to use a patient's genome to use only those drugs that would be beneficial and avoid those that are ineffective or even harmful.

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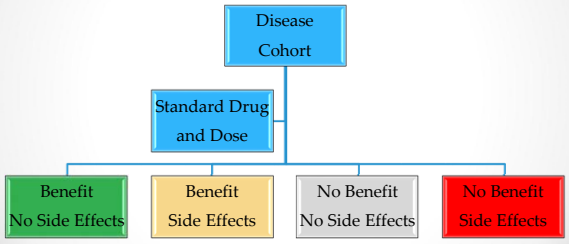
Current Pharmacotherapy



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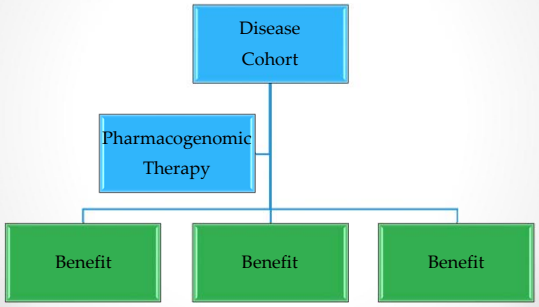
Pharmacogenomics



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Applications of PGx

- Human Epidermal Growth Factor Receptor 2 (HER2/neu) testing of patients with metastatic breast cancer to determine responsiveness to trastuzumab (Herceptin).
- Guided warfarin dosing by testing for Cytochrome P450 2C9 (CYP2C9) and Vitamin K Epoxide Reductase Complex subunit 1 (VKORC1).

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Chronic Disease Applications of PGx

- Genomically-guided treatment would allow choice of the most effective medications for patients.
- Likewise, we would avoid using medication when the individual's genomics suggests the risk of adverse effects.
- Theoretically, this would improve outcomes and reduce healthcare costs.

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Primary Care Physician Perspective

- Primary Care Physicians Experience and Confidence with Genetic Testing and Perceived Barriers to Genomic Medicine. Journal of Family Medicine. 2015;2(2).
  - Chambers CV, Axell-House DB, Mills G, Bittner-Fagnan H, Rosenthal MP, Johnson M, Stello B.

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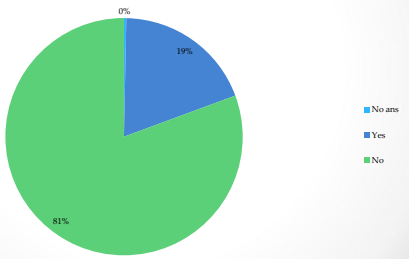
In the last 6 months have you ordered genetic testing?



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Genetic Testing Ordered

Testing	(n)
Cancer Risk	28
Prenatal	11
Other	11
Pharmacogenomics	9
Micro array	6

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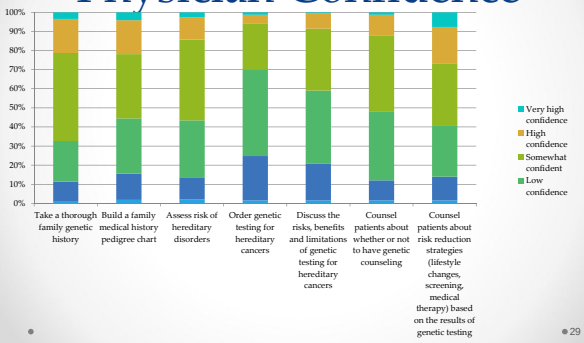
Physician Confidence



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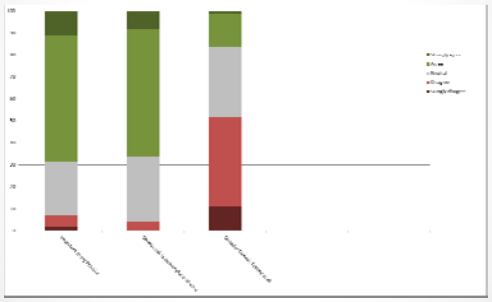
Role of Genomics



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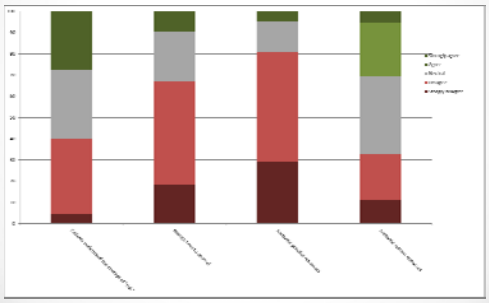
Working With Patients



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Integrating Genomics in HIT

- Identify genomic data with high validity and clinical utility (i.e. Tier 1 data).
- Develop structured data storage for EHRs.
- Integrate genomic data into condition-specific, rules-based decision support.
- Provide the decision support to patients and clinician at the point of care.

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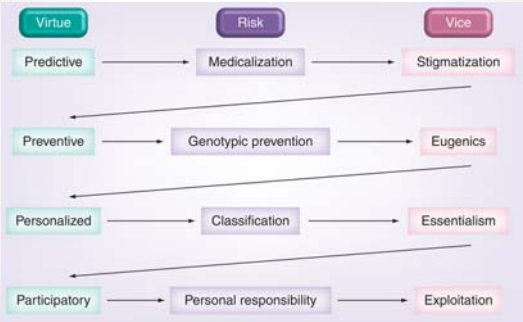
Virtues and Vices of Personalized Genomic Medicine



Juengst E, et al. After the revolution? Ethical and social challenges in 'personalized genomic medicine.' Personalized Medicine. 2012 June 1;9(4):429-39.

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Amara's Law

- ***"We tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run."***

  - Roy Amara, Institute for the Future