Introduction to Genomics and OSUMC/CPMC Research project
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No disclosures to report
I will be talking about research testing and non-FDA regulated genetic testing

Overview
- Introduction
- Personalized medicine at OSUMC
- The Coriell Personalized Medicine Collaborative
- Physician study involvement and informed consent
- Genomic medicine introduction
- Risk analysis education
- Pharmacogenetic introduction

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- Heather Hampel
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- Leigha Senter-Jamieson
- Kate Shane
- Amy Sturm
- Kevin Sweet
OSUMC Center for Personalized Health Care
http://cphc.osu.edu

- Imagine health care that promotes wellness
- Determines a person’s risk for a disease before they have symptoms
- Provides for individual prevention and treatment strategies for each person
- This is the promise of personalized health care, also known as personalized medicine
- Clay Marsh, MD, Executive Director, CPHC

OSUMC - Coriell Personalized Medicine Collaborative (OSUMC-CPMC)

- New partnership between the Ohio State University Medical Center and the Coriell Institute for Medical Research
- To gain a better understanding of the potential uses of genetic, family history, environment and lifestyle information to improve health outcomes
- To do personalized medicine

CPMC is focused on COMMON COMPLEX disease

Multi-Gene (COMPLEX)
- Heart Disease
- Diabetes
- Cancer
- Obesity

Single-Gene
- Marfan syndrome
- Cystic fibrosis
- Huntington disease

What is the OSUMC-CPMC?
Primary Study Aim

- Two patient cohorts receive risk information for common complex diseases
- Randomize to determine whether in-person genetic counseling affects:
  - genetic knowledge
  - perceived risk
  - interactions with the healthcare team
  - information seeking preferences
- To better define how to incorporate genomic information into current healthcare practice
What is the OSUMC-CPMC?

Patient Recruitment

- **Cohort 1**: 900 patients with systolic CHF
  - Ross Heart Hospital
  - University Hospitals East Cardiology

- **Study recruitment**
  - Cardiologist identifies appropriate patients
  - **Study recruiter** meets with patient onsite for informed consent and enrollment, collects sample and provides study brochure

- **Cohort 2**: 900 patients with HTN
  - OSUMC IM at Morehouse, Stoneridge, and Grandview
  - OSUMC Family Practice

- **Study recruitment**:
  - Eligible patients identified by physician
  - Provides study contact and brochure
  - Provides list of eligible patients to study coordinators

- **Study accrual**
  - Study personnel contact patient, arrange for group education/consent session on campus
  - Study recruiters may also be available at clinic sites
  - Patients can also register for education/consent sessions online

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**Genetic Testing**

- DNA isolated from cells in saliva
- DNA processed in CLIA-certified laboratory to determine large part of an individual’s genetic variation

**Intervention Arm**

- Randomized to receive in-person genetic counseling

**Control Arm**

- Randomized not to receive in-person genetic counseling

- Notification via email
- All results considered to be potentially actionable
- Results available for OSUMC study physicians in Epic Ambulatory
Informed Consent & Saliva Collection
Account Activation & Health Questionnaires
Genetic Testing
Participant Randomization

**Participant Randomization**
Study participants will be randomly placed into one of two groups:
- Some will meet with genetic counselor after viewing initial results
- Some will have the option of meeting with a genetic counselor 3-months after viewing initial results
- Genetic counseling will be available at no cost

Cohort 1: Initial Genetic Counseling
6-8 weeks

**Intervention Arm:** In-person Genetic Counseling

**Control Arm:** Randomized not to receive in-person genetic counseling

Outcomes Research
- Periodic follow-up questionnaires
- Did the participant:
  - Discuss information with their physician?
  - Change diet or lifestyle?
  - Begin disease screening?
  - Do nothing?

Conditions Currently Approved to be Reported by the CPMC:
- *Age-related macular degeneration*
- Breast cancer
- Bladder cancer
- Chronic obstructive pulmonary disease
- Colorectal cancer
- *Coronary artery disease*
- *Hemochromatosis*
- Inflammatory bowel disease
- *Systemic lupus erythematosus*
- Melanoma
- Obesity
- *Prostate cancer*
- Rheumatoid arthritis
- Testicular cancer
- Type 1 diabetes
- *Type 2 diabetes*
- CYP2D6, VKORC1, CYP2C9, CYP2C19, UGT1A1, CYP4F2

Conditions will be added during the coming months and years.

Who decides what genetic information is reported?
- **Informed Cohort Oversight Board (ICOB),** an external advisory board. Composed of scientists, medical professionals, ethicist, community members.
  - Vote on whether conditions are potentially actionable.
  - Meet at least twice a year to approve new conditions.
  - New results then reported to ALL participants.
In 2011, Jamile Williams, 48 years old, had a routine check-up with her doctor. She was told she had a family history of coronary artery disease. Her physician suggested a genetic test to identify genetic variations, which showed an increased risk for diabetes as well.
Potential Utility of Personalized Medicine

Jamile can’t change his genes but he can modify non-genetic factors that also increase his risk for coronary artery disease (CAD)

He becomes more aware of his weight and diet, now knowing that diabetes increases risk for CAD, too

His physician is able to put him on the right dose of the right anti-hypertensive related to his genetic make-up

Physician Pilot Study

- **Aim:**
  - To better understand how physicians understand and utilize genetic information for common complex disease
  - Assess changes in knowledge, clinical utility, integration of genetic information into electronic medical records during the course of the study

Physician Study Participation

- Provide signed informed consent and complete baseline genetic knowledge survey
- Attend OSUMC-CPMC study education session
- Assist in identification of potential study participants
- Establish account on Coriell Web Portal
- Follow up surveys at one-week, and annually

Physician Study Participation

- Patient participant risk reports for complex diseases and drug metabolism available as PDF in Epic Ambulatory
  - Study participants seen for genetic counseling will also have a summary research note available in Epic
  - NOT required to act on any information that goes against your best medical judgment
  - Genetic counselors and MD geneticist available for inquiry throughout study
Potential Risks
- Surveys may make you uncomfortable
- Incomplete risk assessment (i.e. limited genetic analysis)
- Inaccurate genetic test results
- Uncertainty with talking to patients about the disease risks involved

Potential Benefits
- Help develop models for further physician education
- Promote utilization of genomic information and genetic resources
- Helping to improve human health in the future

How does OSUMC-CPMC Protect Privacy?
- Genetic Information Non-Discrimination Act of 2009 (S881)
- Ohio Revised Code Annotated, Section 3904.01 and 3904.13
- IRB approval
- Unique barcode numbers
- Secure storage servers

OSUMC-CPMC
- Main CPMC study will enroll 100,000 volunteer study participants
- OSUMC-CPMC: 1800 patient participants
- We are committed to ensuring participants are representative of multiple populations
The CPMC is taking a responsible approach to determine the utility of genome information in healthcare.

http://cpmc.coriel.org

Viewed as “pioneers in the field of personalized medicine” by Federal Health and Human Services.

What is genetics?

- Genetics (historical)
  - Genes code for proteins
  - Changes in chromosome structure and DNA sequence affect disease risk
  - Inheritance of single genetic variants (mutations)
    - Classic Mendelian patterns of inheritance (recessive, dominant, X-linked)
    - Single-gene disorders

What is genomics?

- Genomics
  - Broader application, based on similar genetic principles
  - An individual’s entire DNA sequence
  - Study of the mechanisms whereby gene activity is regulated
    - DNA sequence variation
    - Gene-gene interactions
    - Effects on health and disease

The Human Genome

- DNA nucleotide is made from a sugar deoxyribose, a phosphate group, and a nitrogen-containing base
- Four different types of DNA nucleotides - same deoxyribose and phosphate group, different base
  - Adenine, Cytosine, Guanine, Thymine

5’-ACGCACCCGACGTCACGC-3’
3’-TGCCTGTCGGCTGCGTCGCG-5’
Terms to know

- **SNP: single nucleotide polymorphism**
  - Change in the DNA code compared to the reference sequence
- **Locus**
  - The specific physical location of a gene or DNA sequence on a chromosome
- **Allele**
  - One of a number of alternative forms of the same gene occupying a given position on a chromosome (e.g. we all have two alleles of each gene)
- **Haplotype**
  - Combination of alleles (for different genes) that are located closely together on the same chromosome and that tend to be inherited together

Human Genome

- ~22,000 genes, >80,000 distinct proteins
- Each individual possesses two copies of each gene*
  - Most people possess different versions of the gene’s sequence at each of the two copies
  - Each of the different specific versions of a gene’s sequence in any individual is referred to as an allele of that gene
  - The two alleles an individual possesses at a locus constitute the individual’s genotype for that locus

*except for males having one allele of their X and Y chromosome genes
Genomic Technology

- **Whole-genome sequencing** refers to sequencing the entire human genome
  - 3 billion nucleotide read
- **Genome-wide association (GWA) studies** focus on specific bases in the DNA sequence, and determine which of the four bases the individual has in those positions
  - Microarray technology can test the individual’s DNA sequence for > 1 million different nucleotides

Microarray Technology

- Human Genomic Variation
  - The 1% unique DNA sequence is highly variable
  - Some DNA variants will have no effect (benign polymorphisms)
  - Some will cause a small to moderate increase or decrease in the protein’s activity level
  - Others will completely abolish the protein’s activity or greatly enhance it
  - **Risk-increasing alleles** and **risk-reducing alleles**
Human Genomic Variation

- No single gene or protein acts alone
  - Gene-gene interactions
  - Proteins work in concert with other proteins and other biomolecules in distinct metabolic pathways
- All disease is complex disease
- Each risk-increasing allele may only make a small contribution to absolute risk
- Additional factors (i.e., environment, lifestyle) impact clinical phenotype
  - Gene-environment interactions

SNPs = Single Nucleotide Polymorphisms

Sites of variation in the DNA sequence

>12 million SNPs in the human genome and counting

SNPs and other DNA variants exert a wide range of effects on gene/protein activity

SNP = a single base change (or reflection of another change) from the “reference sequence”

- May be a traditional mutation
- Can be found in non-coding regions
- Often inherited in groups

Some SNPs can impact health
**Example: SNPs in gene for heart function**

Karen: ACAGTCCATGCGTAGGTGTCCTAGACTA
Debo: ACAGTGCATGCGTAGGTGTCCTAGACTA
Jose: ACAGTCCATGCGTAGGTGTCCTAGACTA
Anupriya: ACAGTCCATGCGTAGGTGTCCTAGACTA
Zhijun: ACAGTCCATGCGTAGGTGTCCTAGACTA

**Example:**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No Health impact</td>
<td>No Health impact</td>
</tr>
<tr>
<td>T</td>
<td>Increased Risk for Heart Attack</td>
<td>Increased Risk for Heart Attack</td>
</tr>
</tbody>
</table>

Karen: ACAGTCCATGCGTAGGTGTCCTAGACTA
Debo: ACAGTGCATGCGTAGGTGTCCTAGACTA
Jose: ACAGTCCATGCGTAGGTGTCCTAGACTA
Anupriya: ACAGTCCATGCGTAGGTGTCCTAGACTA
Zhijun: ACAGTCCATGCGTAGGTGTCCTAGACTA

This is NOT a diagnosis. This is NOT TOTAL risk. This is risk based on ONE SNP. This is ONE piece of the puzzle.
Example: SNPs in gene for heart function

- A = No Health impact
- T = Increased Risk for Heart Attack
- C = Modified increased Risk for Heart Attack

Karen: ACAGTCCATGGCTAGCTCCCTAGACTA
Debo: ACAGTCCATGGCTAGCTCCCTAGACTA
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Zhijun: ACAGTCCATGGCTAGCTCCCTAGACTA

Heart disease is a COMPLEX disease

Multiple factors influence disease risk:
- genetics
- lifestyle
- diet
- family history
- environment

Potential Utility of Personalized Medicine

Disease screening and prevention or earlier intervention

- Informed Consent
- Saliva Collection
- Account Activation
- Health Questionnaires
- Genetic Testing
- 6-8 weeks
- Genetic Results
  - Notification via email
  - All results considered to be potentially actionable
  - Results available for OSUMC study physicians to view in Epic Ambulatory
Type 2 Diabetes is caused by a combination of genetic and non-genetic (or environmental) risk factors. It is estimated that non-genetic factors (such as diet and exercise) account for about 74% of the risk for type 2 diabetes. It is estimated that about 28% of the risk of type 2 diabetes is based on genetic risk factors. This estimate accounts for both known and unknown gene variants. Many different genes are thought to contribute to the total genetic risk. A number have been identified and others are yet to be discovered.
What is relative risk?

Relative risk compares the risk of disease in two different groups of people – those with the exposure and those without the exposure.

For example,

- Age > 65 vs. Age < 65
- Smokers vs. Non-Smokers

Relative risk is a ratio.

 Relative risk is found by dividing the risk of disease in the exposed group by the risk of disease in the unexposed group.

\[
RR = \frac{\text{Risk of disease in exposed group}}{\text{Risk of disease in unexposed group}}
\]
Possible RR values
Relative risk can range from almost zero to infinity.

- RR = 1 when the risk of disease is the same in the exposed and unexposed groups
- RR > 1 when the risk of disease is greater in the exposed group than in the non-exposed group
- RR < 1 when the risk of disease is greater in the non-exposed group than in the exposed group

**Smoking and Lung Cancer**

The relative risk for smoking and death due to lung cancer is the risk of dying due to lung cancer for smokers divided by the risk of dying due to lung cancer for non-smokers.

\[
RR = \frac{249 \text{ deaths in 100,000 people per year}}{17 \text{ deaths in 100,000 people per year}} = 15
\]

A relative risk of 15 indicates a strong association between smoking and death due to lung cancer.

**Smoking and Coronary Heart Disease**

The relative risk for smoking and death due to coronary heart disease (CHD) is the risk of dying due to CHD in smokers divided by the risk of dying due to CHD in non-smokers.

\[
RR = \frac{1001 \text{ deaths in 100,000 people per year}}{619 \text{ deaths in 100,000 people per year}} = 1.6
\]

**Smoking and Lung Cancer**

What does a RR=15 mean?

- Smokers are 15 times as likely to die of lung cancer as non-smokers
- Smokers have 15 times the risk of dying due to cancer as compared to non-smokers
- Smoking is associated with a 14-fold increase in the risk of lung cancer mortality
Smoking and Coronary Heart Disease

What does a RR=1.6 mean?

- Smokers are 1.6 times as likely to die due to coronary heart disease as non-smokers
- Smokers have 1.6 times the risk of dying due to coronary heart disease as compared to non-smokers
- Smoking is associated with a 60% increase in the risk of death due to coronary artery disease

Risk Variant and Coronary Heart Disease

Having a genetic risk variant can also be the “exposure”

For a single variant, each person can receive either 2, 1 or no copies from his or her parents

<table>
<thead>
<tr>
<th>Variant</th>
<th>Number of Copies</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>AG</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>AA</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Intervention (exposure) | Outcome (disease) | RR | Meaning
-----------------------|-------------------|----|----------------------------------
Mammography screening in women | Breast cancer mortality | 0.80 | Mammography screening in women is associated with a 20% reduction in the risk of death due to breast cancer
Cholesterol-lowering treatment (statins) in hyperlipidemia | Coronary event* | 0.79 | Treating people who have hyperlipidemia with cholesterol-lowering treatment is associated with a 21% reduction in coronary events

* includes heart attack, stroke, death due to coronary heart disease, revascularization procedure
Relative Risk Values

RR = 1

- Mammography and breast cancer mortality
- Single genetic variant and coronary heart disease
- Cholesterol lowering therapy and coronary events
- Smoking and death due to coronary heart disease
- Smoking and death due to lung cancer

Absolute vs. Relative Risk

Smoking and death due to lung cancer:

10-year risk for smokers: 2.49%
10-year risk for non-smokers: 0.17%

Recall that the relative risk for smoking and death due to lung cancer is high (RR=15).
Yet, the 10-year absolute risk of death due to lung cancer in smokers (2.49%) is relatively low.
Because the risk of lung cancer for non-smokers is very low, multiplying that risk by 15 gives a relatively low risk.

Absolute vs. Relative Risk

Smoking and death due to coronary heart disease:

10-year risk for smokers: 10.0%
10-year risk for non-smokers: 6.2%

Recall that the relative risk for smoking and death due to coronary heart disease is moderate (RR=1.6).
Yet, the 10-year absolute risk of death due to coronary heart disease (10%) is greater than that for lung cancer because the risk of coronary artery disease is higher than the risk of lung cancer in non-smokers.
Despite the difference in RR values (15 vs. 1.6), more smokers are dying due to coronary heart disease than due to lung cancer.

Limitations

SNP is a piece of a much larger puzzle

Gene-Gene interactions
- additive risk
- multiplicative risk

Gene-Environment interactions
- additive risk
- multiplicative risk

Cannot provide an absolute risk without knowing all the factors involved
OSUMC-CPMC

- One goal is to put genetic variant risk into the context of all risk factors, including family history and lifestyle, for our patients and their healthcare providers.

- In an ideal world where absolute risk estimates are available, we would report absolute risk estimates for each disease.

- In practice, accessing these estimates from available published data is not possible because very few prospective studies report absolute risk due to both genetic and non-genetic factors.

Personalized Medicine (also known as Genome-Informed Medicine)

Personalized medicine is the use of genomic information in addition to family history, lifestyle and environmental factors to customize health management.

Current Practice
- One size fits all
- Trial and error

Genome-Informed Medicine
- Pharmacogenomics: the correct treatment for the correct person at the correct time
- Disease screening and prevention

Pharmacogenetics (pharmacogenomics)

- Interaction of medications and genes
  - Drug metabolism
  - Site of activity of a drug
  - Side effect profiles
  - Drug transport

Potential Utility of Personalized Medicine

- Personalized drug selection and dosing for more effective therapies

- Disease screening and prevention or earlier intervention

- More efficient organization of clinical trials for drug development
Potential Utility of Personalized Medicine

Karen Schmale, 49 years old
Gasping for air
Barnes - Jewish Hospital, St. Louis
Diagnosed with PE and DVT
Prescribed warfarin 10mg/5mg/5mg regimen

[Trial and error medicine]

A week later Karen is too weak to walk
She has hematuria, INR is 7.5
Given Vitamin K, CT head negative
$500 genetic test for warfarin performed
Karen Schmale is hypersensitive to warfarin because of her personal genome

2 Million Prescriptions for Warfarin Written Every Year in United States

Karen can take warfarin safely, but at a dose that is tailored to her specifically.

Credit to Karen Weck, PhD at UNC-CH for this slide
Warfarin responders

Coumadin is metabolized by cytochrome P450 system; recognized since 1999 that three common variants exist in the normal population

<table>
<thead>
<tr>
<th>Type</th>
<th>Activity</th>
<th>Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) CYP2C9*1</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>(2) CYP2C9*2</td>
<td>70%</td>
<td>12%</td>
</tr>
<tr>
<td>(3) CYP2C9*3</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
</table>

One study in JAMA with random selection of patients on Coumadin, had a variant rate of 30% in enzyme activity.

“Extensive Metabolizers” also exist:

- Higher complication rate
- Longer time to establish a stable dose
- Significant racial differences

CYP2C9 variant alleles

- CYP2C9*2, CYP2C9*3 – most common variants
- Seen in 20-40% of Caucasians, <10% Asians and African Americans
- Associated with reduced CYP2C9 enzyme activity
- Variant alleles associated with
  - lower mean doses of Warfarin
  - longer times to stabilization of INR
  - higher risk for bleeding events

![Cytochrome P450 Genotype and Warfarin Dose](image)

![Time to Event for Anticoagulation-Related Outcomes](image)
Warfarin non-responders

Additionally the enzyme that is affected by warfarin VKOR (vitamin K epoxide reductase multiprotein complex) has a genetic variant that prevents even high doses of warfarin from being effective.

- Incidentally found from wild warfarin resistant rats in France

Individual Variability in Warfarin Dose

![Individual Variability in Warfarin Dose](chart)

FDA Changes Warfarin Label to Recommend Genetic Test

In 2008, the F.D.A. issued a "recommendation": all patients prescribed Coumadin should have genetic testing to determine "response" level. More recently, specific dosing guidelines based on CYP2C9/VKOR status are included.

- Similar recommendations for Tamoxifen, clopidogrel
- Stronger language for some chemotherapeutic and anti-retroviral medications
- Development of algorithm, multiple factors including genotype
- Small study: algorithm t/o time of <10 hours in determining the genotype to initiate therapy

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Meg Kane, 49 years old
new onset chest pain

EKG changes found as well as elevated troponin

Started on treatment with beta blocker, aspirin and clopidogrel. Stent placed

Need functioning CYP2C19
system to convert pro-drug to the active form of clopidogrel

Patient prescribed a medication (retail cost $160 per month) that has no protective effect for her.

Three months later, she has occlusion of the stent and has to be re-angioplasted and stent replaced.

Meg Kane is a poor metabolizer of clopidogrel because of her personal genome

[Personalized medicine]
Plavix (clopidogrel) was the 11th most prescribed medication in US in 2008 (28 million prescriptions) [#2 worldwide]

Multiple large studies have shown that poor CYP2C19 metabolizers have higher rates of cardiovascular events at 1 year from treatment than normal metabolizers.

Simon et al (NEJM 2009)
- 21.5% vs 13.3% (adjusted hazard ratio of 1.88) for CV event
  - If PCI used, 3.58x risk

Shuldiner et al (JAMA 2009)
- Hazard ratio of 2.42

* On the other side, ultrametabolizers have an increased risk of bleeding complications (Sibbing et al Circulation 2010)

CYP2C19 variant alleles
- CYP2C19
  - ~2-9% of general population are considered poor metabolizers (essentially not *1 for both alleles)
    - Higher in Asian populations (including Far Eastern and South Asians) (15-20%),**
    - Lower in Caucasians (2-6%)
    - Africans (10-20%)
  - CYP2C19*17 are considered ultrametabolizers and would confer a bleeding risk (very rare)

** some populations are much higher such as Polynesians up to 79%

Alternative therapy
Effient (prasugrel) from Eli Lilly can be used but has a stronger risk for bleeding side effects

Other CYP2C19 influenced medications
- Tricyclic antidepressants such as amitriptyline
- Most proton-pump inhibitors: Omeprazole, Esomeprazole, Lansoprazole
- Anti-malarial drug Proguanil
- Propranolol
In 2010, the F.D.A. issued a Black Box label warning about reduced effectiveness in patients who are poor metabolizers of Plavix:

- Similar recommendations for Tamoxifen
- Stronger language for some chemotherapeutic and anti-retroviral medications

Concerns over time to testing and availability of testing limited the FDA’s warning.

Contradictory studies

Recent study in NEJM (Pare et al) used the largest set of patients to date (over 3600) from two long term Plavix studies:

No change in outcome based on 2C19 status.

Some strengths to the study:

- Randomized control trial for Plavix that were consistent with previous studies as to the clinical utility of Plavix
- Large study

Some potential weakness however in the studies:

- Vast majority were European Caucasians (10% Latin American)- small percentage likely affected
- Done on bare metal stents (versus most studies done on drug-eluding stents)
- Potential bias as the study was sponsored by Sanofi-Aventis and Bristol-Myers Squibb

The Goal

- The right drug for the right person at the right time
- Anti-hypertensives- large variety and number of drugs available with a large difference in cost and side effects
  - What if you could give the appropriate drug/combination of drugs from the start rather than trial and error?