Pharmacogenomics

COSBBI
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Personalized Medicine

What is personalized medicine?
Personalized Medicine

**What is personalized medicine?**

- Someone greeting you personally at the hospital?
- Tailoring treatments to you personally?
  - Based on what?
    - Lab values?
    - Genes?
- What does that mean?

**Personalized Medicine**

- Making treatment decisions based on the patient’s genes and biomarkers

  - Requires genetic testing
    - Rare
    - Expensive (but getting cheaper)

  - Requires knowing what to do with the results
Personalized Medicine

• Requires knowing what the implications of the gene/biomarker are
  – How strong is the association?
  – How strong is the evidence?
  – How severe is the risk?
  – How severe are the consequences?
  – What are the alternatives?
  – What are the risks of the alternatives?

How do genes affect medicine?

**Fundamental Theorem of Biology:**
DNA -> RNA -> Protein

Genotype -> Phenotype
Drugs & Genes

• **Pharmacokinetics:** effect of the body on the drug
  – **Absorption:** how it passes from digestive system into the blood stream
  – **Distribution:** how it is passed into the tissues of the body to its effector site via the blood stream
  – **Metabolism:** how it is broken down into metabolites, usually in the liver
  – **Excretion:** how it is removed from the body, via the kidneys (urine) and feces

Drugs & Genes

• **Pharmacodynamics:** effect of the drug on the body
  – Mimic or inhibit biochemical activity via
    • Binding to receptors to activate or inactive them
    • Interact with enzymes
    • Interact with structural proteins
    • Interact with ion channels
  – Cause therapeutic effects, such as lower blood pressure or pain relief
Drugs & Genes

• Every pharmacokinetic step involves proteins
• Every pharmacodynamic effect can involve proteins

DNA -> RNA -> Protein

Genes influence drug response!

Example: Clopidogrel

• Generic name: Clopidogrel
• Brand name: Plavix
• Indication: Patients with elevated risk of cardiac events (stroke, myocardial infarction)
• Drug class: anti-platelet agent
  – Prevents blood clots from forming that could cause cardiac events
• One of the most popular drugs in the US
Clopidogrel Pharmacokinetics

- **Absorption/Distribution:** rapidly absorbed via oral administration
- **Metabolism:** Clopidogrel is a prodrug, so it has to be metabolized into its active form by CYP2C19
- **Excretion:** excreted in urine and feces

Clopidogrel: Mechanism of Action

Inhibits adenosine diphosphate (ADP) to prevent platelet aggregation
Types of metabolism phenotypes:

- **Poor metabolizers**: gene variants that don’t break the drug down as fast as the wildtype
- **Ultra-rapid metabolizers**: gene variants that break the drug down much faster than the wildtype
- **Extensive metabolizers**: another word for the wildtype

**What do you think would happen to a CYP2C19 poor metabolizer?**

**A poor metabolizer would:**

- Convert clopidogrel into the active metabolite much slower than normal
- **Decreased efficacy**: less anti-platelet activity
- **Increased toxicity**: increased levels of unmetabolized clopidogrel
- **Poor metabolizers are more likely to have a cardiac event and die** [link](http://content.onlinejacc.org/article.aspx?articleid=1143005)
Clopidogrel Pharmacogenomics

What should a clinician do if they have a poor metabolizer who needs an anticoagulant?

a) Prescribe a higher dose of clopidogrel
b) Prescribe a lower dose of clopidogrel
c) Prescribe the same dose of clopidogrel
d) Prescribe another anticoagulant
Clopidogrel Pharmacogenomics

Prescribe another anticoagulant!

• Clopidogrel is a prodrug, so:
  • a poor metabolizer would metabolize clopidogrel slower leading to
    • Decreased efficacy
    • Increased toxicity
    • Increased risk of cardiac events and death

CYP2C19 Prevalance

• Poor metabolizer variants

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<th>African-American</th>
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<td>2-5%</td>
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http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349992/
Amitriptyline: anti-depressant

- Amitriptyline + CYP2D6:
  - rapid metabolizers have reduced efficacy
    - Drug is metabolized into inactive form too fast
    - Consider alternative
  - poor metabolizers have increased risk of toxicity
    - Drug is metabolized and excreted too slowly
    - Consider alternative
  - Intermediate metabolizers have slightly increased risk of toxicity
    - Consider lower dose

Pharmacodynamic genes

- Abacavir + HLA-B*5701: anti-retroviral HIV drug.
  - Increased risk of severe hypersensitivity reaction
Pharmacodynamic genes

• Warfarin + VKORC1 + CYP2C9: anticoagulant.
  – VKORC1 influences efficacy of warfarin
  – Combined genotypes influence initial dose

<table>
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<tr>
<th>VKORC1 Genotype (16364A, rs9923231)</th>
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<tr>
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<td>0.5-2</td>
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<td>0.5-2</td>
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Breaking news!

• “A single variant in CYP4F2 (rs2108622) is significantly associated with small, but significant alterations in warfarin dosage in Asian and Caucasian populations.”
  – July 14, 2014

• Because two genes weren’t problematic enough!
Oncology Pharmacogenomics

- Tumors express genes and biomarkers that are different from the rest of the body
  - Differentially expressed (higher or lower)
  - Modern chemotherapies target these biomarkers, in hopes of killing the cancer cells while minimizing toxicity to the rest of the body

Oncology Pharmacogenomics

- Different from regular pharmacogenomics
  - Biomarkers and genes are not the same as somatic DNA
  - Tumor gene expression can change over time, from tumor to tumor. Every cancer is different.
  - Biomarkers predict whether a chemotherapy will be effective or not
    - Less concerned with pharmacokinetics and metabolism
Example: HER2+ Breast Cancer

• HER2+ and Breast Cancer
  – HER2 (Human epidermal growth factor receptor) is a gene that is present in all human cells
    • EGF protein binds to the receptor, which triggers a cascade of events in the cell, including cellular division
  – Commonly over-expressed in breast cancer tumors
    • Encourages the rapid growth of HER2+ breast cancers
    • Often very aggressive cancers
    • 1 out of 5 breast cancers are HER2+

HER2+ and Herceptin

• Herceptin (trastuzumab): monoclonal antibody that binds to the receptor, turning it off
• Cells arrest in the G1 cell phase, so they do not divide uncontrollably
• Herceptin increases survival in HER2+ cancers, not in other cancers
Herceptin in other cancers

• Herceptin is indicated in breast cancer, primarily
  – But other cancers can overexpress HER2+
Scenario 1

- Jake is a 40 year old male and a father of three
- He is a smoker and has been working for more than a decade as a diesel engine mechanic
- A checkup following a few uncontrollable coughing events to led Jake to have some concerns about his lung health
- Further testing led to a diagnosis of Non-small cell lung carcinoma
Scenario 1 cont...

Treatment considerations
• Jake’s lung cancer is thought to be relatively early stage
• Doctors are considering treatment with a tyrosine kinase inhibitor
• Specifically, one that targets epidermal growth factor receptor (EGFR)

Scenario 1 - Your task
• Divide into two teams
• Learn about the EGFR inhibitors Gefitinib and Erlotinib
  – Wikipedia will suffice
• Get an account for the PharmGKB
• Learn about EGFR PharmGKB: https://www.pharmgkb.org/gene/PA7360
• Note especially the Clinical Annotations
  – What genetic test might inform a treatment decision?
Scenario 2

• Meredith is a 32 year old new mother of a 3 day old baby, about to be discharged from the hospital

  – She had to have a planned Caesarian section due to her baby being breech

  – She is breastfeeding her baby

Scenario 2 continued

• Meredith is experiencing significant pain from her surgery
• Her obstetrician is considering options for pain relief
  – Codeine
  – Oxycodone
  – Vicodin
• Meredith tells him she needed a much higher dose of codeine than expected to treat pain in the past
Scenario 2 continued

- Meredith’s obstetrician decides to order a test to determine her CYP2D6 status
- It will tell him what kind of codeine metabolizer she is
- **Question:**
  - What should he prescribe?
    - Codeine? Higher or lower dose?
    - Another analgesic like oxycodone or vicodin?
    - How will it impact Meredith?
    - How will it impact her newborn?

Scenario 2 – the Medication Safety Code

Try it!
Scenario 2 - Any concerns?

How the QR code works – 1/2

Giménez, JAM., Blagec, K., Boyce, RD., Adlassnig, KP., Samwald, M.. An Ontology-Based, Mobile-Optimized System for Pharmacogenomic Decision Support at the Point-of-Care. PLOS ONE. 2014 May 9(5). DOI: 10.1371/journal.pone.0093769
How the QR code works – 2/2

A complementary approach

• PGx @ Pitt:
  https://www.youtube.com/watch?v=Te546vOi
  ruo
Real-world Pharmacogenomics Consequences

- Codeine ultra rapid metabolizer
  - A CYP2D6 ultra-rapid metabolizer nursing mother was taking codeine
    - She needed a higher dose for pain relief
    - She excreted high levels of morphine into her breastmilk, which she gave to her baby
    - The baby died of a morphine overdose at 13 days old
  - Guidelines now recommend that NO nursing mothers be given codeine, in lieu of genetic testing
HER2+ Lung Cancer

• Diane had stage 4 non small cell lung cancer
  – Non smoker
  – 43 years old
  – Her cancer was HER2+!
    • She was eventually treated with herceptin
    • It slowed the growth of her tumors for a while
    • She lived 19 months after diagnosis (9 months longer than average for her cancer)

  In cancer, that’s considered a success
Another Scenario

- Kathy is on an antidepressant (citalopram) that depends on metabolism by CYP2C19 for much of its clearance
- Her doctor prescribes fluconazole to treat a fungal infection
  - fluconazole is a strong inhibitor of CYP2C19
- She is homozygous for the *3 allele of CYP2C19 making her an “poor metabolizer”
Will the drug-interaction matter?

Interaction scenario:
Drug i inhibits CYPX, a primary clearance enzyme for Drug j

Patient A
CYPX Poor metabolizer

Drug i NOT likely to affect Drug j

Patient B
CYPX Extensive metabolizer

Drug i likely to have a significant affect on Drug j

Patient A is theoretically less likely to have an unexpected change in exposure to Drug j because, unlike Patient B, the inhibition of CYPX by Drug i should have little or no effect on the clearance of Drug j.
**Interaction scenario:**
CYPX is a primary clearance pathway for Drug j and Drug k inhibits CYPY, a secondary clearance pathway for Drug j

**Possible states in which Patient A is theoretically more likely to be affected by CYPY inhibition than Patient B.**

<table>
<thead>
<tr>
<th>Patient A CYPX poor metabolizer?</th>
<th>Patient A CYPX pathway inhibited?</th>
<th>Patient A more likely affected by CYPY inhibition than Patient B?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
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</tr>
<tr>
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</tr>
<tr>
<td>N</td>
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Research question

• Is the combination of PDDI and pharmgx information more effective than pharmgx information alone at identifying risky medication combinations than relying on PDDI knowledge alone?