<table>
<thead>
<tr>
<th>Time</th>
<th>Name(s)</th>
<th>Topic</th>
<th>Details</th>
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<tbody>
<tr>
<td>8:30-9:15</td>
<td>Sara/Alie</td>
<td>Journal Club</td>
<td>Benonis-dottir, S et al. &quot;Epigenetic and genetic components of height regulation&quot;</td>
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<tr>
<td>9:15-10:00</td>
<td>Alie</td>
<td>Bioethics and Implementation</td>
<td>PPV, NPV, sensitivity, specificity, principles of bioethics</td>
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<tr>
<td>10:30-12:00</td>
<td>Sara</td>
<td>Gene-Environment Interactions</td>
<td>Definitions, methods, practical issues</td>
</tr>
<tr>
<td>1:30-2:15</td>
<td>Alie</td>
<td>Pharmacogenetics</td>
<td>Pathways and analysis, analysis</td>
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<tr>
<td></td>
<td>Sara</td>
<td>Mendelian Randomization</td>
<td>Concept, methods</td>
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<tr>
<td>2:15-3:00</td>
<td>Sara</td>
<td>Risk prediction</td>
<td>_methods, applications</td>
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<td>3:30-4:30</td>
<td>Sara</td>
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<tr>
<td>4:30-5:00</td>
<td>Alie/Sara</td>
<td>Wrap-up</td>
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Pharmacogenetics

Section 12

(45 minutes)
Learning objectives

• Describe the ways genetic variation can affect drug response.
• Place odds ratios in the context of population impact.
• Interpret genotyping results to make a pharmacogenetic recommendation.
What is pharmacogenetics?

- How genetic variation affects drug and xenobiotic response, including therapeutic effect and adverse events (side effects).
- GlaxoSmithKline executive, “90% of drugs only work in 30-50% of people”
- Cornerstone of precision medicine. “Right drug, right dose, right time”.

Hicks, 2017
Classes of pharmacogenetics

• Drug target
Example – Ivacaftor (Kalydeco)

- Ivacaftor “potentiates” CFTR protein on the cell surface that cannot activate to transport chloride ions.
- Ivacaftor only works in people who specific CFTR variants (5% of total cystic fibrosis).
Example – Ivacaftor (Kalydeco)

- FDA approved ivacaftor only for specific variants (class III and class IV).
- First FDA approval process to allow molecular data to expand approval.
Classes of pharmacogenetics

• Drug target
• Drug metabolism
### Pharmacogenetic nomenclature

**Pharmacogenetic nomenclature**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Variants (variant = variants with dbSNP rsID)</th>
<th>Impact</th>
<th>Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*60</td>
<td>1888_1889insTA, 2304C&gt;T</td>
<td>S183X</td>
<td>unknown function</td>
<td>Lee et al. 2009</td>
</tr>
<tr>
<td>CYP2D6*61</td>
<td>CYP2D6-CYP2D7 hybrid gene; see ReadMe</td>
<td></td>
<td>unknown function</td>
<td>Kramer et al. 2009</td>
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<tr>
<td>CYP2D6*62</td>
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<td>Klein et al. 2007</td>
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<tr>
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Example – CYP2D6 and Codeine

- Codeine blood concentration

- Ultrarapid/rapid CYP2D6
- Intermediate “Normal” CYP2D6
- Poor CYP2D6

Morphine → pain killing effects
Example – CYP2D6 and codeine

Nerenz, 2017
Example – CYP2D6 and codeine

Death of 3 children in 2012

Kirchheiner 2007
Classes of pharmacogenetics

- Drug target
- Drug metabolism
- Drug transport
Example – SLCO1B1 and simvastatin

Sadee 2013
Example – SLCO1B1 and simvastatin

A

Simvastatin acid (ng/ml)

Time (h)

CC genotype
TC genotype
TT genotype

B

Cumulative percentage of patients who have had a myopathy

Years since starting simvastatin 80 mg/day

CC genotype
TC genotype
TT genotype
Global variant frequencies – *SLCO1B1*
Compare myopathy in global populations

- OR=4.5 for TC compared to TT at rs4149056
- OR = 16.1 for CC compared to TT at rs4149056
- C allele frequency in African populations: 3%
- C allele frequency in European populations: 15%
- C allele in South/Central American: 20%
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  - 2% CC, 26% TC, 72% TT
- C allele in South/Central American: 20%
  - 4% CC, 32% TC, 64% TT

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2) 2% of TT patients will experience muscle pain. How many people out of 1000 taking simvastatin in each of these populations you would expect to have muscle pain.
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</tr>
<tr>
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\[\text{OR} = \frac{ad}{bc}\]

\[40 = a + b; 40 - b = a\]

\[16.1 = \frac{a \times 627}{b \times 13}\]

\[16.1 = \frac{627(40 - b)}{b \times 13} = \frac{25080 - 627b}{b \times 13}\]

\[209.3b = 25080 - 627b\]

\[836.3b = 25080\]

\[b = \frac{25080}{836.3} = 30\]

\[640 \times 0.02 = 12.8\]
Compare myopathy in global populations

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In the South/Central American population, 10 (CC) + 27 (TC) + 13 (TT) = 50 out of 1000 on simvastatin will experience muscle pain.
Compare myopathy in global populations

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  - 0.1% CC, 6% TC, 94.1% TT

In African populations,

1 (CC) + 5 (TC) + 19 (TT)

25 out of every 1000 patients will experience muscle pain

*screening in different populations
*who actually develops muscle pain
*compared to in population not taking simvastatin and impact on study size, implementation
Classes of pharmacogenetics

• Drug target
• Drug metabolism
• Drug transport
• Hypersensitivity/allergy
Example – HLA-B and abacavir

T-cell receptor

Antigen

Tolerized endogenous peptide

Drug

New peptide recognized as foreign

HLA on antigen-presenting cell

Roujeau 2014
How do we ethically, effectively target?

Adapted from David Nolan et al. J HIV Ther. 2003 May;8(2):36-41.
Warfarin response – target and metabolism

Ethnic Differences in Warfarin Dose

Mean weekly warfarin dose (95% CI) adjusted for age, gender, weight, disease and potentially interacting drugs

Average dose worldwide = 36.4 mg/wk (unadjusted)

Warfarin dose algorithm

<table>
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<tr>
<th>Variable</th>
<th>Regression coefficient</th>
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<tbody>
<tr>
<td>Race (African Americans=1)</td>
<td>−0.08</td>
</tr>
<tr>
<td>Age</td>
<td>−0.01</td>
</tr>
<tr>
<td>VKORC1 1173 (CT=1)</td>
<td>−0.39</td>
</tr>
<tr>
<td>VKORC1 1173 (TT=1)</td>
<td>−0.82</td>
</tr>
<tr>
<td>CYP2C9 (any*2=1)</td>
<td>−0.16</td>
</tr>
<tr>
<td>CYP2C9 (any*3=1)</td>
<td>−0.30</td>
</tr>
<tr>
<td>BMI (less than 25=1)</td>
<td>−0.18</td>
</tr>
<tr>
<td>BMI (25 to 30=1)</td>
<td>−0.23</td>
</tr>
<tr>
<td>Number of interacting medications</td>
<td>−0.08</td>
</tr>
</tbody>
</table>
Warfarin pharmacogenetics clinical utility

• Accounting for CYP2C9 *2 and *3 and VKORC1 rs9923231 explains ~40% of the variability in warfarin dose in whites, but only ~20% in people of African descent.
• EU-PACT study ~99% white patients, improved time in therapeutic range and time to therapeutic anticoagulation.
• COAG study 27% African ancestry found gene-based dosing actually performed worse than clinical dosing.
Warfarin pharmacogenetic variants

• **VKORC1 rs9923231** does not seem to be functional and is likely linked to a causative locus in White populations but not African.

• **Frequencies of CYP2C9 variants:**

![Graph showing frequencies of CYP2C9 variants across different ethnic groups.](image)
Warfarin response – target and metabolism

Summary

- Genetics can change drug response by altering drug target, drug metabolism, and drug transport, and by triggering allergies. It can also affect pathogen resistance.
- Using genetic information can improve toxicity and efficacy of drugs.
- These variants only matter when faced with an external substance.
- Frequencies of variants vary greatly across the world.
- Genetic tests can inform treatment but are based on probabilities in a complex system.
Compare risk of muscle pain in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 in each of these populations you would expect to have muscle pain.

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<td>a+b</td>
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<tr>
<td>TT</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
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<tr>
<td>total</td>
<td>a+c</td>
<td>b+d</td>
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\[
\text{OR} = \frac{ad}{bc}
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<td>d</td>
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<td>total</td>
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\[
4.5 = \frac{627(320 - b)}{b \times 13} = \frac{200640 - 627b}{b \times 13}
\]

\[
58.5b = 200640 - 627b
\]

\[
685.5b = 200640
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\[
b = \frac{200640}{685.5} = 293
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<td>a+c</td>
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\[
\text{OR} = \frac{ad}{bc}
\]

\[
58 = a + b
\]

\[
4.5 = \frac{a \times 922}{b \times 19}
\]

\[
4.5 = \frac{922(58 - b)}{b \times 19} = \frac{53476 - 922b}{b \times 19}
\]

\[
85.5b = 53476 - 922b
\]

\[
1007.5b = 53476
\]

\[
b = \frac{53476}{1007.5} = 53
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Compare risk of muscle pain in global populations

2) 2% of TT patients will experience muscle pain. Calculate how many people out of 1000 in each of these populations you would expect to have muscle pain.

- OR = 4.5 for TC at rs4149056
- OR = 16.1 for CC at rs4149056

C allele frequency in African populations: 3%
- 0.1% CC, 6% TC, 94.1% TT

\[
\text{OR} = \frac{ad}{bc} \quad 1 = a + b; 1 - b = a
\]

\[
16.1 = \frac{a \times 922}{b \times 19}
\]

\[
16.1 = \frac{922(1 - b)}{b \times 19} = \frac{922 - 922b}{b \times 19}
\]

\[
305.9b = 922 - 922b
\]

\[
1227.9b = 922
\]

\[
b = \frac{922}{1227.9} = 0.75
\]

<table>
<thead>
<tr>
<th>Disease status</th>
<th>Muscle pain</th>
<th>No muscle pain</th>
<th>Total</th>
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<tbody>
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<td>1</td>
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<tr>
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</tr>
<tr>
<td>total</td>
<td>20</td>
<td>922</td>
<td>942</td>
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