Genomic Medicine: A New Frontier in Pharmacotherapy

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Disclosure

I have no conflicts of interest to disclose.
Learning Objectives

1. Describe the evolution of pharmacogenetics (What was first and how did we get here) and the complexities.

2. Describe existing therapies that require testing prior to initiation of therapy.

3. Analyze the limitations of pharmacogenetic testing commercial or otherwise.

4. Apply pharmacogenetic information given available resources.
Test Questions

1. Name 3 non-oncologic medications that FDA requires pharmacogenetic testing prior to therapy initiation.

2. Excluding cost, describe at least 3 challenges limiting implementation of pharmacogenetic into practice.
Hyperpersonalization: A theme of our time
Internet: The driving force
With the exception of medicine and health care
One Size Fit All

A Population Based Approach
Adverse drug reactions problem
ADR’s Cause 770,000 Injuries and Deaths Each Year and Cost $5.6 Million per Hospital

SIGNIFICANT PROBLEM

➢ To patient care
➢ Financial burden

ONE SIZE FIT ALL

➢ Population based

PREVENTION METHODS

➢ Based on drug-drug interaction
➢ Clinical judgment/experience
➢ Drug-Gene Interaction?

AHRQ Publication Number 01-0020. . Research in Action 2001
Statins: 5 years of treatment for heart disease prevention

**WITHOUT KNOWN HEART DISEASE**

**BENEFITS in NNT**
- None were helped (life saved)
- 1 in 104 were helped (preventing heart attack)
- 1 in 154 were helped (preventing stroke)

**HARM in NNH**
- 1 in 100 were harmed (develop diabetes)
- 1 in 10 were harmed (muscle damage)

**WITH KNOWN HEART DISEASE**

**BENEFITS in NNT**
- 1 in 83 were saved from death
- 1 in 39 were helped (preventing non-fatal heart attack)
- 1 in 125 were helped (preventing stroke)

**HARM in NNH**
- 1 in 100 were harmed (develop diabetes)
- 1 in 10 were harmed (muscle damage)
Precision Medicine: A national effort

Precision Medicine
- Tailoring of medical treatment to individual characteristics such as lifestyle, environmental and biological uniqueness (i.e., genome, microbiome, etc.)

Goal
- Focusing therapeutic interventions on those who would benefit
- Sparing expense and adverse effects for those who will not

Driver
- Advances in technology

Gov. Brown To Launch New California Precision Medicine Initiative

Pharmacogenetics

**Definition:** Science of applying genomic technology to determine the impact of relevant inherited or somatic gene(s) variation on drug’s behavior or response.
- PG use is prevalent in oncology which is primarily based on selecting therapy based on cancer genome
  - Somatic vs. germline

**Terminology:**
- **Pharmacogenetics**
  - Studies targeted on limited number of genes
- **Pharmacogenomics**
  - Studies focused on entire genome
Your poll will show here

1. Install the app from pollev.com/app
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or
Open poll in your web browser
Drug response and variability

- **Environmental factors** (diet, smoking)
- **Physiological factors** (age, disease, wt, sex, pregnancy)
- **Genetic factors** (drug-metabolizing enzymes, transporters, therapeutic targets)
- **Drug interactions** (inhibitors, inducers)
Early observations of interindividual variations

**Pythagoras (510 BC)**
- Observed variation in occurrence of hemolytic anemia in response to ingestion of fava beans

**Archibald Garrod (1902)**
- Alkaptonuria

**Arthur Fox (1932)**
- Phenyl thio carbamide

**Albert Blakeslee (1932)**
- Phenol thio carbamide phenotype followed Mendelian pattern of inheritance

Phenotypes are observed upon exposure to a particular drug or chemical


Fox, A.L. *Proc Natl Acad Sci* 18, 115-120 (1932)
Blakeslee, A.F. *Proc Natl Acad Sci* 18, 120-130 (1932)
Pharmacogenetics: The first drugs

**Succinylcholine** (Kalow & Lehmann, 1956)
- Malignant hyperthermia and variation in human serum cholinesterase
- Used the term “inborn error of metabolism”
- “It is important for people to know that they have a low pseudocholinesterase level. They should be given a letter to be handed to the anaesthetist should they ever require an operation. They should be warned that an employment bringing them into contact with anticholinesterases might entail a risk. It now seems to us that not only should every patient who has a prolonged apnea after “succinylcholine” be examined for a lowered pseudocholinesterase level, but that his relations should be investigated as well.”

**Primaquine** (Alf Alving, 1956)
- Hemolytic anemia was due to a deficiency in glucose-6-phosphate dehydrogenase (G6PD)

**Isoniazid** (Evans and White, 1960)
- Peripheral neuropathy was due to polymorphism in hepatic N-acetyltransferase (NAT) enzyme
Central dogma in biology

DNA

Promoter

........CGAC

........GCTG

Exon

TACGCCATG

ATGCGGTAC

Intron

GTATTAG

CATATTC

Exon

AAT

TTA

Transcription/splicing

mRNA

AUGGUGUAGUUA

Translation by ribosomes

Protein – AA chain

NH2 – MET – ARG – TYR – LEU – COOH

Posttranslational modification

Finished Protein
Your poll will show here

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or

Open poll in your web browser
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
Genome contents

1. Genes
   - Protein coding (1.5% of genome)
     - Only ~20,000 genes?!

2. Repeats
   - Tandem repeats ~ 8% of genome
   - Interspersed repeats ~45% of genome

3. Other unique sequences
   - Conserved non-coding ~3%
   - Nonconserved, nonrepetitive ~ 40%

<table>
<thead>
<tr>
<th>Organism</th>
<th># of protein coding genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>23,000</td>
</tr>
<tr>
<td>Drosophila</td>
<td>14,000</td>
</tr>
<tr>
<td>Yeast</td>
<td>6,200</td>
</tr>
<tr>
<td>E. Coli</td>
<td>4,400</td>
</tr>
</tbody>
</table>
Example: CYP2C19 Gene

Size: 90,209 bp
Coding size: 1473 bp
Protein: 490 AA

https://genome.ucsc.edu
Genome variation

Risk: disease, ADR

Benefits: material for evolution

Types

- Polyploidy
  - Triploidy (incompatible with life)

- Aneuploidy
  - Trisomy 21

- Gross rearrangements
  - Cancer: translocations/deletions of chromosome arms (CML)

- Segmental duplications/copy number variations (CNV)
  - CYP2D6

- Indels
  - UGT1A1

- Single nucleotide substitutions
  - Most common types of variation (~1/300 bp)

Technologies used to establish genotype-phenotype associations: High-throughput genotyping

Genome Wide Association Studies (GWAS)
- Looking at 5 million common SNPs (>5%) per individual
- Not hypothesis driven
- Discover novel regions/genes associated with trait of interest
- Hypothesis: Markers tested are either causal or highly correlated with causal marker(s)
- Missing heritability

As of 2016-09-27, the GWAS Catalog contains 2,554 studies and 25,037 unique SNP-trait associations.

NHGRI-EBI catalog of published GWAS:http://www.ebi.ac.uk/gwas/
GWAS: Association between myopathy and each SNP in cases and controls on simvastatin 80 mg daily

<table>
<thead>
<tr>
<th>SNP</th>
<th>Risk Allele (RA)</th>
<th>RA Frequency</th>
<th>Gene</th>
<th>OR for myopathy in heterozygotes (TC)</th>
<th>OR for myopathy in homozygotes (CC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs4363657</td>
<td>C</td>
<td>0.46</td>
<td>0.13</td>
<td>SLCO1B1</td>
<td>4.5 (2.6-7.7)</td>
</tr>
</tbody>
</table>

rs4363657
P=4x10⁻⁹

Technologies used to establish genotype-phenotype associations: High-throughput sequencing

Next Generation sequencing
- Comprehensive interrogation of genome
- Most expensive
- Multiple platforms in the market
- Produce enormous amount of data
- Can identify novel, rare genetic variants
  - Medical Genetics clinics
Advances in sequencing technology

https://www.sciencenews.org/article/gene-sequencing-future-here
Summary

1. Technology is no longer the rate limiting step for precision medicine/pharmacogenetics.

2. Technological and scientific advances are the driver of the demand for precision medicine

3. Determining clinical implication of the data produced is the rate limiting step!!!
   ◦ Show me the evidence!
Clinical implementation of PG: Steps for evaluating evidence

1. Analytic validity
   i. How accurately and reliably the test reports the presence or absence of particular genetic variant
   ii. Clinical Laboratory Improvement Amendment (CLIA) certification or FDA approval

2. Clinical validity
   i. How consistently and accurately the genetic variant predicts the outcome of interest

3. Clinical utility
   i. How likely the test will significantly improve patient outcomes or provider management (i.e., test is clinically and cost effective)

4. Ethical, level and social implications
Consumer based tests: Level of evidence

Developers of genetic tests DO NOT have to provide evidence in support of clinical validity and clinical utility.

Laboratories must only meet CLIA requirement:
- Labs must verify at least twice a year the accuracy of their test!!
<table>
<thead>
<tr>
<th>Allele</th>
<th>Variant</th>
<th>dbSNP ID</th>
<th>Protein change</th>
<th>Functional effect</th>
<th>African</th>
<th>American</th>
<th>East Asian</th>
<th>European</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>EM</td>
<td>68%</td>
<td>69%</td>
<td>60%</td>
<td>63%</td>
</tr>
<tr>
<td>*2</td>
<td>681G&gt;A</td>
<td>rs4244285</td>
<td>Splicing defect</td>
<td>PM</td>
<td>15%</td>
<td>12%</td>
<td>29%</td>
<td>15%</td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>rs7986893</td>
<td>W212X</td>
<td>PM</td>
<td>0.52%</td>
<td>0.028%</td>
<td>8.9%</td>
<td>0.42%</td>
</tr>
<tr>
<td>*4</td>
<td>1A&gt;G</td>
<td>rs28399504</td>
<td>M1V</td>
<td>PM</td>
<td>0.093%</td>
<td>0.24%</td>
<td>0.049%</td>
<td>0.25%</td>
</tr>
<tr>
<td>*4B</td>
<td>1A&gt;G,</td>
<td>rs28399504,</td>
<td>M1V</td>
<td>PM</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>-806C&gt;T</td>
<td>rs12248560</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*5</td>
<td>1297C&gt;T</td>
<td>rs56337013</td>
<td>R433W</td>
<td>PM</td>
<td>ND</td>
<td>0%</td>
<td>0.062%</td>
<td>0.0073%</td>
</tr>
<tr>
<td>*6</td>
<td>395G&gt;A</td>
<td>rs72552267</td>
<td>R132Q</td>
<td>PM</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0.017%</td>
</tr>
<tr>
<td>*7</td>
<td>819+2T&gt;A</td>
<td>rs72558186</td>
<td>Splicing defect</td>
<td>PM</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0%</td>
</tr>
<tr>
<td>*8</td>
<td>358T&gt;C</td>
<td>rs41291556</td>
<td>W120R</td>
<td>PM</td>
<td>0%</td>
<td>0.12%</td>
<td>0%</td>
<td>0.35%</td>
</tr>
<tr>
<td>*17</td>
<td>-806C&gt;T</td>
<td>rs12248560</td>
<td>Increased gene expression</td>
<td>UM</td>
<td>16%</td>
<td>18%</td>
<td>2.7%</td>
<td>21%</td>
</tr>
</tbody>
</table>

EM: Extensive Metabolizer; PM: Poor Metabolizer; UM: Ultrametabolizer; ND: Not Determined

### Consumer based tests: CYP2C19 example

<table>
<thead>
<tr>
<th>CYP2C19 genotyping assays</th>
<th>Alleles interrogated</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmpliChip CYP450 test¥</td>
<td>*2, *3</td>
<td>HOFFMANN-LA ROCHE</td>
</tr>
<tr>
<td>INFINITI CYP2C19 Assay¥</td>
<td>*2, *3, *17</td>
<td>AUTOGENOMICS, INCORPORATED</td>
</tr>
<tr>
<td>Verigene¥</td>
<td>*2, *3, *17</td>
<td>NANOSPHERE, INC</td>
</tr>
<tr>
<td>xTAG CYP2C19 Assay¥</td>
<td>*2, *3, *17</td>
<td>LUMINEX MOLECULAR DIAGNOSTICS, INC.</td>
</tr>
<tr>
<td>Spartan Rx CYP2C19 Test System¥</td>
<td>*2, *3, *17</td>
<td>SPARTAN BIOSCIENCE INC</td>
</tr>
<tr>
<td>Genelex panel</td>
<td>????</td>
<td>GENELEX</td>
</tr>
<tr>
<td>Genomind panel</td>
<td>????</td>
<td>GENOMIND</td>
</tr>
</tbody>
</table>

¥: FDA approved test

**Process of designating EM (i.e., *1) for CYP2C19 may vary on the basis of testing methods**

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm
Evidence threshold for clinical practice

What is the evidence threshold for translation of PG?

- Gold Standard: Randomized Clinical Trial (RCT)
- Proof through RCT for PG faces many challenges such as:
  - Cost
  - Rare variant sampling

It is important to have an acceptable threshold for adopting PG testing that is scientifically rigorous and not limited to RCT.

- i.e., observational studies, enrichment studies
- Despite evidence linking CYP2C19 polymorphisms to stent failure with clopidogrel, ACC & AHA recommends against PG testing pending RCT.
- KRAS testing is common in oncology despite same level of evidence.

<table>
<thead>
<tr>
<th>Alleles</th>
<th>MAF: Black</th>
<th>MAF: White</th>
</tr>
</thead>
<tbody>
<tr>
<td>R57Q</td>
<td>0</td>
<td>0.4%</td>
</tr>
<tr>
<td>*5</td>
<td>0</td>
<td>7%</td>
</tr>
<tr>
<td>FS</td>
<td>0</td>
<td>0.4%</td>
</tr>
<tr>
<td>*14</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>*15</td>
<td>0</td>
<td>14%</td>
</tr>
</tbody>
</table>
Bristol-Myers, Sanofi Sued by Hawaii Over Plavix Labeling

by Karen Gullo

March 19, 2014 – 6:03 PM PDT
Drugs w/ PG biomarkers information

Federal Agency
◦ Currently 142 therapeutics carrying information related to a specific PG biomarker in their FDA package insert
  ◦ 45 oncologic
  ◦ 97 non-oncologic

Expert Groups
◦ There are 60 medications with specific dosing guidelines established by clinical pharmacology experts in both the US an Europe.
  ◦ Europe: The Royal Dutch Association for the Advancement of Pharmacy: PG Working Group [n= 50]
  ◦ US: Clinical Pharmacogenomics Implementation Consortium (CPIC) [n= 31]

Discrepancies between the Expert groups and FDA package insert
◦ Simvastatin, Tacrolimus, Allopurinol – No FDA info in package insert

http://www.fda.gov/drugs/scienceresearch/Researchareas/pharmacogenetics/ucm083378.htm
Pharmacogenetic biomarkers included in FDA approved package insert

<table>
<thead>
<tr>
<th>Therapeutic areas</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>45</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>24</td>
</tr>
<tr>
<td>Infectious Diseases</td>
<td>15</td>
</tr>
<tr>
<td>Cardiology</td>
<td>9</td>
</tr>
<tr>
<td>Neurology</td>
<td>9</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>8</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>7</td>
</tr>
<tr>
<td>Hematology</td>
<td>5</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>5</td>
</tr>
<tr>
<td>Inborn Errors of Metabolism</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
</tr>
<tr>
<td>Analgesic</td>
<td>2</td>
</tr>
<tr>
<td>Dermatology</td>
<td>2</td>
</tr>
<tr>
<td>Dental</td>
<td>1</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1</td>
</tr>
<tr>
<td>Gynecology</td>
<td>1</td>
</tr>
<tr>
<td>Toxicology</td>
<td>1</td>
</tr>
<tr>
<td>Transplantation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>142</td>
</tr>
</tbody>
</table>

43 Genes

- Oncology, 45
- Non-oncology, 97
Medications with FDA approved companion diagnostics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Therapeutic Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>ALK</td>
<td>Oncology</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>BRAF</td>
<td>Oncology</td>
</tr>
<tr>
<td>Tramatenib</td>
<td>BRAF</td>
<td>Oncology</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>Oncology</td>
</tr>
<tr>
<td>Olaparib</td>
<td>BRCA</td>
<td>Oncology</td>
</tr>
<tr>
<td>afatinib</td>
<td>EGFR</td>
<td>Oncology</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>Oncology</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>Oncology</td>
</tr>
<tr>
<td>Gilotrif</td>
<td>EGFR</td>
<td>Oncology</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>EGFR</td>
<td>Oncology</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR/KRAS</td>
<td>Oncology</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR/KRAS</td>
<td>Oncology</td>
</tr>
<tr>
<td>Adotrastuzumab</td>
<td>HER2</td>
<td>Oncology</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>HER2</td>
<td>Oncology</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>Oncology</td>
</tr>
<tr>
<td>Imatininib</td>
<td>KIT/5q31~33</td>
<td>Oncology</td>
</tr>
</tbody>
</table>

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
**FDA approved medications with required/recommended genetic testing**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5</td>
<td>Maraviroc</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Eloglostat</td>
<td>Gaucher</td>
</tr>
<tr>
<td>HLA-B*57:01</td>
<td>Abacavir</td>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>HLA-B*15:02</td>
<td>Carbamazepine</td>
<td>Anticonvulsant</td>
</tr>
<tr>
<td>CFTR</td>
<td>Ivacaftor</td>
<td>CFTR potentiator</td>
</tr>
<tr>
<td>HCV 1 or 4</td>
<td>Grazoprevir/Elbasvir</td>
<td>HCV</td>
</tr>
</tbody>
</table>

“Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*15:02 prior to initiating treatment with carbamazepine” - PI
## Clinical practice guidelines for inherited PG biomarkers: CPIC & RD

<table>
<thead>
<tr>
<th>Gene(s) [N=12]</th>
<th>Drug(s) [N= 60]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Warfarin, Phenytoin, Tolbutamide, Glimepiride, Gliclazide, GlyBuride</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Trimipramine, Sertraline, Imipramine, Escitalopram, Doxepin, Clopidogrel, Clomipramine, Citalopram, Amitriptyline, Voriconazole, Rabeprazole, Pantoprazole, Omeprazole, Moclobemide, Lansoprazole, Esomeprazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Trimipramine, Paroxetine, Imipramine, Fluvoxamine, Doxepin, Desipramine, Codeine, Clomipramine, Amitriptyline, Venlafaxine, Tramadol, Tamoxifen, Risperidone, Propafenone, Oxycodone, Olanzapine, Mirtazapine, Metoprolol, Haloperidol, Flupenthixol, Flecainide, Duloxetine, Clozapine, Carvedilol, Atomoxetine, Aripiprazole</td>
</tr>
<tr>
<td>TPMT</td>
<td>Thioguanine, Mercaptopurine, Azathioprine</td>
</tr>
<tr>
<td>IFNL3</td>
<td>Telaprevir*, Ribavirin, Peginterferon, Bocepravir</td>
</tr>
<tr>
<td>DPYD</td>
<td>Tegafur, Fluorouracil, Capecitabine</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>G6PD</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>HLA-B</td>
<td>Phenytoin, Carbamazepin, Allopurinol, Abacavir, Ribavirin</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Atazanavir, Irinotecan</td>
</tr>
</tbody>
</table>

**Royal Dutch (RD)**

RD + CPIC

CPIC

* Discontinued
Challenges surrounding wide use of PG

- Limited number of established guidelines
- Insufficient emphasis on prevention
- Payer’s restrictions
- Turnaround time of the test results
- Lack of cost-effectiveness data
- Limited clinical utility data
- Fragmentation of our health-care system interferes w/ linking genetic test screening results w/ all future care
- Limited professional education
- Test evaluation

Implementing clinical PG: A complex process

Developing infrastructure

- Identify stakeholders
  - Patients, clinicians, insurers, regulatory agencies, health information technology, ethics
- Selecting drug-gene interaction of interest
  - Start with CPIC/FDA, but have to consider other institution specific factors
- Identifying a body or a process for ongoing evaluation of PG literature/science
  - Provide institution specific guidelines
  - Develop Clinical Decision Support
- Integration into care process
- Identifying laboratory process
  - Pre-emptive vs. reactive
- Billing and reimbursement
- Education
- Evaluating the program
- Evidence of cost-effectiveness
Pharmacogenetics: The expectation and the delay

FDA started incorporating PG information in package inserts in 2007

The human genome project was declared complete in 2003

The general (public) expectation/perception is that genomic medicine will be a reality sooner than later

PG is limited primarily to large academic centers

- NIH Clinical Center
- University of Chicago
- University of Florida
- St. Jude Hospital
- Vanderbilt University
- Mayo Clinic
Example CDS: Vanderbilt University Medical Center

Electronic prescription for simvastatin

- **80 mg daily**
  - FDA recommends against 80 mg dose unless patient has tolerated >12 mo (unless normal CK and no myalgias)
  - TT
  - Proceed based upon clinical risk

- **40 mg daily**
  - FDA recommends against 40 mg dose if the patient is also using any of these: amiodarone, amiodipine, ranolazine
  - TC
  - WARNING: genetic testing indicates this patient is at increased risk of myopathy with 40 mg simvastatin
  - Lower dose
  - 20 mg simvastatin + monitor serial CK (Consider lipid clinic)

- **20 mg daily**
  - FDA recommends against 20 mg dose if the patient is also using any of these: verapamil, diltiazem
  - CC
  - Alternative statin
  - Choice #1
  - Choice #2
  - Choice #3

PREDICT at Vanderbilt University Medical Center
SLCO1B1 521T>C SNP and simvastatin

OR: 4.5 (95% CI, 2.6-7.7).

OR: 16.9 (95% CI, 4.7-61.1).

SLCO1B1 PG data and statins

Statin Exposure in Healthy Volunteers w/ SLCO1B1 521CC Genotype

A case example

Patient with ACS and history of PCI currently on clopidogrel 75 mg po daily.

Provider believes in the PG data related to clopidogrel and would like to integrate genetics in this patient’s care.

Where do you start?
- Does patient’s insurance cover PG testing?

How do you identify a lab to run your test?
- Genetic Testing Registry is a good place to start (http://www.ncbi.nlm.nih.gov/gtr/)
Case continues

How to interpret the results?

- Start with CPIC guidelines
Convergence of Technology: A system biology approach

- Genome
- Transcriptome
- Microbiome
- Glycome
- Metabolome
- Proteome
- Epigenome
- Exposome
- Interactome
- Lipidome

“Individulome”

Eric Topol
Summary

• Our understanding of variability associated with drug response has come a long way.

• This progress has been possible through technological advances in computer science and genomics.

• These advances have and will continue to produce large quantities of genomic and other system biology related biomarkers that could aid in describing variation associated to drug response.

• Translation of such findings into clinical practice faces challenges.

• Overcoming some of these challenges (i.e., demonstrating clinical utility, economic, educational) would require development of new tools, strategies and a willingness to accept changes in established paradigms.

• Despite challenges, a limited number of genetic biomarkers are successfully implemented in clinical practice.

• Ultimately the databases/networks created in the PM efforts will provide the ability for healthcare providers to deliver a more targeted therapy, correcting for biological uniqueness and other distinctive individual circumstances.
Test Questions

1. Name 3 non-oncologic medications that FDA requires pharmacogenetic testing prior to therapy initiation.

Maraviroc, Eloglostat, Abacavir, Carbamazepine, Ivacaftor, Grazoprevir/Elbasvir

2. Excluding cost, describe at least 3 challenges associated with implementing pharmacogenetic into practice.

- Fragmentation of our health-care system
- Turnaround time of the test results
- Limited education
- Limited number of established guidelines,
- PG tests not FDA approved,
- Limited clinical utility data
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