Personalized Medicine: The Future is Now!

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Overview

• What is Personalized Medicine?
  – Examples in oncology clinical care
  – Examples in clinical care of non-cancer conditions
  – How can this information be used to optimize care?

• Current State of Science and Successful Implementation Efforts
  – Pharmacogenetic information in FDA labeling
  – Clinical Pharmacogenetics Information Consortium (CPIC) guidelines
  – Examples of implementation at Academic and Community Medical Centers
  – Behavioral Health as an emerging area

• Barriers to PM testing coverage and strategies to justify costs
  – Current state of reimbursement for testing
  – Economic value of personalized medicine testing
  – What type of data are missing?
Personalized Medicine

- Shift in medical practice
- Integrating relevant information
- Individual and population Health

Personalized Care

Personalized (Precision) Medicines:
Using genetics and genomics to predict response to drugs

Personalizing the prevention of chronic diseases
(President’s Precision Medicine Initiative)
Personalized Medicine:
Personalizing patient care with a focus on genetics

• Utilize genetic and genomic information to minimize adverse responses and maximize drug effectiveness
• Distinguish patients likely to have adverse drug response and/or not respond from those who will respond without severe adverse events
  – Cancer: focus on predicting response to anti-cancer drugs, where testing is already standard of care
  – Non-cancer: focus on addressing drug–gene associations with highest level of evidence, where testing is emerging as a best practice
CANCER: THE LOW HANGING FRUIT
Personalized Cancer Medicine: Explosion of Treatment Advances for Individual Cancer Patients

• Bringing a science-based genetic approach to patient care in oncology
• Targeted treatment of tumors based on mutations
• Stimulating the cancer patient’s immune system to trick and destroy cancer cells
• Using the patients inherited genetic make-up to predict:
  – Likelihood of severe side effects from chemotherapy
  – Better choice of pain management, anti-nausea drugs
Genome guided information to enhance cancer treatment

• Tumor markers predicting response to targeted therapy
  
  **Standard of Care:**
  
  Ex) Stage IV: Non Small Cell Lung Cancer: EGFR, ALK, ROS

• **Tumor Genomic Profiling in Advanced Refractory Cancer:**
  
  **Best Practice:**
  
  • Identify mutations to match to FDA approved drug (off label)
  • Identify mutations to match to ongoing local clinical trial

• Tumor markers predicting response to Immunotherapy
  
  **Investigational:** Panels and individual markers

• Tumor markers as surrogates for disease progression
  
  **Investigational:** Circulating DNA sequences in plasma, urine

• **Utilizing patient’s germline information:**
  
  • Enhance selection of targeted therapy (BRCA/PARP)
  • Supportive care therapies (nausea, pain); Minimize toxicities
National Cancer Institute MATCH trial

IF A PATIENT’S TUMOR HAS A GENETIC ABNORMALITY THAT MATCHES ONE TARGETED BY A DRUG USED IN THE TRIAL, THE PATIENT WILL BE ELIGIBLE TO JOIN THE TREATMENT PORTION OF NCI-MATCH

NOT ALL PATIENTS WILL HAVE TUMORS WITH AN ABNORMALITY THAT MATCHES A DRUG BEING TESTED

PATIENTS WITH TUMORS THAT SHARE THE SAME GENETIC ABNORMALITY, REGARDLESS OF TUMOR TYPE, WILL RECEIVE THE DRUG THAT TARGETS THAT ABNORMALITY
GENETICS OF DRUG RESPONSE IN NON-CANCER PATIENTS
Predicting Response to Drugs: Pharmacogenomics (PGx)

- Utilizing an individual’s genetic makeup to predict response to drug therapy
  - Pharmacokinetic
    - CYP drug metabolizing enzymes
    - Drug transporters
  - Pharmacodynamic
    - Drug targets
  - Immune response
    - Hypersensitivity (HLA-B)
- Prevent/minimize toxic drug reactions
- Select most effective drug/dose at diagnosis
- Optimally, BEFORE patient gets the drug
Patients with the same diagnosis receiving the same medication at the same dose

- Some patients will experience no therapeutic benefit.
- Most patients will receive benefit with little to no toxicity.
- Some patients will experience adverse events and toxicities.
Genetic testing can identify these patients

Patients with the same diagnosis receiving the same medication at the same dose

These patients should receive alternative therapy (i.e. a different dose or medication)

These patients should receive standard therapy
Promise of pharmacogenomics

- Shift the emphasis in medicine from reaction to prevention
- Direct the selection of optimal therapy and reduce trial-and-error prescribing
- Help avoid adverse drug reactions
- Increase patient adherence to treatment
- Improve quality of life
- Reveal additional or alternative uses for medicines and drug candidates
- Help control the overall cost of health care

http://www.personalizedmedicinecoalition.org/
# Table of Pharmacogenomic Biomarkers in Drug Labeling

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
There are > 140 FDA approved drugs with pharmacogenomic information

- Majority are related to cancer drugs, especially targeted therapy
- Others associated with drug metabolism/transport and hypersensitivity
- **Adverse Drug events**: 6% hospitalizations; $5.5 million/hospital annually
  - Many ADRs predictable; some preventable through testing
- FDA boxed warnings related to risk for adverse response:
  - **Abacavir (HIV)**: recommend screening before use
  - **Carbamazepine (Psych, neurology)**: recommend screening before use (Asian ancestry)
  - **Clopidogrel (Cardio)**: poor metabolizers exhibit higher cardiovascular event rates at recommended doses - CYP2C19 testing available
  - **Codeine (Pain)**: death related to ultra-rapid metabolism of codeine to morphine in children post tonsillectomy and/or adenoidectomy
Pharmacogenetics of codeine

- In our bodies, codeine is converted to morphine
- Poor metabolizers cannot activate codeine
- Ultrarapid metabolizers are at risk of toxicity due to high morphine concentrations

Pharmacogenetics of codeine

- Poor Metabolizer - low or no activity (10%)
- Intermediate Metabolizer - lower activity (10%)
- Ultra-rapid Metabolizer - very high activity (2%)
- Extensive Metabolizer - normal activity (78%)

2013- present: National effort to prevent lethal response to codeine in children (and infants)

- NEJM, JAMA: 5-8 deaths following tonsillectomy for sleep apnea; codeine given for post-op pain.
- JAMA: Nursing mothers on codeine, can pass high levels of morphine in breast milk, 3 infant deaths documented
- FDA boxed warning on codeine for post op pain in tonsillectomy for sleep apnea in children
- WHO takes codeine off pain ladder
- Many children’s hospitals removed codeine from formulary
- Mission health removed from pediatric formulary, embedded alerts in electronic health record
• **>160 Members**
  – Clinicians and scientists
  – 86 institutions, 16 countries
  – 14 Observers (NIH and FDA)
  – CPIC Informatics
  – 19 members from 11 organizations

• **~30 drugs with good evidence base and published clinical guidelines**

• **CPIC gene/drug pair guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy**
What are the drug–gene associations with high evidence and clinical guidelines?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene(s)</th>
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<tbody>
<tr>
<td>abacavir</td>
<td>HLA-B*57:01</td>
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<tr>
<td>allopurinol</td>
<td>HLA-B*58:01</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>CYP2C19,CYP2D6</td>
</tr>
<tr>
<td>atazanavir</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>azathioprine</td>
<td>TPMT</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>HLA-B*15:02</td>
</tr>
<tr>
<td>citalopram (Celexa)</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>clomipramine</td>
<td>CYP2C19,CYP2D6</td>
</tr>
<tr>
<td>clopidogrel (Plavix)</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>codeine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>desipramine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>doxepin</td>
<td>CYP2C19,CYP2D6</td>
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<tr>
<td>escitalopram (Lexapro)</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>imipramine</td>
<td>CYP2C19,CYP2D6</td>
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</table>

<table>
<thead>
<tr>
<th>Drug</th>
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</thead>
<tbody>
<tr>
<td>mercaptopurine</td>
<td>TPMT</td>
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<tr>
<td>nortriptyline</td>
<td>CYP2D6</td>
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<tr>
<td>ondansetron (Zofran)</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>paroxetine (Paxil)</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>phenytoin (Dilantin)</td>
<td>CYP2C9, HLA-B*15:02</td>
</tr>
<tr>
<td>sertraline (Zoloft)</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>simvastatin</td>
<td>SLCO1B1</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>CYP3A5</td>
</tr>
<tr>
<td>5FU, capecitabine</td>
<td>DPYD</td>
</tr>
<tr>
<td>tramadol (Ultram)</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>trimipramine</td>
<td>CYP2C19,CYP2D6</td>
</tr>
<tr>
<td>voriconazole</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>warfarin</td>
<td>CYP2C9, VKORC1</td>
</tr>
</tbody>
</table>

https://cpicpgx.org/genes-drugs/
CLINICAL IMPLEMENTATION AT ACADEMIC AND COMMUNITY CENTERS
PREDICT Prognostic Model

- Implemented January 2012
- Predicts probability of patient receiving **clopidogrel, a statin, or warfarin** within three years based on information contained within a patient’s EMR:
  - Demographics
  - Weight or BMI (where height is available)
  - Hypertension
  - Diabetes
  - Coronary artery disease
  - Atherosclerosis
  - Congestive heart failure
  - Atrial fibrillation
  - Dialysis
  - Previous clot

A Case for Prospective Genotyping

52,942 Vanderbilt “Medical Home” patients followed for up to 5 years....

How many patients received drug(s) that have a recognized pharmacogenetic story?

- 65% received ≥1 med within 5 years

Estimated number of severe adverse events mitigated: 383
Patient Care

Did you know health care providers can use genetic information to help identify which medication or dose is likely to work best for a patient? Learn how UF Health is using this approach to guide treatment decisions involving certain medications.

Read More
1) Enroll on study during appointment with your doctor

2) Give a single blood sample

3) Pharmacogenomic testing performed to look at portions of your DNA that may influence drug response or side effects

4) Your doctor receives your individualized pharmacogenomic results

5) Results may help your doctor choose the safest and most effective medications for you

1200 Patients Project: Understanding How Individual Genetics Influence Medications
Physician Portal

Patient Name: Smith, Mike
Sex: M
DOB: 10/2/1948

Back to Patient Roster

Legend - Levels of Evidence

Level 1 - From a well-performed study including at least 1000 patients and replicated in another independent population of at least 1000 patients.

Level 2 - Evidence from a single well-performed study of at least 100 patients implicates the relationship.

Level 3 - Evidence from a relatively small single study (<100 patients) or from several smaller studies implicates the relationship; similarly-executed contradictory studies may exist.

Legend - StopLight Definitions

- Favorable: your patient has a genotype which suggests an improved chance of benefit or a decreased risk of toxicity with this medication.
- Caution: your patient has a genotype associated with possible undesirable outcomes when using this medication.
- Warning: your patient has a genotype which confers a significant increase in risk with use of this medication.
- There is no known pharmacogenomic information relevant to this medication.

Patient's Current Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patient-&gt;Drug Association</th>
<th>Level of Evidence</th>
<th>Evidence References</th>
</tr>
</thead>
<tbody>
<tr>
<td>adalimumab</td>
<td>Level 3</td>
<td>PMID: 16720636, PMID: 17343250</td>
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</tr>
<tr>
<td>atenolol</td>
<td>Level 2</td>
<td>PMID: 18615004, PMID: 20235788, PMID: 12709726</td>
<td></td>
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</tbody>
</table>
Data from >800 patients who were genotyped using preemptive panel

PG4KDS: CLINICAL IMPLEMENTATION OF PHARMACOGENETICS at ST. JUDE

Goal: migrate pharmacogenetic tests from laboratory (array-based) into routine patient care, to be available preemptively

**PG4KDS:** Use array to test for 225 genes

Establish process to move one gene/drug pair at a time into medical record

### Process for migrating PG data to medical record

- **Consensus guidelines**
- **Genotyping Platform evaluation**
- **Patient/family consent**

Determine eligibility for migrating individual test results

<table>
<thead>
<tr>
<th>Gene-drug pairs targeted for implementation</th>
<th>Primary Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Warfarin, Phenytoin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clopidogrel, Tricyclic antidepressants, Voriconazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine, Tramadol, Tricyclic antidepressants, SSRIs, Venlafaxine</td>
</tr>
<tr>
<td>DPYD</td>
<td>Fluoropyrimidines</td>
</tr>
<tr>
<td>G6PD</td>
<td>Rasburicase, Sulfa drugs</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Statins</td>
</tr>
<tr>
<td>TPMT</td>
<td>Thiopurines</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>VKORC1</td>
<td>Warfarin</td>
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</tbody>
</table>

What is Pharmacogenomics?

Pharmacogenomics is the study of how our DNA influences our response to different medications. DNA (deoxyribonucleic acid) carries our genetic code and serves as the blueprint for building the cells of the human body. We all have small differences, or variants, in our DNA that make each of us unique. Some are inherited (germline variants) and others (somatic variants) are acquired throughout life, frequently due to environmental factors. Our distinctive genetic makeup often means that a one-size-fits-all approach to drug treatment may not be optimal. Two people receiving the same medication at the same dose for the same health condition may have vastly different experiences.

NorthShore features highly specialized clinical pharmacogenomics expertise uncommon in most health systems. Pharmacogenomics lets our expert clinicians optimize your care. Our pharmacogenomics experts and clinicians tailor treatments based on your genes, not just your age, lifestyle and overall health. This innovative approach reduces the potential trial and error of prescribing medications and allows us to choose the right drug and right dose the first time.
At Mission Health, personalized medicine focuses on trying to predict how you will respond to drugs. Personalized Medicine offers a scientific, individually guided approach to improve the health of individuals and our population. It has the potential to replace the trial-and-error approach to drug treatment to manage cancer and other chronic diseases. Building on the advances in genomic medicine, personalized medicine testing provides patients and their healthcare providers with information that could help minimize toxic side effects from drug treatments and maximize drug effectiveness.

Mission Health is one of the few community health systems in the U.S. to develop a Personalized Medicine Program. Currently these programs are mainly found at major medical centers and institutions.
Personalized Medicine at Mission Health

**Program Services**
- Education/training/resource
- Meeting/exceeding national guidelines for tumor markers, including QI studies
- PGx testing for drugs with boxed warnings; CDS alerts
- Clinical consultation
  - Healthcare providers
  - Personalized Medicine Clinic (Patients w MD referral)
- Clinical research
  - Pilot study in primary care, employee health

**Personalized Medicine Team:**
- VP, Jonathan Bailey, MHA
- Director, Lynn Dressler, Dr.P.H.
- Clinical Pharmacist, Gillian Bell, PharmD
- Coordinator: Paige Krug, B.S.
- Part time:
  - Research Nurse (Pearl Abernathy, RN);
  - Peds Pharmacist (Karl Ruch, PharmD)
- Trainees: Students, Residents, Fellows
- Consultants: Howard McLeod (Moffitt Cancer Center, Tampa); Mark Dunnenberger (North Shore, Chicago)
- Partners: UNC, Duke, Vanderbilt, St Jude, UFl
PGx in Behavioral Health

• 11% of Americans aged 12+ take an antidepressant medication as of 2008
  – Third most common prescription drug taken by Americans of all ages in 2005-2008
• Estimated up to 42% of variation in antidepressant response due to common genetic variation
• Numerous behavioral health medications with PGx information in FDA labeling as well as guidelines from CPIC
• Cincinnatti Children’s has largest pediatric inpatient unit in US and uses “psychiatry” PGx panel as routine care (~1900 per year)
• UF, Vanderbilt, Mt. Sinai, and St. Jude use CPIC guidelines to inform antidepressant prescribing (i.e. SSRIs and TCAs)
• Many reference laboratories heavily marketing “psych” PGx panels

Pratt, LA, et al. NCHS Data Brief No. 76, October 2011.
Challenges to using pharmacogenomics into routine clinical practice

- Clinician acceptance – lack of education
- Complexity of test results
- Increasing number of relevant drug/gene pairs
- Pharmacogenetic results different from other test results
  - Lifelong results
  - Pre-emptive testing critical
- Cost of testing – need more studies involving clinical utility and economic analysis

Cost of pharmacogenetic testing depends on perspective and test-specific factors

- Test-specific factors
  - In-house vs. outsourced testing
  - Technology used for testing
  - Number of variants analyzed
  - Complexity of test
  - Turnaround time
- Whose perspective do you need to consider?
  - Payer – amount reimbursed
  - Clinician – price of test
  - Reference Lab/Hospital Lab – cost to perform/interpret test
  - Patient – out-of-pocket cost
Clinical value is critical component of any financial analysis in healthcare

- Standard costs such as labor, equipment, and supplies are easy to estimate
- Clinical benefits can be more challenging, but are important
  - Toxicity costs avoided
  - Reduced readmissions
  - Improved outcomes are likely to be tied to increased reimbursement in the future
- Reimbursement offsets costs, but continues to be a challenge
INCREASING APPROVALS OF GENOMIC TESTS MAKE REIMBURSEMENT DECISIONS CHALLENGING

• Submissions for FDA approval of pharmacogenomic and personalized medicine tests are already increasing

• Evidence requirements for regulatory approval are not the same as those for coverage decisions
  – FDA approval is based on analytical and clinical validity
  – Coverage decisions are based on the above criteria in addition to clinical utility

• Payers must evaluate each new test and make coverage and reimbursement decisions based on the available data, often requiring significant resources to perform these analyses
Review of papers investigating cost-effectiveness of PGx tests from Aug 2010-Sept 2014

80 studies included using cost utility, cost effectiveness, and cost minimization analyses

Application of PGx tests was mostly found to be cost-effective or cost-saving

- Observational study comparing:
  - Tested group: Prospective cohort of 205 patients ≥65yo and prescribed ≥3 meds (1 known to be impacted by PGx) who had PGx testing (panel of 6 genes)
  - Untested group: propensity-score matched history cohort of 820 patients from claims database without testing

- Results:
  - ED visit rate 4.4% in tested group vs. 15.4% in untested group (95% CI 0.1-0.55, p=0.0002)
  - Hospitalization rate 9.8% in tested group vs. 16.1% in untested group (95% CI 0.3-0.95, p=0.027)
  - Mean potential cost savings estimated at $1142 (prior to testing)

Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression

J Winner¹, JD Allen¹, C Anthony Altar¹ and A Spahic-Mihajlovic²

- Blinded retrospective study, 96 patients with depression or anxiety

Figure 3  Annual number of healthcare visits (left) and medical visits (right) per patient, by the GeneSight-designated category of subjects' medication regimen.
Summary

• Personalized medicine utilizes genetics information to optimize drug therapy
• Testing is standard of care in oncology, starting to become more common in non-cancer conditions
• Lots of guidance on how to use PM from FDA labeling and guidelines
• Many academic and some community institutions have successfully implemented into clinical care
• Need more real world economic evaluations to prove value and justify reimbursement

Novak K. Nat Med 2000 May;6(5)487-8
MISSION HEALTH AIM:
“To get every person to their desired outcome, first without harm, also without waste and always with an exceptional experience for each person, family and team member.”

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Thank You!!!

www.mission-health.org/personalizedmedicine