Pharmacogenomics: The Evidence, The Experience, The Future

Introduction to pharmacogenomics: The evidence and benefits

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Professor and Associate Dean
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Learning Objectives

• Understand what pharmacogenomics is
• Explain the importance of pharmacogenomics
• List benefits of pharmacogenomics testing
• Give examples of evidence for pharmacogenomics testing
Definitions

• **Pharmacogenetics**
  - “the study of genetic causes of individual variations in drug response” (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)

• **Pharmacogenomics**
  - “more broadly involves genome-wide analysis of the genetic determinants of drug efficacy and toxicity” (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)

• The terms are used interchangeably. For the purposes of this presentation we will use the term pharmacogenomics (PGx)
Current Drug Therapy

• Drug response rate
  • 30-60% response rate of drug therapies for Alzheimer’s, depression, rheumatoid arthritis, hypertension, osteoporosis (Physician's Desk Reference)

• Adverse drug reactions (ADRs)
  • ↑ Morbidity and Mortality
    • Up to 100,000 people/year die of ADRs in the U.S. (Lazarou 1998)
  • ↑ Cost
Molecular Biology 101

- Gene Mutations/Modifications
  - Duplication
  - Deletion
  - Insertion

https://public.ornl.gov/site/gallery/detail.cfm?id=403&topic=&citation=&general=genomics energy&restsection=all
Pharmacogenomics Impacts Pharmacokinetics and Pharmacodynamics

• Variations in a gene may impact either pharmacokinetics or pharmacodynamics
  – Pharmacokinetics = process by which a drug is absorbed, distributed, metabolized, and eliminated
  – Pharmacodynamics = action or effect of a drug on the body

• These impact efficacy and toxicity
Patient/Provider Concerns

- **Patients have high expectations**
  - They expect healthcare providers to explain and interpret pharmacogenomics test results

- **Providers lack knowledge and evidence-based resources**
  - Reluctant to order pharmacogenomics tests due to limited information about clinical utility
  - There are logistical challenges to testing
  - Health informatics tools (Electronic Medical Records, Computerized Provider Order Entry) do not have pharmacogenomic information at the point of care
Patient/Provider Concerns

- **Patients and providers have concerns about privacy issues** (Rogausch 2006, Fargher 2007)
  - Genetic testing policies vary from state to state
- **Current healthcare professionals need education** (Frueh 2004)
- **Future healthcare providers need education**
  - Pharmacogenomics curricula have increased in pharmacy schools (Murphy 2010)
  - Pharmacogenomics is not adequately taught in medical schools (Gurwitz 2005)
Benefits of Pharmacogenomics

• Personalize medicine using genotyping technologies
• Optimize drug therapy
  • May maximize drug effectiveness
  • May minimize drug toxicity
  • May minimize pharmacokinetic and pharmacodynamic variability of drug therapy
  • May avoid unnecessary treatment
• Optimize drug development
Examples of topic areas for required or voluntary submissions to FDA
(Attachment to Guidance on Pharmacogenomic Data Submissions 2005)
- Metabolizing Enzymes, Transporters, Receptors, Clinical Outcomes: Efficacy and Safety, Nonclinical Safety

Of 1,200 drug labels reviewed from 1945-2005
- 121 labels contained pharmacogenomic information (Frueh 2008)
- 69 of these referred to human genomic biomarkers

Currently, FDA lists more than 150 approved drugs with valid genomic biomarkers described their labels
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
(Table: Pharmacogenomic Biomarkers in Drug Labeling)
Abacavir Black Box Warning

ZIAGEN™
(abacavir sulfate)
Oral Solution

WARNING: FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH THERAPY WITH ZIAGEN. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF HYPERSENSITIVITY (WHICH INCLUDE FEVER, SKIN RASH, FATIGUE, AND GASTROINTESTINAL SYMPTOMS SUCH AS NAUSEA, VOMITING, DIARRHEA, OR ABDOMINAL PAIN) SHOULD DISCONTINUE ZIAGEN AS SOON AS A HYPERSENSITIVITY REACTION IS SUSPECTED. ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY REACTION BECAUSE MORE SEVERE SYMPTOMS WILL RECUR WITHIN HOURS AND MAY INCLUDE LIFE-THREATENING HYPOTENSION AND DEATH.

Ref: FDA-Approved Package Information
Other Evidence-Based Resources

- Centers for Disease Control and Prevention (CDC)
  - Evaluation of Genomic Applications in Practice and Prevention (EGAPP)
    - Independent, multi-disciplinary panel reviews available evidence on genetic tests, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios (http://www.egappreviews.org/about.htm)

- PharmGKB
  - https://www.pharmgkb.org/

- NIH National Human Genome Research Institute
  - https://www.genome.gov

- NIH G2C2: Genetics/Genomics Competency Center for Education
  - http://www.g-2-c-2.org/index.php

- Pharmacogenomics Education Program
  - http://www.pharmacogenomics.ucsd.edu
## Challenges of Pharmacogenomic Testing

### Access
- Availability of test
- Providers
- Insurance coverage

### Feasibility
- Turnaround time
- Sensitivity/specificity of tests
- Efficiency

### Cost
- Genetic test
- Disease management
- Counseling

### Limited evidence
- Need more quality studies
- Prospective vs retrospective studies
- Predictive value
- Analytical and clinical validity
- Phenotyping of clinical presentation
- Clinical utility of testing
- Efficacy
- Expertise
- Cost-effectiveness
Practice Gap

- The field of pharmacogenomics is growing rapidly, with many new discoveries coming to light
- It is critical for clinicians and clinical lab personnel to...
  - Appropriately interpret emerging data on pharmacogenomic tests
  - Become familiar with resources applicable to their practice
  - Develop an evidence-based and efficient model of clinical service
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The Changing Healthcare Environment and the Value of Pharmacogenetics

Rick Shigaki
Director of Business Development
Objectives

1. Be able differentiate the fee for service healthcare model with the new value based healthcare model

2. Identification of key data that will help enable the use of pharmacogenetic testing in a value based healthcare model
Fee for Service Model
"Well, Bob, it looks like a paper cut, but just to be sure let's do lots of tests."
The Next (Final?) Frontier

To boldly go...
Value Based Healthcare

\[ V = \frac{Q + S}{\$} \]

(Quality) + (Service) / (Cost)
Bundled Payment Model

Payment for comprehensive, coordinated intervention
Hospital Readmissions

Patient Readmission Cycle

$17 Billion Per Year

30 DAYS

Translational software
Medicare Admissions Result in a Bounce Back within 30 Days of Discharge

Medicare Payment Reductions Due to Readmissions

CMS Penalties

- 2013: Up to 1%
- 2014: Up to 2%
- 2015+: Up to 3%
The Value of PGX Testing

Clinical Literature
### 3 Scenarios of Genotyping ACS and PCI Patients

<table>
<thead>
<tr>
<th>Scenario</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotyping for 2C19</td>
<td>No Genotyping</td>
<td>50% Genotyping</td>
<td>100% Genotyping</td>
</tr>
<tr>
<td>Antiplatelet Therapy Based on Genotyping Results</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Cohort of 1,000 Patients*

### Annual Cost Difference Between Scenarios A, B and C

<table>
<thead>
<tr>
<th></th>
<th>Cost Difference Between Scenarios A and B ($)</th>
<th>Cost Difference Between Scenarios A and C ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Costs</td>
<td>222,426</td>
<td>444,852</td>
</tr>
<tr>
<td>Cost Per Patient</td>
<td>222</td>
<td>445</td>
</tr>
<tr>
<td>CVD</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Nonfatal bleeding</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

*CVD= cardiovascular death; MI= myocardial infarction*

Summary

1. Third party payers are moving away from a *fee for service reimbursement* to *value based reimbursement*

2. Laboratories must show *value* of the testing on the new payment criteria that is being applied to the healthcare team.

3. *Pharmacogenetics (PGX)* shows great promise to improve the value of healthcare delivery.

4. Technology is being developed that will better position PGX to add greater *value* to the overall care delivery for patients.
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Bringing PGx Testing into the Laboratory: Important Considerations

Doug Rains
Chief Scientific Officer, Quantigen Laboratory
TOPICS COVERED

- Background on thermo fisher scientific’s PGx technology
- PGx workflow; plus, what does my lab need to get started?
- How do we select a testing menu (genes, mutations)?
- How does my lab analyze and interpret data?
- Miscellaneous considerations
CHOOSING A PGX PLATFORM

• Six key factors to consider:

  - **Turnaround time:** minimum time from sample receipt to reporting
  - **Labor requirements:** number of personnel and hands-on time needed to complete workflow
  - **Throughput:** maximum number of samples per day, per instrument set
  - **Cost** per sample
  - **Testing content:** availability and flexibility
  - **Versatility of instrumentation:** can we expand to other types of tests?
CHOOSING A PGX PLATFORM

• The QuantStudio™ 12K Flex system with OpenArray™ technology:
  
  - **Turnaround time** from DNA to genotype is approximately one day.
  - **Labor requirements:** one well-trained technician can easily handle ~100 samples per day, including data analysis.
  - **Throughput:** one instrument can handle 184 samples per run (46 samples per array x 4 arrays) using a 60-assay testing panel.
CHOOSING A PGX PLATFORM

• The QuantStudio™ 12K Flex system with OpenArray™ technology:
  
  □ Cost is easily the lowest in the industry, and averages $25-$30 per sample for all consumables and reagents.
  
  □ Content is customizable: user can put whatever TaqMan™ SNP assays they want on an OpenArray™ plate.
  
  □ QuantStudio™ 12K Flex is assay-agnostic: can accommodate any real-time PCR-based assay (non-quantitative or quantitative; women’s health, viral detection, TB, bacterial resistance markers, etc., etc.).
TAQMAN TECHNOLOGY FOR PGX TESTING

Gold-standard technology, universal protocol (no optimization)

Broad assay collection available

- 2,700 TaqMan™ Drug Metabolism Assays – SNPs, MNP, Indels
- 7.0 Million TaqMan™ SNP Genotyping Assays
- 1.6 Million TaqMan™ Copy Number Assays
- Custom TaqMan™ Assays

[Images and diagrams showing TaqMan technology]
**OPENARRAY TECHNOLOGY FOR PGX TESTING**

**Flexibility to customize your own panels**

<table>
<thead>
<tr>
<th>TaqMan SNP Genotyping Assays</th>
<th>Number of Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>X</td>
</tr>
<tr>
<td>60</td>
<td>X</td>
</tr>
<tr>
<td>120</td>
<td>X</td>
</tr>
<tr>
<td>180</td>
<td>X</td>
</tr>
<tr>
<td>240</td>
<td>X</td>
</tr>
</tbody>
</table>

- x represents the number of samples for each TaqMan SNP Genotyping Assay.

- Hydrophilic
- Hydrophobic

Each sample size is 33 nL.
TAQMAN COPY NUMBER VARIATION ASSAYS FOR PGX

• Accurate interpretation of one gene – CYP2D6 – requires copy number analysis – “CNV.”

• CNV reactions are performed on the same QuantStudio™ instrument; however, a different thermal block is required (either 96- or 384-well).

• Assay selection is somewhat subjective; most labs look at either one or two CYP2D6 markers to gauge the likely number of functional copies (e.g., assays designed to intron 2 and exon 9).
OVERVIEW OF WORKFLOW

Lab receives swab samples + testing requisition

Sample isolation on KingFisher™ Instrument

OR

Accessioning of sample info into LIMS (if necessary)

DNA quality control check (quantification)

Pre-amplify DNA / dilute
OVERVIEW OF WORKFLOW

Combine DNA and master mix / load OpenArray™ plate

Run on QuantStudio™ system (Duration: 3.5 hours)

Set up Copy Number Assay(s) in 384-well plates; store at 4°

Run CNV plate(s) on QuantStudio™ system (Each run takes ~1.5 hours)
Analyze raw data

SNP genotyping data using Genotyper software

CNV data using CopyCaller software
OVERVIEW OF WORKFLOW

Export Genotyper and CopyCaller software data

Pharmacogenetic interpretation

Results
ANALYZING SNP DATA: GENOTYPER

- Analysis options: unsupervised ("algorithmic") vs. Supervised ("trained") calling
- Users can have the software call clusters using internal algorithms...
ANALYZING SNP DATA: GENOTYPER

- Users can even add **control samples** to aid the software in identifying clusters.
**ANALYZING SNP DATA: GENOTYPER**

- Alternatively, users can set their own **classification boundaries** based on a training set of DNA controls (supervised calling).
ANALYZING COPY NUMBER DATA: COPYCALLER

- CopyCaller accepts exported data from QuantStudio™ for both CNV assays and control assay (in multiplex).
- It then generates relative values for each sample, along with confidence values for CNV calls.
WHAT’S NEEDED TO GET STARTED IN THE LAB?

• QuantStudio™ 12K Flex Real-Time PCR instrument with OpenArray™ block, and either a 96- or 384-well block
• AccuFill™ sample loader
• MagMax™ Express for either 24 or 96 samples
• OpenArray™ cards for PGx
• MagMax™ sample prep reagents (Ultra™ Kit)
• Standard PCR machine (only if doing pre-amplification)
• Fluorometer or spectrophotometer (only if quantifying DNA)
• Dry bath + lab armour bath beads
• Plate centrifuge
• PCR Master Mixes and single-tube assays for SNP genotyping and copy number
• Various consumables for PGx testing
HOW DOES MY LAB SELECT TESTING CONTENT?

Which genes and SNPs?

• A few considerations:
  • Start with your lab’s focus: Cardiology? Pain management? Psych?
  • Make a gene list based on target market(s).
  • Determine which SNPs are most informative.
  • Balance this list with the number of available assays per OpenArray™ subarray (60 or 120).
Differential quantification of CYP2D6 gene copy number by four different quantitative real-time PCR assays

Anuradha Ramamoorthy, 1,2 David A. Flockhart, 1,2 Naoya Hosono, 3 Michiaki Kubo, 3 Yusuke Nakamura, 3,4 and Todd C. Skaar 1
THIRD-PARTY TRANSLATIONAL REPORTING

Third-party groups can provide assistance in building testing panels based on lab’s needs; also, provide full PGx interpretations.
WORKFLOW VALIDATION PACKAGE

• Service confirms workflow is functioning to manufacturer specifications
• Performed by qualified field applications and compliance service specialist
• 2-3 weeks for execution

Package includes:

✓ Experimental Design Plan and Protocol
✓ Protocol Execution/Controls Sourced
✓ Workflow Optimization (Performance Qualification)
✓ Data Analysis
✓ Technical Review
✓ Workflow Training
✓ Final Report
RESOURCES TO LEARN MORE

• THERMO FISHER PGX WEB LANDING PAGE
  THermoFisher.COM/PGX

• WEBINAR ON DEMAND: A COMPARISON OF GENOTYPING PLATFORMS FOR PHARMACOGENETIC TESTING
  HTTP://LABROOTS.COM/USER/WEBINARS/DETAILS/ID/91

• OPENARRAY TECHNOLOGY OVERVIEW

• PGX USER GUIDE
  HTTP://TOOLS.LIFETECHNOLOGIES.COM/CONTENT/SFS/MANUALS/MAN0009612_PHARAMACOGENOMICS_U G.PDF

• QUANTSTUDIO 12K FLEX REAL-TIME PCR SYSTEM