Pharmacogenetic-guided Intervention: Current Landscape & Future Trends

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Topics

• The growth of pharmacogenetic testing
• Reported measures of effectiveness and outcomes
• Quality and Quantity of Evidence
• Trends and future directions for genetic guided interventions
• Pricing implications and potential payment models
Pharmacogenetic Testing?

• Testing genetic variants to determine how a patient will likely respond to a particular medication – a form of personalized medicine

• Rationale
  – particularly for medications with a narrow therapeutic index (NTI), small changes in dose can significantly affect outcomes

• Goals
  1. To identify the right dose for the specific patient to improve efficacy and safety, including reduced adverse events
     • E.g. clopidogrel [“Plavix”] (CYP2C19 Genotyping)
     • Normal, poor, intermediate, extensive, or ultra-rapid metabolizer of the drug
  2. To identify patients who may have a better response to alternative drugs
     • Instead of clopidogrel use alternative therapy e.g. prasugrel

* Genetic variations seldom account for 100% of the differences we see in patients treatment responses
The Growth of Pharmacogenetic Testing

Outpatient Diagnostic Pharmacogenetic Testing

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Unique Patient Counts</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>2011</td>
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<tr>
<td>81206</td>
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<tr>
<td>81207</td>
<td>BCR/ABL1 MINOR BREAKPNT QUALITATIVE/QUANTITATIVE</td>
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<tr>
<td>81226</td>
<td>CYP2D6 GENE ANALYSIS COMMON VARIANTS</td>
<td>0</td>
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<tr>
<td>81227</td>
<td>CYP2C9 GENE ANALYSIS COMMON VARIANTS</td>
<td>0</td>
</tr>
<tr>
<td>81267</td>
<td>CHIMERISM W/COMP TO BASELINE W/O CELL SELECTION</td>
<td>0</td>
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<tr>
<td>81275</td>
<td>KRAS GENE ANALYSIS VARIANTS IN CODONS 12 AND 13</td>
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</tr>
<tr>
<td>81310</td>
<td>NPM1 NUCLEOPHOSMIN GENE ANAL EXON 12 VARIANTS</td>
<td>0</td>
</tr>
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</table>

Courtesy of Symphony Health Solutions Private Practitioner Medical Claims (CMS1500)
Reported Measures of Effectiveness and Outcomes: Surrogate Proxies & Markers to Clinical Events

Clopidogrel (Plavix):

• **FDA** Black Box Warning: “poor metabolizers may not receive the full benefit of Plavix treatment and may remain at risk for heart attack, stroke and cardiovascular death” (2010)

• **AHA/ACC**: “Because of the lack of evidence, routine genetic testing before initiating clopidogrel treatment cannot be recommended” (2010)

• **Mayo Clinic**: “The clopidogrel/CYP2C19 pair [evidence] is among the highest AGREE II scores in overall quality and domain” (2015)
Reported Measures of Effectiveness & Outcome: Surrogate Proxies & Markers to Clinical Events

How do we judge treatment failure due to drug in a multi-factorial environment? Who should bear the responsibility and ultimately the cost?

Original figure modified for this publication. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010; 56:919. Illustration used with the permission of Elsevier Inc. All rights reserved.
Health Economics & Outcomes Research

• 2004 Clopidogrel resistance is associated with increased risk of recurrent atherothrombotic events in patients with acute myocardial infarction

• 2013 Genetic Testing In Patients With ACS Undergoing PCI: A Cost-effectiveness Analysis
  “A genotype-guided strategy yields similar outcomes to empiric approaches to treatment, but is marginally less costly and more effective.”

• 2014 Pharmacogenetic-Guided [Psychiatric] Intervention Associated With Increased Adherence and Cost Savings
Quality & Quantity of Evidence

• Multiple approaches and frameworks exist
• Start early, build high quality evidence, generate complimentary RCT & observational studies, replicate and validate the findings (NCI)

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Trends and Future Directions for Genetic Guided Interventions: Tx at the Point of Care
Trends and Future Directions for Genetic Guided Interventions: Testing Prior to PCSK9 Rx?

Genomic Prescribing System™ [GPS]

Patient Name:
Sex:
DOB:

Drug Search Results for: Simvastatin

Your patient carries a genotype that confers up to a 17-fold increased risk for developing simvastatin-induced myopathy compared to individuals with no risk alleles.

This translates to an 18% cumulative risk of myopathy over 6 years, compared to 0.6% risk in those without the alleles. Almost all patients with the high-risk genotype who develop myopathy developed it within the first 8 months of therapy.

These data were first derived from a study of 175 individuals—and the results were replicated in a group of over 16,000 individuals—taking simvastatin at doses between 40-80 mg.

Another study of 509 patients taking statins found that those with your patient’s genotype (two copies of the risk allele) had a 50% incidence of either premature discontinuation of the drug, myalgias, or creatine kinase elevations >3 times the upper limit of normal, compared to a 27% incidence in patients with only one copy of the risk allele, and 19% in patients with no risk alleles (P trend = 0.01). In sub-group analysis, the adverse risks remained statistically significant and were greatest in the 162 patients taking simvastatin at 80 mg.

Published data do suggest the myopathy risk for simvastatin may be particularly due to use of the 80 mg dose, and FDA recommendations against using this dose (regardless of genotype) unless a patient has tolerated simvastatin for >12 months have been published.

Guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC) also recommend caution when using simvastatin at 40 mg doses in patients with your patient’s genotype.

Evidence
Level 1

Primary Literature Sources
J Am Coll Cardiol (2010)
Clin Pharmacol Ther (2012)

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Trends and Future Directions for Genetic Guided Interventions

The Hawaii clopidogrel lawsuit: The Possible Effect on Clinical Laboratory Testing*

• Standard 75 mg dose is not efficacious for Hawaiians
• Who (if anyone) is at fault for deaths involving failed clopidogrel?
• What affect will this have on CYP2C19 pharmacogenomics testing for clopidogrel?

Pricing Implications and Potential Payment Models

- Cost of Genotyping: $450 for Self-Pay/uninsured/uncovered patients
- Rx Cost: 75 mg $161 for 30 day supply (+ Load of 300 mg) Self-Pay
- Incidence of ACS-related 30-day re-hospitalization: 5.5% Hess et al
- MI Readmission: $7216/patient*- absorbed by the hospital!

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Manufacturer</th>
<th>Hospital</th>
<th>Patient</th>
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</thead>
<tbody>
<tr>
<td>Clopidogrel Testing</td>
<td>Patients</td>
<td>Rx Resistance</td>
<td>Re-Admission Rate</td>
</tr>
<tr>
<td>No</td>
<td>5000</td>
<td>25%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Yes</td>
<td>5000</td>
<td>0%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

Who pays for and who benefits from the test, the drug, and avoided re-hospitalizations?

Who conducts the analyses based on what scope of data?

Pricing Implications: Greater Transparency/Value

- Increasing pricing transparency for all payers
  - Unstacked codes: less ‘bundling’ of tests
  - FAIR Health national independent, not-for-profit: “mission is to bring transparency to healthcare costs and health insurance information”
  - “Database of billions of billed medical and dental services to power a free website that enables consumers to estimate and plan their medical and dental expenditures.” Articles on how reimbursement works, etc.
  - Consumer Reports.com, insurer websites, etc.

- Impact of greater efficacy and greater safety on pricing
  - Lower sales volume for many drugs, especially acute care medications
  - Value-based pricing: multiple considerations including political environment
  - Profitability as a more important metric vs. market share or revenue

- Increasing trend toward global reference pricing

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Condition</th>
<th>Change</th>
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</thead>
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<td>Metabolism</td>
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<td>CYP2C9</td>
<td>Metabolism</td>
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<tr>
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<tr>
<td>81207</td>
<td>JAK2</td>
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<td>81267</td>
<td>Chimerism</td>
<td>Transplant</td>
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<tr>
<td>81275</td>
<td>KRAS</td>
<td>Colorectal CA</td>
<td>-74%</td>
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</table>
Potential Pharmacogenomic Payment Models

• Payment Models
  – Classic Pharma: companion diagnostic “bundling” – e.g. free testing for Iressa therapy
  – CMS: ‘systematically re-evaluate reimbursement’ – lower prices as technology improves?
  – PBMs: bundled driver but perhaps for generics only
  – Patients: discretionary spending moving from defined benefits to defined contributions
  – Insurer Risk-Sharing: outcomes/performance: show me the difference e.g. Oncotype Dx

Johnson D B et al. The Oncologist 2014;19:616-622
Summary

- Development of pharmacogenetics will continue and accelerate
- While ‘necessary’ for healthcare to become more efficient, alone it is not fully sufficient
- The applied use is here today and will also accelerate
  - For patient care
  - For clinical trials
  - For significant decisions
- Transparency in pricing and payment models tied to demonstrated performance will help to drive the success or failure of individual tests
- The consumer will increasingly be the patient and the payer, as well as the decision maker
- Commercial success will hinge on demonstrated action and value