Pharmacogenomics Will Not Be A Critical Part of Drug Dosing

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Human Genome Project Timeline

1985: Feasibility of sequencing human genome discussed
1986: 5.3 million committed to a feasibility program
1987: DOE designates multidisciplinary human genome centers. NIH NIGMS begins funding of genome projects.
1990: 15 year plan to map human genome begins
2000: Map completed
2001: Map published
2008: Genetic Information Nondiscrimination Act (GINA) Becomes Law, May 2008

Bottom Line: 20 years, billions and billions
Pharmacogenomics: The Questions

• Clinical relevance
• Social and ethical aspects
• Economic impact

Valid Biomarkers

• A valid biomarker is described as a “biomarker that is measured in an analytical test system with well established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.” The classification of biomarkers is context specific.

• Reference is made to the requirement of testing for the biomarker:
  1 = test required;
  2 = test recommended; 2* test for at-risk populations
  3 = information only

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm
### Valid Biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Test</th>
<th>Drug with Label Change</th>
<th>Associated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ckit expression</td>
<td>3</td>
<td>Imatinib</td>
<td></td>
</tr>
<tr>
<td>CCR-5 chemokine</td>
<td>1</td>
<td>Maraviro</td>
<td></td>
</tr>
<tr>
<td>receptor CYP2C19</td>
<td>2</td>
<td>Voriconazole</td>
<td>Omeprazole, Pantopazol, Esmeprazole,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diazepam, Nelfinavir, Rabeprazole</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>2</td>
<td>Celacoxib</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>2</td>
<td>Warfarin</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
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<th>Test</th>
<th>Drug with Label Change</th>
<th>Associated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>3</td>
<td>Atomexatine</td>
<td>Venlafaxine, rispridone, tamoxifen, timolol</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>3</td>
<td>Fluoxetine</td>
<td>Many</td>
</tr>
<tr>
<td>5q-deletion</td>
<td>3</td>
<td>Lenalidomide</td>
<td></td>
</tr>
<tr>
<td>DPD</td>
<td>3</td>
<td>Capecitabine</td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td>3</td>
<td>Erlotinib, cetuximab (head and neck cancer)</td>
<td>Gefitinib</td>
</tr>
<tr>
<td>EGFR</td>
<td>1</td>
<td>Cetuximab (Colon cancer)</td>
<td>Panitumomab, Gefitinib</td>
</tr>
</tbody>
</table>
## Valid Biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Test</th>
<th>Drug with Label Change</th>
<th>Associated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>2</td>
<td>Atorvastatin</td>
<td></td>
</tr>
<tr>
<td>G6PD</td>
<td>2</td>
<td>Rasburicase</td>
<td>Dapsone</td>
</tr>
<tr>
<td>G6PD</td>
<td>3</td>
<td>Primaquine</td>
<td>Chloroquine</td>
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<tr>
<td>Her-2-neu</td>
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<td>Trastuzumab</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>HLA-B*1502 allele presence</td>
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<td>Carbamezapine</td>
<td></td>
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<tr>
<td>NAT</td>
<td>3</td>
<td>Isoniazid, pyrazinamide, rifampin</td>
<td>Isosorbide, Hydralazine</td>
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</table>

## Valid Biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Test</th>
<th>Drug with Label Change</th>
<th>Associated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philadelphia chromosome</td>
<td>3</td>
<td>Busulfan</td>
<td></td>
</tr>
<tr>
<td>Philadelphia chromosome</td>
<td>1</td>
<td>Imatinib, Dasatinib</td>
<td></td>
</tr>
<tr>
<td>PML/RAR (alpha) fusion gene presence</td>
<td>3</td>
<td>Tretinoin</td>
<td>Arsenic trioxide</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>2</td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>TPMT</td>
<td>2</td>
<td>Azathioprine</td>
<td>6-mercaptopurine, Thioguanine</td>
</tr>
<tr>
<td>UGT</td>
<td>2</td>
<td>Irinotecan</td>
<td></td>
</tr>
</tbody>
</table>
Valid Biomarkers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Test</th>
<th>Drug with Label Change</th>
<th>Associated Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGT</td>
<td>3</td>
<td>Nilotinib</td>
<td></td>
</tr>
<tr>
<td>Urea cycle disorder</td>
<td>2</td>
<td>Valproic acid</td>
<td></td>
</tr>
<tr>
<td>VKORC1</td>
<td>2</td>
<td>Warfarin</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Relevance

- Pharmacogenomics is still in early developmental stage, prospective trials have not been performed or completed.
- Environmental, behavior, disease characteristics, other drugs and dietary factors all effect drug effect.
- Complex traits and complex response. Unlikely that a single gene will explain all variability.
Social and Ethical Concerns

• Direct to consumer marketing
  – http://www.genotypedietchannel.com/
• Genetic discrimination
• Coverage by insurance companies

Cost

• Genetic tests are expensive- $250-$3500
• Cost of the test needs to be balanced with the cost of avoiding unnecessary treatment and the cost of toxicity
• Unclear whether PG testing is cost effective

Tucker L. Pharmacogenomics: Primer for Policy Makers, NHPF 2008;

Doloresco F, etal AJHP 2008, submitted
Current State Of The Art In Using Pharmacogenomics To Determine Appropriate Doses And Drugs

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Clinical Pharmacogenetics: Already in Routine Practice

- Selective therapy
  - Her-2-neu testing for trastuzumab
  - Philadelphia chromosome for imatinib
- Minimize toxicity
  - TPMT testing for 6-mercaptopurine (6-MP)
  - UGT testing for irinotecan
Clinical Pharmacogenetics: Close to Routine and Will Be Covered Today

• Selective therapy
  – Cetuximab, panitumomab, gefitinib and erlotinib and the EGFR/Kras pathway

• Minimize toxicity
  – Tamoxifen and CYP2D6

Case: Controlling Costs

• YT is a 64-year-old man with metastatic colon cancer set to begin therapy with cetuximab. His tumor is mutated for Kras. What do you suggest?
  – Start cetuximab as planned
  – Switch to panitumumab
  – Best supportive care or phase 1 trial
The KRAS Oncogene

- The KRAS gene encodes the human cellular homolog of the transforming gene Kirsten rat sarcoma-2 virus
- KRAS is a self-inactivating signal transducer
  - It cycles from GDP bound ("off" state) to GTP bound ("on" state) in response to receptor activation
  - This response is transient due to the intrinsic GTPase activity
- KRAS oncogenes harbor activating mutations yielding proteins with reduced GTPase activity
- These activating KRAS mutations are among the most common oncogenic alterations in cancer


Mutated KRAS Activates the RAS-RAF-MEK-ERK-MAP Kinase Cell Signaling Pathway Independently Despite the Inhibition of EGFR (HER) by Cetuximab

Cetuximab and Kras Mutations

- Retrospective evaluation of individuals with metastatic colorectal cancer (n = 59) receiving cetuximab in combination with irinotecan or oxaliplatin
- Response rate in those without Kras mutation 32% (5% CR, 28% PR)
- Response rate in those with a Kras mutation 0


Cetuximab and Kras Mutations

- Retrospective evaluation of individuals with metastatic colorectal cancer (n = 30) receiving cetuximab in combination with irinotecan, oxaliplatin, or as a single agent
- 11 patients with a response (no Kras mutations)
- 19 patients without response (13 with a Kras mutation)

Cetuximab and Kras Mutations

Overall survival according to KRAS mutation

Percent survival
0 25 50 75 100
0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0

non mutated KRAS
mutated KRAS
p=0.016

Randomization stratification
• ECOG score: 0-1 vs. 2
• Geographic region: Western EU vs. Central & Eastern EU vs. Rest of World

Panitumumab PD Follow-up
6.0 mg/kg Q2W + BSC

BSC PD Follow-up

Option Panitumumab Crossover Study

Hypothesis: The treatment effect of panitumumab monotherapy is larger in patients with wild-type KRAS compared to patients with mutant KRAS

**Results: Prevalence of Mutant KRAS**

<table>
<thead>
<tr>
<th></th>
<th>Panitumumab + BSC</th>
<th>BSC alone</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized, n</td>
<td>231</td>
<td>232</td>
<td>463</td>
</tr>
<tr>
<td><strong>KRAS not tested, n (%)</strong></td>
<td>11 (5)</td>
<td>7 (3)</td>
<td>18 (4)</td>
</tr>
<tr>
<td><strong>KRAS tests failed, n (%)</strong></td>
<td>12 (5)</td>
<td>6 (3)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Patients included in KRAS analysis, n (%)</td>
<td>208 (90)</td>
<td>219 (94)</td>
<td>427 (92)</td>
</tr>
<tr>
<td>Wild-type KRAS, n (%)</td>
<td>124 (60)</td>
<td>119 (54)</td>
<td>243 (57)</td>
</tr>
<tr>
<td>Mutant KRAS, n (%)</td>
<td>84 (40)</td>
<td>100 (46)</td>
<td>184 (43)</td>
</tr>
</tbody>
</table>

BSC, best supportive care

**Objective Tumor Response (Central Radiology)**

<table>
<thead>
<tr>
<th>KRAS</th>
<th>All Evaluable n (%)</th>
<th>Mutant n (%)</th>
<th>Wild-type n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pmab (N = 208) BSC (N = 219)</td>
<td>Pmab (N = 84) BSC (N = 100)</td>
<td>Pmab (N = 124) BSC (N = 119)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0) 0 (0)</td>
<td>0 (0) 0 (0)</td>
<td>0 (0) 0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (10) 0 (0)</td>
<td>0 (0) 0 (0)</td>
<td>21 (17) 0 (0)</td>
</tr>
<tr>
<td>SD</td>
<td>52 (25) 22 (10)</td>
<td>10 (12) 8 (8)</td>
<td>42 (34) 14 (12)</td>
</tr>
<tr>
<td>PD</td>
<td>104 (50) 149 (68)</td>
<td>59 (70) 60 (60)</td>
<td>45 (36) 89 (75)</td>
</tr>
<tr>
<td>CR, PR, SD</td>
<td>73 (35) 22 (10)</td>
<td>10 (12) 8 (8)</td>
<td>63 (51) 14 (12)</td>
</tr>
</tbody>
</table>

Pmab, panitumumab; BSC, best supportive care; CR, complete response; PR partial response; SD, stable disease; PD, disease progression
Single-Arm Studies Support the Hypothesis for
KRAS as a Biomarker for EGFr Inhibitors

<table>
<thead>
<tr>
<th>Reference</th>
<th>Treatment</th>
<th>No of patients (WT:MT)</th>
<th>Objective Response N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Lièvre, et al. (AACR Proceedings, 2007)</td>
<td>cmab ± CT</td>
<td>76 (49:27)</td>
<td>0 (0) 24 (49)</td>
</tr>
<tr>
<td>S. Benvenuti, et al. (Cancer Res, 2007)</td>
<td>pmab or cmab or cmab + CT</td>
<td>48 (32:16)</td>
<td>1 (6) 10 (31)</td>
</tr>
<tr>
<td>W. De Roock, et al. (ASCO Proceedings, 2007)</td>
<td>cmab or cmab + irinotecan</td>
<td>113 (67:46)</td>
<td>0 (0) 27 (40)</td>
</tr>
<tr>
<td>D. Finocchiaro, et al. (ASCO Proceedings, 2007)</td>
<td>cmab ± CT</td>
<td>81 (49:32)</td>
<td>2 (6) 13 (26)</td>
</tr>
<tr>
<td>F. Di Fiore, et al. (Br J Cancer, 2007)</td>
<td>cmab + CT</td>
<td>59 (43:16)</td>
<td>0 (0) 12 (28)</td>
</tr>
<tr>
<td>S. Khambata-Ford, et al. (J Clin Oncol, 2007)</td>
<td>cmab</td>
<td>80 (50:30)</td>
<td>0 (0) 5 (10)</td>
</tr>
</tbody>
</table>

WT, wild type; MT, mutant; cmab, cetuximab; CT, chemotherapy; pmab, panitumumab

Cost of Cetuximab in Metastatic Colon Cancer (Unselected Patients)

- **Single Agent**
  - The LYG ranged between 1.7 and 2.0 years. The median cost per patient treated was calculated to 34,256 Euro to 45,764 Euro yielding a cost per LYG in the range between 205,536 Euro and 323,040 Euro.

- **Combination with irinotecan**
  - “While it is difficult to suggest whether cetuximab represents value for money, indirect comparisons suggest that the incremental cost-utility of cetuximab plus irinotecan is unlikely to be better than pound 30,000 per QALY gained”
  - Incremental cost per life-year gained with cetuximab/irinotecan therapy compared with active/best supportive care was 42,975 pounds. The incremental cost per quality adjusted life-year gained was 57,608 pounds

Case: Controlling Costs

• YT is a 64-year-old man with metastatic colon cancer about to begin therapy with cetuximab. His tumor is EGFR positive and mutated for Kras. What do you suggest?
  – Start cetuximab as planned
    • Response rates range from 0-6%
  – Switch to panitumumab
    • Response rates range from 0-6%
  – Best supportive care

EGFR, Kras, and EGFR Inhibitors

• Mounting evidence suggests that EGFR expression and wild-type Kras predict better response to EGFR inhibitors
• Why do we continue to use these expensive drugs in unselected populations
  – Many patients have already exhausted all other therapeutic options
  – EGFR inhibitors less toxic than standard chemotherapy
Case: Preventing Drug Interactions

• LL is a 57-year-old postmenopausal woman with stage III breast cancer who was recently started on adjuvant tamoxifen. She comes to the clinic complaining of hot flashes and the oncology fellow gives her a prescription for fluoxetine.
  – What should you do?

Tamoxifen: Indications

<table>
<thead>
<tr>
<th>Indications</th>
<th>Year of Approval</th>
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</thead>
<tbody>
<tr>
<td>Metastatic breast cancer (postmenopausal)</td>
<td>1977</td>
</tr>
<tr>
<td>Adjuvant breast cancer (postmenopausal node +)</td>
<td>1986</td>
</tr>
<tr>
<td>Metastatic breast cancer (premenopausal)</td>
<td>1989</td>
</tr>
<tr>
<td>Adjuvant breast cancer (postmenopausal node -)</td>
<td>1990</td>
</tr>
<tr>
<td>Metastatic breast cancer (male)</td>
<td>1993</td>
</tr>
<tr>
<td>Reduction in breast cancer incidence</td>
<td>1998</td>
</tr>
<tr>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>2000</td>
</tr>
</tbody>
</table>
Tamoxifen

- 4-hydroxyTAM is more potent than tamoxifen as an estrogen antagonist
- Endoxifen has same potency and efficacy as 4-OH tamoxifen


CYP2D6 Polymorphism

<table>
<thead>
<tr>
<th>Allele</th>
<th>Enzyme Activity</th>
<th>Caucasian</th>
<th>African American</th>
<th>Japanese</th>
</tr>
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<tbody>
<tr>
<td>*2xn</td>
<td>Increased</td>
<td>1%-5%</td>
<td>0-2%</td>
<td>2%</td>
</tr>
<tr>
<td>*4</td>
<td>None</td>
<td>18%-23%</td>
<td>7%-9%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*5</td>
<td>None</td>
<td>2%-4%</td>
<td>6%-7%</td>
<td>5%-6%</td>
</tr>
<tr>
<td>*6</td>
<td>None</td>
<td>1%</td>
<td>&lt;1%</td>
<td>N/A</td>
</tr>
<tr>
<td>*10</td>
<td>Reduced</td>
<td>4%-8%</td>
<td>3%-8%</td>
<td>39%-41%</td>
</tr>
<tr>
<td>*17</td>
<td>Reduced</td>
<td>N/A</td>
<td>15%-26%</td>
<td>N/A</td>
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</tbody>
</table>

Background

Selective serotonin reuptake inhibitors (SSRIs)

- Antidepressants that are often prescribed to treat hot flashes in women who take tamoxifen
- Paroxetine, sertraline, citalopram, fluoxetine, and venlafaxine
- Inhibition of CYP2D6 by SSRIs likely to affect metabolism of tamoxifen

Study Design and Methods

- 80 women newly diagnosed with breast cancer
- Baseline blood sample taken
- Measured plasma concentrations of tamoxifen and its metabolites (after 1 and 4 months of therapy)
- Genotype analysis (CYP2C9, CYP3A5, SULT1A1, CYP2D6)
- Examined effects of CYP2D6 inhibitors on plasma endoxifen concentrations
- Examined association of SSRIs and plasma endoxifen concentration
Results

• Mean plasma concentrations of tamoxifen and its metabolites after 1 and 4 months of tamoxifen therapy

![Graph showing mean plasma concentrations of tamoxifen and its metabolites.](image)


Results (cont.)

• CYP2D6: no significant difference in plasma concentrations of tamoxifen, NDM or 4-OH between Wt/Wt & Wt/Vt or between Wt/Wt & Vt/Vt

![Graph showing significant difference in mean endoxifen plasma concentration.](image)

A significant difference in mean endoxifen plasma concentration was noted

Results

• Lower plasma concentration of endoxifen in patients taking CYP2D6 inhibitors

![Graph showing plasma concentration of endoxifen with and without inhibitors.]


Results

• Association between SSRIs and plasma endoxifen concentrations.

- **Venlafaxine** (weak inhibitor) seemed to have little effect on endoxifen concentration
- **Paroxetine** (strong inhibitor) seemed to have a large effect on endoxifen concentration

![Graph showing plasma concentrations of endoxifen with different SSRIs.]

Design

- Retrospective evaluation of a prospective adjuvant tamoxifen trial (NCCTG 89-30-52) in postmenopausal women with surgically resected ER-positive breast cancer (stages I–III) to determine the role of genetic variation in CYP2D6
- "Extensive" metabolizers were defined as patients without a CYP2D6*4 allele who were not prescribed a CYP2D6 inhibitor
- "Decreased" CYP2D6 metabolism was defined as patients with one or two *4 alleles, or the confirmation that a CYP2D6 inhibitor was coadministered with tamoxifen (regardless of genotype)

In a multivariate analysis, patients with "decreased" metabolism had significantly shorter time to recurrence ($P = .034; HR=1.91$) and worse RFS ($P = .017; HR=1.74$) relative to patients with "extensive" metabolism.

CYP2D6 Substrates

• 25% of all therapeutic drugs, 50 of the 100 best selling drugs

<table>
<thead>
<tr>
<th>Substrates of CYP2D6</th>
<th>Cardiac Drugs</th>
<th>Antidepressants</th>
<th>Antipsychotics</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>Alfentanil</td>
<td>Amitriptyline</td>
<td>Haloperidol</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Carvedilol</td>
<td>Clomipramine</td>
<td>Perphenazine</td>
<td>Codeine</td>
</tr>
<tr>
<td>S-Metoprolol</td>
<td>S-Metoprolol</td>
<td>Desipramine</td>
<td>Naproxen</td>
<td>Desfenfluramine</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Propranolol</td>
<td>Doxepin</td>
<td>Thioridazine</td>
<td>Metaxoxyamphetamine</td>
</tr>
<tr>
<td>Timolol</td>
<td>Timolol</td>
<td>Fluoxetine</td>
<td>Zuclopenthixol</td>
<td>Endoxin</td>
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<td>Metoprolol</td>
<td>Metoprolol</td>
<td>Fluconazole</td>
<td></td>
<td>Phenocetin</td>
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<td>Propranolol</td>
<td>Imipramine</td>
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<td>Phenformin</td>
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<tr>
<td>Nortriptyline</td>
<td>Nortriptyline</td>
<td>Maprotiline</td>
<td></td>
<td>Tamofoxen</td>
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<tr>
<td>Nortriptyline</td>
<td>Nortriptyline</td>
<td>Paroxetine</td>
<td></td>
<td>Tramilide</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paroxetine</td>
<td>Venlafaxine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Using Genetic Information to Predict Drug Metabolism: The AmpliChip CYP450

Depending on your own spelling of the CYP450 genes, you may need much higher or much lower doses of many different drugs to get the benefit.

Caraco Y. N Engl J Med, 2004;
Case: Preventing Drug Interactions

- LL is a 57-year-old postmenopausal woman with stage III breast cancer who was recently started on adjuvant tamoxifen. She comes to the clinic complaining of hot flashes and the oncology fellow gives her a prescription for fluoxetine.
  - What should you do?
    - Start fluoxetine as planned
    - Pick another SSRI with less CYP2D6 inhibition (sertraline)
    - Switch to an aromatase inhibitor