Personalized Medicine and Pharmacogenomics: Benefits and Possible Implications

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“All things are poison, only the dose permits something not to be poisonous”

...well that and inter-individual genetic variation, and polypharmacy, and comorbidity, and environment, and...
Case report: Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

Healthy 2-yo boy, underwent outpatient elective adenotonsillectomy; After surgery, instructions to take 10-12.5mg of codeine + 120 mg APAP q 4-6 hr prn; 2 days post surgery, child died
Autopsy results: Codeine (0.70 mg/L) & morphine (32 ng/ml) → toxic levels
CYP2D6 genotyping → 3 copies of CYP2D6 allele → ultrarapid-metabolizer phenotype

\[ \text{Ultrarapid metabolizers may metabolize codeine too efficiently leading to morphine intoxication} \]
Polymorphic drug metabolizing enzymes

Relative contribution of known variants

(Evans and Relling, Science 286: 487-91, 1999)
What are the Reasons a New Compound Doesn’t Get FDA Approval?
Four Main Reasons the Development of a Drug Is Halted

• Lack of Efficacy
• Side Effects
• Pharmacokinetics
• Pharmacogenetic Profile
34 FDA approved Agents have been Removed from the Market since 1990

• Annual economic value at the time of removal - $31 billion
34 FDA approved Agents have been Removed from the Market since 1990

• Annual economic value at the time of removal - $31 billion

• Twenty of these might have been saved or not developed if we had fully understood the pharmacogenetics
Responders and patients not experiencing severe toxicity

All patients with same diagnosis

Non-responders and toxic responders

Responders and patients not experiencing severe toxicity
Pharmacogenomics and FDA

“Pharmacogenomics holds great promise to shed scientific light on the often risky and costly process of drug development, and to provide greater confidence about the risks and benefits of drugs in specific populations. Pharmacogenomics is a new field, but we intend to do all we can to use it to promote the development of medicines.”

Mark McClellan, M.D
FDA Commissioner  Nov, 2003
Introduction - Pharmacogenetics

- Genetic polymorphisms in proteins involved in drug metabolism or transport might be of clinical relevance.

- Variation in genes encoding for drug target proteins (e.g., receptors) may result in differences in efficacy.

- The most commonly observed variants are single-nucleotide polymorphisms (SNPs; i.e., a variant with a population frequency of >1%).

- SNPs are responsible for >90% of all genetic variation in the human genome.

- Goal of pharmacogenetics is to aid in individualized treatment with drugs.
Introduction - Pharmacogenetics

Remember – this is germline DNA, not somatic mutations
Drug Exposure-Effect Relationship

Diagnosis: Drug & Dose are Selected

Absorption
Distribution
Metabolism
Elimination

Pharmacokinetics (PK)
(Drug Disposition)

Genetic variation

Pharmacodynamics (PD)
(Drug Effects)

Target Organ/Tissue Effect:
Toxicity
Efficacy
Biological Effect
Sources of Pharmacokinetic and Pharmacodynamic Variability

**Morphometric:**
- Body Size
- Body Composition

**Drug Specific:**
- Dose & Schedule
- Dosage form

**Demographic:**
- Age
- Race/Ethnicity
- Sex

**Physiologic:**
- Disease
- Hepatic Function
- Renal Function

**Genetics:**

**Environment:**
- Drug-drug interactions
- Drug-CAM interactions
- Drug-formulation interactions
- Drug-food constituent interactions
Pharmacogenomics and Oncology

Pharmacogenomic Strategies Most Relevant When:

- Narrow therapeutic indices
- High degree of inter-individual variability in response
- Little or no available methods to monitor safety or efficacy
- Few alternative treatment options

Flowers and Veenstra 2004
Pharmacogenomics and Oncology

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Anticancer agents meet all of these criteria

Flowers and Veenstra 2004
Molecular Targeted Agents: The same old Therapeutic Window concept Still Applies!

- Regimen B
- Regimen A
- Regimen C

Therapeutic failure

therapeutic success

therapeutic failure

Plasma concentration

Time after drug administration

toxic responders

therapeutic window

non-responders
Pharmacogenetics

Implications of polymorphisms on Pharmacokinetics

- Drug Absorption
- Drug Metabolism
- Drug Elimination
- Drug Distribution
- Drug Activation
Pharmacogenetics

Implications of polymorphisms on Pharmacokinetics

• Drug Absorption
• Drug Metabolism
• Drug Elimination
• Drug Distribution
• Drug Activation

Implications of polymorphisms on Drug Effect (Response and Toxicity)

• Receptors
• Target Proteins
• Resistant
• Toxicity
Genotyping Strategies in Medical Oncology

Example of anticancer drug metabolism by polymorphic enzymes

<table>
<thead>
<tr>
<th>Drug</th>
<th>pathway</th>
<th>variability in CL</th>
</tr>
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<tbody>
<tr>
<td>Amonafide</td>
<td>N-acetyl transferase (NAT)</td>
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</tr>
<tr>
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<td>Glutathione S-transferase (GST)</td>
<td>10-fold</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Cytochrome P-450 (CYP) 3A4 and 3A5</td>
<td>4 to 9-fold</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Dihydropyrimidine dehydrogenase (DPD)</td>
<td>10-fold</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UDP glucuronosyltransferase (UGT)</td>
<td>50-fold</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Thiopurine methyltransferase (TPMT)</td>
<td>&gt;30-fold</td>
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Evans and Relling, Science 286: 487-91, 1999
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6-MP is administered to children with acute lymphoblastic leukemia (ALL), while related compounds (6-thioguanine and azathioprine) are also administered to individuals with ALL, inflammatory bowel disease, and autoimmune disorders.

MP drugs incorporate cytotoxic thioguanine nucleotides into DNA as their primary mechanism of action. May also inhibit de novo purine synthesis.
TPMT and 6-Mercaptopurine

- TPMT is expressed in heart, blood cells, pancreas, and intestine.
- TPMT methylates mercaptopurine drugs, thus inactivating them.
- Metabolism of MP drugs is decreased with polymorphic TPMT variation up to 200-fold.
- Rapid metabolizers require higher dosing.
- Slow metabolizers are at high risk for developing fatal neutropenia and require 7-15% of the normal dose of 6-MP due to accumulation of excessive thioguanine nucleotides in hematopoietic cells. Also risk secondary malignancies (i.e. brain tumors, and AML).
TPMT and 6-Mercaptopurine

- **Rapid metabolizers** ("wild-type" individuals) - require highest doses for efficacy (~ 80-98% of the population)

- **Intermediate metabolizers** (carry one copy of TPMT*2A, *3A, *3C) - require ~65% of normal dose, but have highest cure rate (~ 2-20% of the population)

- **Slow metabolizers** (carry two copies of TPMT*2A, *3A, *3C) - require 7-15% of original dose, and are at risk for secondary malignancies (~0.01 - 1% of the population)

Genetic variation in TPMT explains 95% of phenotype
Pharmacogenetics

Implications of polymorphisms on Pharmacokinetics

• Drug Absorption
• Drug Metabolism
• Drug Elimination
• Drug Distribution
• Drug Activation

Implications of polymorphisms on Drug Effect

• Receptors (somatic)
• Target Proteins
• Resistant
• Toxicity
IGF and EGF Signaling Pathways

IGF and EGF bind to their respective receptors (IGFR and EGFR) which lead to the activation of downstream signaling molecules such as IRS, p85, P110 PI3K, Shc, Ras, Akt, and MAPK. These pathways regulate cell proliferation, angiogenesis, and invasion/metastasis.

Cell proliferation
Angiogenesis
Invasion/metastasis
Response to Gefitinib (Iressa®)

- Somatic mutations identified in the tyrosine kinase domain of the EGFR gene in 8 of 9 patients with lung cancer responding to gefitinib

- No somatic mutations were identified in 7 patients not responding to gefitinib

Lynch et al. NEJM 2004; 350:2129
Tumors with a Major Clinical Response to EGFR Inhibitors

- ~10%–20% of tumors have a major response (dramatic shrinkage) to EGFR inhibitor
- Majority of responders have mutations in EGFR tyrosine kinase domain (exon 19 deletion, point mutation)
- Mutation led to constitutive activation of EGFR and increased sensitivity to EGFR inhibition
- Amplification of EGFR may also increase sensitivity
- Never smokers and patients of Asian origin had a high frequency of EGFR mutations

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ABCG2 (BCRP, ATP-binding cassette)

- Involved in intrinsic or acquired multidrug resistance (MDR) phenotype of tumor cells

- \textit{ABCG2} encodes a half transporter

- Located on chromosome 4q-22

- 66 kb; 16 exons; 15 introns

- 69 Known genetic polymorphisms including 65 SNPs; 13 SNPs in exons; 7 SNPs cause amino acid substitutions
## ABCG2 421 C>A Genotype Frequencies

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>WT</th>
<th>C/A</th>
<th>A/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Caucasian</td>
<td>88</td>
<td>68 (77)</td>
<td>19 (22)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>European Caucasian</td>
<td>84</td>
<td>68 (81)</td>
<td>14 (17)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>African American</td>
<td>94</td>
<td>85 (90)</td>
<td>8 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>African (sub-Sahara)</td>
<td>938</td>
<td>923 (98.4)</td>
<td>14 (1.5)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Han Chinese</td>
<td>95</td>
<td>41 (43)</td>
<td>43 (45)</td>
<td>11 (12)</td>
</tr>
</tbody>
</table>

*Clin Can Res 2004 Sep 1;10(17):5889-94*
Race is a social identification, and doesn’t correspond to genetic differences (esp as it relates to pharmacogenetics). Furthermore, populations within the US are rather difficult to define by categories because of admixture.
Efficacy of Imatinib in Chronic Myelogenous Leukemia (CML)

(Druker et al, NEJM 2001)

• Imatinib inhibits BCR-ABL

• Of 54 patients treated with imatinib who had failed interferon-alpha (300 mg or higher bid), 53 complete hematological responses
Imatinib $C_{ss,\text{min}}$ is highly variable in CML

351 patients receiving 400 mg daily on IRIS study

26-fold variation

Higher Imatinib Concentrations are associated with adverse events*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Q1 (N=87)</th>
<th>Q2 &amp; Q3 (N=179)</th>
<th>Q4 (N=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention</td>
<td>53 (2.3)</td>
<td>62 (3.4)</td>
<td>76 (3.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>32 (3.4)</td>
<td>39 (2.2)</td>
<td>51 (1.2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>20 (0)</td>
<td>25 (2.2)</td>
<td>30 (1.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8.0 (0)</td>
<td>12 (2.4)</td>
<td>20 (7.0)</td>
</tr>
</tbody>
</table>

*data are % of toxicity in the Q (% of grade 3/4 toxicity in the Q); significant association with adverse events within 3 months and 5 years (shown)
Selection of Appropriate Genes

- **Imatinib**
  - ABCB1
  - ABCG2
  - ABCC3*
  - ABCC4**

- **CGP71422** (urine only)
  - CYP3A4
  - CYP3A5
  - CYP2D6

- **CGP74588**
  - CYP3A4
  - CYP1A1

- **Unknown metabolites**

* identified as one of the genes with expression features unique to imatinib relapers in CML (Radich et al, *PNAS* 2006); ** S Hu et al, *CCR* 2008
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CYP2D6 and Tamoxifen

CYP2D6 catalyzes the formation of the major active metabolite of tamoxifen - endoxifin

30-100 fold more active than TAM (low plasma conc.)

30-100 fold more active than TAM (higher plasma conc.)
CYP2D6 and Tamoxifen

CYP2D6 is highly polymorphic

Combinations of multiple SNPs in haplotypes, and knowing the diplotype allows for more effective prediction

This table arranges the SNPs from slow metabolizers (top) to rapid metabolizers (bottom)
Genotype vs. Endoxifen Conc

* No CYP2D6 inhibitors
Sure, but ~12% of the population doesn’t make sufficient endoxifen to have efficacy (PMs), and ~40% of the tamoxifen population (EMs) may benefit MUCH more from tamoxifen than anatrozole.
Strategies to Dose Warfarin based on Genotype

• From package insert:

“Identification of risk factors for bleeding and certain genetic variations in CYP2C9 and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses.”

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>Wild-type</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>Variant</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

†Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.
One ultimate goal of pharmacogenetics is to provide a patient with individualized therapy ("getting the dose right")

Using candidate gene approach - It will be virtually impossible to assign a patient to an unequivocal phenotype and especially to an unequivocal genotype
Current Genotyping Platforms
Current Genotyping Platforms
DMET Genotyping Platform

1936 variants (actual causative variants) in 235 PK/PD genes.
Useful for haplotype determination.
Captures the vast majority of SNPs involved in PK/PD.

<table>
<thead>
<tr>
<th>Phase I Enzymes</th>
<th>Phase II Enzymes</th>
<th>Transporters</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>CYP4F2</td>
<td>MAOB</td>
<td>ABCB1</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>CYP4F3</td>
<td>ABCB4</td>
<td>SLC16A1</td>
</tr>
<tr>
<td>CYP1B1</td>
<td>CYP4F8</td>
<td>SLC19A1</td>
<td>AHR</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>CYP4F11</td>
<td>SLC22A1</td>
<td>ALB</td>
</tr>
<tr>
<td>CYP2A7</td>
<td>CYP4F12</td>
<td>SLC22A11</td>
<td>ARNT</td>
</tr>
<tr>
<td>CYP2A13</td>
<td>CYP4Z1</td>
<td>SLC22A12</td>
<td>PON2</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>CYP7A1</td>
<td>SLC22A14</td>
<td>ARSA</td>
</tr>
<tr>
<td>CYP2B7</td>
<td>CYP7B1</td>
<td>SLC22A2</td>
<td>CBR1</td>
</tr>
<tr>
<td>CYP2B7P1</td>
<td>CYP8B1</td>
<td>SLC22A3</td>
<td>CBR3</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>CYP11A1</td>
<td>SLC22A4</td>
<td>CDA</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>CYP11B1</td>
<td>SLC22A5</td>
<td>CDA</td>
</tr>
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<td>CYP2C18</td>
<td>CYP11B2</td>
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<td>CROT</td>
</tr>
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<td>CYP2C19</td>
<td>CYP17A1</td>
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<td>CROT</td>
</tr>
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<td>CYP2D6</td>
<td>CYP19A1</td>
<td>SLC22A8</td>
<td>CROT</td>
</tr>
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<td>CYP2E1</td>
<td>CYP20A1</td>
<td>SLC28A1</td>
<td>EPXH2</td>
</tr>
<tr>
<td>CYP2F1</td>
<td>CYP21A2</td>
<td>SLC28A2</td>
<td>FAAH</td>
</tr>
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<td>CYP2J2</td>
<td>CYP24A1</td>
<td>SLC28A3</td>
<td>G6PD</td>
</tr>
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<td>CYP2S1</td>
<td>CYP26A1</td>
<td>SLC28A4</td>
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</tr>
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<td>CYP3A4</td>
<td>CYP27A1</td>
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</tr>
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<td>HMGCR</td>
</tr>
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<td>CYP46A1</td>
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<td>MAT1A</td>
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Deeken (Figg) et al. (2009) Pharmacogenomics J; [epub ahead of print]
Where is Pharmacogenetics Going?
Where is Pharmacogenetics Going?

I can envision a day in which an infant is genotyped with a PG chip, from that day forward that information can aid in all prescriptions that individual receives.
How much would you pay to know this information for your child or grandchild?
Barriers to Pharmacogenomics Progress

- Complexity of finding gene variation that affect drug outcome
- Limited drug alternatives for patients with gene variations that prevent them from using certain drugs
- Disincentives for pharmaceutical companies
- Educating healthcare providers
- Concerns about how personal genetic information would be stored and who would have access to this information
Difficulty Moving from Research to Routine Clinical Practice

Prospective validated data showing a clinical benefit for using PG data in patient care is needed.

A cost savings data is needed – decrease hospitalization due to side effects or data showing prolong survival associated with PG testing.
Difficulty Moving from Research to Routine Clinical Practice

The largest expense won’t be the genotyping, but the bioinformatics to handle the data…

Where will the data be housed? Who has access?

The data needs to be accessible for all future physicians who are prescribing a drug to an individual patient that has been genotyped

The system needs to quickly determine if a drug is a problem for an individual patient
What about Truly Personalized Medicine?
PROVENGE (sipuleucel-T) Production and Delivery

Day 1
Leukapheresis
The patient gets standard blood collection where white blood cells are extracted for treatment.

Day 2–3
PROVENGE (SIPULEUCEL-T) is manufactured
The patient’s peripheral blood mononuclear cells (PMBCs) are separated from other white blood cells using proprietary technology.

Day 3–4
Patient in infused
The physician administers the patient’s PROVENGE intravenously.

Complete course of therapy: 3 cycles
Study D9902B: Overall Survival
Additional Analysis (349 events)

HR = 0.759 (95% CI: 0.606, 0.951)
p = 0.017 (Cox model)
Median Survival Benefit = 4.1 months

---

**Sipuleucel-T (n = 341)**
Median Survival: 25.8 mo.
36 mo. survival: 32.1%

**Control (n = 171)**
Median Survival: 21.7 mo.
36 mo. survival: 23.0%

---

<table>
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<tr>
<th>Time from Randomization (months)</th>
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<th>Control</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>341</td>
<td>171</td>
</tr>
<tr>
<td>12</td>
<td>274</td>
<td>123</td>
</tr>
<tr>
<td>24</td>
<td>142</td>
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<td>36</td>
<td>56</td>
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<td>48</td>
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<td>5</td>
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<td>60</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>72</td>
<td>3</td>
<td>2</td>
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Kantoff, ASCO-GU March 2010
Questions Related to Implications on Publication Activity

• What will be the impact on pharmaceutical research?
• Are there any lessons learned to date about the challenges of performing pharmacogenomics research?
• Will journals need more specialized editors to review such research?
• Will medical writers require additional background to understand and optimally support authors in manuscript assistance?
Conclusion

- Pharmacogenetics hold tremendous promising in guiding clinical care, as well as drug development
- Difficult to predict pharmacogenetics based on simply on race
- The PG chip appears to provide important data in the understanding of pharmacogenetics
- The potential for the PG chip goes beyond drug development, to altering the patient care paradigm
Personalized Medicine and Pharmacogenomics: Benefits and Possible Implications