Integrating Pharmacogenomics into Decision Making

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Definitions

Pharmacogenetics
(after Vogel, 1957)

The study of variations in DNA sequence as related to drug response

Pharmacogenomics
(after Marshall, 1997)

The study of variations of DNA and RNA characteristics as related to drug response

ICH Topic E15, November 2007

PGx is a part of the drive towards precision medicine
Regulatory Decision Making

Benefit | Risk
---|---
Based on population data

Benefit | Risk
---|---
Based on individual/small group data

Moving closer to what happens in the clinic
15% of EMA evaluated medicines containing PGx information

- Therapeutic indication (3.5%)
- Posology and method of administration (4.4%)
- Contraindications (6.4%)

Number of PGx biomarkers increasing
## EMA SmPCs With Mandatory Genomic Testing

**The Pharmacogenomics Journal (2015), 1–10**

<table>
<thead>
<tr>
<th>Name</th>
<th>INN</th>
<th>Year of approval</th>
<th>PGx biomarker</th>
<th>Indication</th>
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<td>Hypereosinophilic syndrome</td>
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<td>Vemurafenib</td>
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<td>Dabrafenib</td>
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<td>Adcetris</td>
<td>Brentuximab vedotin</td>
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<td>Ivacaftor</td>
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<td>Arsenic trioxide</td>
<td>2002</td>
<td>PML-RARα t (15;17)</td>
<td>Acute promyelocytic leukaemia</td>
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</tbody>
</table>

*Only 3 drugs outside the cancer area*
Comparing cytochrome P450 pharmacogenetic information available on United States drug labels and European Union Summaries of Product Characteristics

J Reis-Pardal¹, A Rodrigues², E Rodrigues³ and F Fernandez-Llimos⁴

The Pharmacogenomics Journal (2016), 1–6

US labels:

- Presented more PGx subheadings (51 vs 26%)
- More prevalence and PK data for each phenotype
- More information about dose modification
- Need for more harmonization

75% of US labels scored higher
Clinical Evidence Supporting Pharmacogenomic Biomarker Testing Provided in US Food and Drug Administration Drug Labels

Bo Wang, PharmD; William J. Canestaro, MSc; Niteesh K. Choudhry, MD, PhD

119 drug-biomarker combinations
- 43 (36.1%) had convincing clinical validity evidence
- 18 (15.1%) evidence of clinical utility
- 61 labels (51.3%) – clinical decisions based on results of biomarker test: 36 (30%) contained convincing clinical utility data

“It may be premature to include biomarker testing recommendations in drug labels when convincing data that link testing to patient outcomes do not exist.”
Drug Development and Companion Diagnostics

- Co-development of targeted drug with a companion diagnostic
- Usually evidence based on randomised controlled trials and reflected in the label
- Guidance available from EMA and FDA

**Looking to the future:**
- With single biomarkers, tests from multiple providers can pose issues in terms of analytic validity
- We may be moving from single biomarkers to biomarker panels or ultimately to next generation sequencing
- Regulation of such multiple biomarker panels will be challenging – single provider, multiple providers etc?
- Debate on how to regulate next generation sequencing.
New Cystic Fibrosis Drug Offers Hope, at a Price

- New CF drug, ivacaftor
- Targets G551D mutation in the CFTR gene (4% of CF population)
- Fantastic innovation with increases in FEV1 ~10%

- 200 scientists
- 600,000 compounds screened
- In silico screening of 2.7 million compounds
- 3 possible candidates

Indication expanded in 2014:
**CFTR defect type:**

- **I:** No protein
- **II:** No traffic
- **III:** No function
- **IV:** Less function
- **V:** Less protein
- **VI:** Less stable

**Mutation examples:**
- G542X (a)
- F508del
- N1303K
- S549R
- R117H
- A455E
- A455E 3272-26A>G
- 3849+10 kb C>T
- c.120del23
- rF508del

**Corrective therapy:**
- Rescue synthesis
- Rescue traffic
- Restore channel activity
- Correct splicing
- Promote stability

**Drug:**
- Read-through compounds
- Correctors
- Potentiators
- AONs
- Correctors
- Potentiators
- Stabilizers
The Evidence Hierarchy

- RCTs are top of the hierarchy
- Challenges:
  - Smaller populations
  - Multiple mutations
  - Cost
  - Existing drugs
Novel trial designs – acceptability for registration

Umbrella trial – investigation of single tumour type but stratification by different mutations linked to specific candidate drugs

Basket study – in multiple tumour types but with a focus on one or few biomarkers
# Associations of Serious Adverse Drug Reactions with HLA Alleles

<table>
<thead>
<tr>
<th>HLA Alleles</th>
<th>Associated Drugs</th>
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<tbody>
<tr>
<td>A*31:01</td>
<td>Carbamazepine</td>
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<tr>
<td>A*33:03</td>
<td>Ticlopidine</td>
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<tr>
<td>A*68:01</td>
<td>Lamotrigine</td>
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<tr>
<td>A*02:06</td>
<td>Cold medicines</td>
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<td>B*13:01</td>
<td>Dapsone</td>
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<td>B*15:02</td>
<td>Carbamazepine</td>
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<td>B*35:05</td>
<td>Nevirapine</td>
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<td>B*44:03</td>
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<td>B*58:01</td>
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<td>C*04:01</td>
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<td>DRB1*11:01</td>
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<td>DRB1*13:02</td>
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<td>DQB1*05:02</td>
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<tr>
<td>DQB1*06:09</td>
<td>Aspirin</td>
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</tbody>
</table>
Carbamazepine Hypersensitivity

- More complicated than abacavir hypersensitivity
- Different phenotypes
  - Skin (mild → blistering)
  - Liver
  - Systemic (DRESS)
- Predisposition varies with ethnicity and phenotype
  - HLA-B*1502 (Chinese)
  - HLA-A*3101 (Caucasian)
HLA Genotype and Carbamazepine-Induced Cutaneous Adverse Drug Reactions: A Systematic Review

VL Yip\textsuperscript{1}, AG Marson\textsuperscript{2}, AL Jorgensen\textsuperscript{3}, M Pirmohamed\textsuperscript{1} and A Alfirevic\textsuperscript{1}

HLA-B*1502
Replicated in Japanese, Chinese, South Korean, Canadian and EU populations

- NNT = 47
- SmPC/drug label changed (for information). NOT MANDATORY
Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy

*Catrin O. Plumpton, †Vincent L. M. Yip, †Ana Alfirevic, †Anthony G. Marson, †Munir Pirmohamed, and *Dyfrig A. Hughes

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Graph showing the probability of cost-effectiveness against cost-effectiveness threshold (£ / QALY) for 'Test' and 'No-Test' scenarios.

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Epilepsia 2015
Treating Patients with Renal Impairment

- Degree of dose reduction based on PK (occasionally with PD) modelling
- RCTs not usually done
- Accepted as standard practice by clinicians
- Implementation helped by ready availability of renal function tests

- Genetic polymorphism with the same effect size usually not acted upon
- Lack of availability of tests may be one factor
• €15 million, H2020, 10 EU countries
• Implement pre-emptive PGx testing in a real world clinical setting across 7 EU sites
• Evaluate patient outcome and cost effectiveness using solid scientific methodology
• Start 1-1-2016, 5 years
• Consortium members:
  - H-J Guchelaar (Coordinator), JJ Swen, M Kriek, LUMC
  - M Pirmohamed, R Turner, UOL
  - J Stingl, FDMD
  - M Ingelman-Sundberg, KI
  - M Karlsson, S Jönsson, PBUU
  - M Schwab, E Schaeffeler, IKP
  - VHM Deneer STZHM
  - M Samwald, G Sunder-Plassmann, MUWV
  - M van Rhenen, KC Cheung, KNMP
  - C Mitropoulou, GHXF
  - D Steinberger, BIOL
  - CL Davila Fajardo, SAS
  - G Patrinos, UPAT
  - V Dolžan, ULMF
  - A Cambon-Thomsen, UPS
  - G Toffoli, E Cecchin, CROA
Project Outline

N=8,000

Process Indicators Implementation

Cost-effectiveness

Patient Benefit

A next step into the future

- Next Generation Sequencing
- Drug - Drug Interactions
- Systems Pharmacology

Enabling Tools

- ICT Tools
- PGx infrastructure
- DPWG guidelines
- Training and Education

Dissemination, Communication, ELSI

Data Analysis + A next step into the future
100,000 Genomes Project in England

- A transformational project for the NHS to embed genomic medicine into practice
- 100,000 genomes from 70,000 individuals
- Accompanied by Genomics England Clinical Interpretation Partnerships (to undertake research) - GeCIP
- Pharmacogenomics sub-domain GeCIP to explore issues related to PGx variants
The Only Thing That Is Constant Is Change

Heraclitus (535BC - 475BC)