Practical recommendations for pharmacogenomics-based prescription: 2010 ESF–UB Conference on Pharmacogenetics and Pharmacogenomics

The present article summarizes the discussions of the 3rd European Science Foundation–University of Barcelona (ESF–UB) Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics, which was held in June 2010 in Spain. It was focused on practical applications in routine medical practice. We provide practical recommendations for ten different clinical situations, that have either been approved or not approved by regulatory agencies. We propose some comments that might accompany the results of these tests, indicating the best drug and doses to be prescribed. The discussed examples include K/RAS, cetuximab, panitumumab, E/FR–gefitinib, CYP2D6–tamoxifen, TPMT–azathioprine–6-mercaptopurine, VKORC1/CYP2C9–warfarin, CYP2C19–clopidogrel, HLA-B*5701–abacavir, HLA-B*5701–flucloxacillin, SLC01B1–statins and CYP3A5–tacrolimus. We hope that these practical recommendations will help physicians, biologists, scientists and other healthcare professionals to prescribe, perform and interpret these genetic tests.

KEYWORDS: adverse drug reaction azathioprine cetuximab clopidogrel gefitinib genetic testing pharmacogenetics statins tacrolimus tamoxifen

Oncology drugs
A full day was dedicated to oncology covering germline as well as tumor pharmacogenomics. Three major examples were discussed.

■ Response to tyrosine kinase inhibitors owing to activating EGFR mutations in non-small-cell lung cancer
Miguel A Molina from Instituto Universitario USP Dexeus, Barcelona, presented the results of a national survey indicating the usefulness of tumor EGFR pharmacogenomics in order to define tumors that will respond (owing to activating mutations) to EGFR receptor (EGFR) antagonists (tyrosine kinase inhibitors) [1]. Additional recent publications have confirmed the usefulness of EGFR pharmacogenomics in non-small-cell lung cancer (NSCLC) [2,3]. Tumor samples can be obtained from tumor biopsies, possibly followed by laser microdissection – or circulating blood tumor cells. Activating mutations are observed in 15% of...
Caucasians [1] and 60% of Asians [3]. They are mainly located in exon 19 and 21 of EGFR; the two most frequent mutations are deletions in exon 19 and L858R [2–4]. The T790M mutation which confers acquired resistance to gefitinib or erlotinib [5] is already present in a small subpopulation of tumor cells before treatment initialization. Mutations can be analyzed by direct sequencing, fragment analysis or allelic discrimination, but more sensitive assays are needed to detect the T790M in pretreatment samples or if EGFR mutations are to be tested in blood. One of these assays involves the use of a protein nucleic acid clamp, designed to inhibit the amplification of the wild-type allele. This and other techniques can improve the sensitivity and specificity [2,5] up to 97 and 100%, respectively [2].

The presence of an EGFR activating mutation in advanced stages of NSCLC treated with gefitinib or erlotinib increases the median survival from 10 up to 27 months [1]. In the absence of such EGFR activating mutations, gefitinib therapy is not superior to conventional chemotherapy (see Box 1). The presence of the T790M resistance mutation at presentation, together with an EGFR activating mutation, predicts a shorter time to progression of the disease. Whereas the absence of EGFR activating mutations is clearly associated with a nonresponse to gefitinib, it has been described that patients without EGFR activating mutations seem to have a slightly better outcome with erlotinib compared with a placebo group [6]. Clinical trials are needed to confirm that chemotherapy is also preferable to erlotinib in the absence of EGFR activating mutations.

### Resistance to cetuximab owing to KRAS mutations in metastatic colon carcinoma

Pierre Laurent-Puig from Paris Descartes University, Paris, presented a review on KRAS tumor mutations, which confer resistance to monoclonal antibodies raised against EGFR in metastatic colon cancer [7,8]. Several independent teams confirmed the relationship between colon cancer KRAS mutations and resistance to cetuximab and panitumumab [9–11]. KRAS is a component of the EGF signaling pathway. Its activating mutations cause RAS to accumulate in the active GTP-bound state by impairing intrinsic GTPase activity and conferring resistance to GTPase-activating proteins. If a KRAS activating mutation occurs in the tumor, blocking EGFR at the membrane becomes useless [8]. These activating mutations are observed in approximately 40% of colon tumors. They mainly occur in exon 2 at amino acid residues G12 and G13 [9–11]. The response rate to anti-EGFR monoclonal antibodies seems to be null in the presence of a KRAS activating mutation and approximately 40% in KRAS wild-type tumors. The European Medicines Agency (EMA) has introduced a mandatory pharmacogenetic/pharmacogenomic label for these EGFR antibodies indicating that tumors with KRAS mutations should not be treated with...

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**Box 1. EGFR pharmacogenomics in non-small-cell lung cancer.**

**Indication**  
- Advanced or metastatic NSCLC, first- or second-line therapy  
- Detect the poor responders to gefitinib

**Regulatory status of the PG test**  
- EMA  
  - Mandatory for gefitinib, proposed for erlotinib  
- US FDA  
  - None

**Material**  
- Lung tumor (or circulating tumor cells from serum or plasma)

**Mutations to be detected**  
- Activating tumor EGFR mutations: mainly deletions in exon 19 and L858R  
- Resistance tumor mutation: T790M

**Interpretation of the results**  
- Presence of EGFR activating mutations = response to gefitinib and erlotinib  
- Absence of EGFR activating mutations = nonresponse to gefitinib (do not prescribe the drug) and insufficient data for erlotinib  
- Presence of EGFR T790M mutation at presentation = shorter time to progression to gefitinib or erlotinib  
- Presence of EGFR T790M mutation (progression) = resistance to gefitinib or erlotinib

this drug (see Box 2). Additional tumor pharmacogenetic/pharmacogenomic targets (EGFR amplification, BRAF, PTEN and PIK3CA) might be interesting in the future but validation studies are needed before introducing such tests into routine medical practice.

CYP2D6 & resistance to tamoxifen in early breast cancer

Hiltrud Brauch from Dr Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, made a contribution in the field of tamoxifen pharmacogenetics. Tamoxifen (in addition to aromatase inhibitors) is a treatment option for estrogen receptor positive breast cancer in postmenopausal patients. Tamoxifen is the standard of care for estrogen receptor positive premenopausal and male breast cancer. Postmenopausal patients with two loss of function alleles of CYP2D6, an enzyme that bioactivates the prodrug, have a poor response to tamoxifen compared with women with the wild-type CYP2D6 genotype [12,13]. This relationship has been demonstrated for the first time in a sufficiently powered study of patients treated with tamoxifen monotherapy [13]. The data strongly support other studies from independent groups [14–16], and there is now solid evidence that comprehensive coverage of CYP2D6 variant alleles increases the likelihood to detect the risk for disease recurrence. These studies provide an excellent basis for the application of a CYP2D6 pharmacogenetic/pharmacogenomic test towards individualized endocrine treatment of postmenopausal early breast cancer.

Tamoxifen is a prodrug that is bioactivated into the active metabolite endoxifen that inhibits estrogen receptors [17]. CYP2D6 activity is genetically determined, with the 8% of the occidental population having no CYP2D6 activity or expression (presence of two non-function alleles called poor metabolizers). Approximately 50% of the Occidental population has a decreased CYP2D6 activity defined by the presence of at least one loss-of-function allele or at least one decreased function allele (see Box 3, [18,102]). In cases with absent or decreased CYP2D6 activity, tamoxifen bioactivation is

<table>
<thead>
<tr>
<th>Box 3. CYP2D6–tamoxifen pharmacogenomics in postmenopausal early breast cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>• Postmenopausal breast cancer positive for estrogen receptors</td>
</tr>
<tr>
<td>• Detect potential poor outcome of tamoxifen</td>
</tr>
<tr>
<td><strong>Regulatory status of the PG test</strong></td>
</tr>
<tr>
<td>• EMA</td>
</tr>
<tr>
<td>– None</td>
</tr>
<tr>
<td>• US FDA</td>
</tr>
<tr>
<td>– None</td>
</tr>
<tr>
<td><strong>Material</strong></td>
</tr>
<tr>
<td>• Blood or saliva sample</td>
</tr>
<tr>
<td><strong>SNPs or deletion to be detected</strong></td>
</tr>
<tr>
<td>• Main CYP2D6 loss-of-function alleles: CYP2D6<em>3 (rs35742686); CYP2D6</em>4 (rs3892097); CYP2D6<em>5 (gene deletion); CYP2D6</em>6 (rs5030655); CYP2D6*7 (rs5030867)</td>
</tr>
<tr>
<td>• Main CYP2D6 decreased function alleles: CYP2D6<em>10 (rs1065852); CYP2D6</em>41 (rs28371725); CYP2D6*9 (rs5030656)</td>
</tr>
<tr>
<td><strong>Interpretation of the results</strong></td>
</tr>
<tr>
<td>• Postmenopausal women</td>
</tr>
<tr>
<td>• Carriers with at least one decreased function allele, or carriers with at least one loss-of-function allele are at risk for decreased response to tamoxifen; do not prescribe the drug, choose an aromatase inhibitor</td>
</tr>
<tr>
<td>• Carriers of two functional alleles including gene duplication are likely to respond to tamoxifen</td>
</tr>
<tr>
<td>• Premenopausal women: no data available</td>
</tr>
<tr>
<td>• Male breast cancer: no data available</td>
</tr>
</tbody>
</table>

EMA: European Medicines Agency; PG: Pharmacogenetic/pharmacogenomic.
significantly reduced and the clinical response is markedly decreased in poor metabolizers and less decreased in intermediate metabolizers. As a consequence, postmenopausal women with an estrogen receptor positive breast tumor and decreased or absent $CYP2D6$ activity should be treated with aromatase inhibitors instead of tamoxifen.

**Box 4. TPMT–azathioprine and 6-mercaptopurine pharmacogenomics.**

<table>
<thead>
<tr>
<th>Indication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's disease before the introduction of AZA or 6-MP</td>
<td></td>
</tr>
<tr>
<td>Prevention of hematological toxicity of AZA and 6-MP</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory status of the PG test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>None</td>
</tr>
<tr>
<td>US FDA</td>
<td>Recommended ($TPMT$ genotyping or phenotyping)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood or saliva sample</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNPs to be detected</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$rs1800462$, c.238G&gt;C, Pro80Ala ($TPMT^*$2)</td>
<td></td>
</tr>
<tr>
<td>$rs1142345$, c.719A&gt;G, Tyr240Cys ($TPMT^<em>$3C) $rs1800460$, c.460G&gt;A, Ala154Thr ($TPMT^</em>$3B)</td>
<td></td>
</tr>
<tr>
<td>$TPMT^*$3A combines $rs1142345$ and $rs1800460$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interpretation of the results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of two loss-of-function alleles</td>
<td></td>
</tr>
<tr>
<td>High risk of AZA or 6-MP hematological toxicity in the first weeks of drug intake using recommended standard dosages</td>
<td></td>
</tr>
<tr>
<td>Dependent on disease entity, the use of alternative drugs should be considered (e.g., inflammatory bowel disease: anti-TNF monoclonal antibody or methotrexate)</td>
<td></td>
</tr>
<tr>
<td>In cases of ALL therapy and cases with no alternative treatment option, 6-MP dose reduction to 10% of standard dosage is recommended to avoid hematotoxicity</td>
<td></td>
</tr>
<tr>
<td>Therapeutic drug monitoring of thioguanine nucleotides is recommended to guide thiopurine dose escalation</td>
<td></td>
</tr>
<tr>
<td>Carriers of one loss-of-function allele</td>
<td></td>
</tr>
<tr>
<td>Potential risk of AZA or 6-MP hematological toxicity depending on disease entity and treatment regimens</td>
<td></td>
</tr>
<tr>
<td>In patients with IBD 50% of standard dose at commencement of therapy is recommended with dose increase being possible during the course</td>
<td></td>
</tr>
<tr>
<td>Therapeutic drug monitoring of thioguanine nucleotides may be used to guide thiopurine dose escalation</td>
<td></td>
</tr>
</tbody>
</table>

6-MP: 6-mercaptopurine; ALL: Acute lymphoblastic leukemia; AZA: Azathioprine; EMA: European Medicines Agency; IBD: Inflammatory bowel disease.

**Box 5. CYP2C9–warfarin and VKORC1–warfarin pharmacogenomics.**

<table>
<thead>
<tr>
<th>Indication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of bleeding in the first days following warfarin introduction</td>
<td></td>
</tr>
<tr>
<td>Individual dosing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulatory status of the PG test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>None</td>
</tr>
<tr>
<td>US FDA</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood or saliva sample</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNPs to be detected</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Main CYP2C9 loss-of-function alleles: CYP2C9<em>2 ($rs1799853$); CYP2C9</em>3 ($rs1057910$)</td>
<td></td>
</tr>
<tr>
<td>Tag for VKORC1 decreased expression haplotype: VKORC1 -1639G&gt;A ($rs9923321$)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interpretation of the results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin maintenance dose according to the FDA Coumadin label – see below (Table 1) or a dosing algorithm (see in text)</td>
<td></td>
</tr>
<tr>
<td>Initial warfarin dosing also requires the regular monitoring of hemostasis (INR)</td>
<td></td>
</tr>
<tr>
<td>No algorithms presently available for other oral anticoagulants such as phenprocoumon, acenocoumarol or fluindione</td>
<td></td>
</tr>
</tbody>
</table>

Practical recommendations for pharmacogenomics-based prescription

**Table 1. Range of expected therapeutic warfarin doses based on CYP2C9 and VKORC1 genotypes**.

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/1 (mg)</td>
</tr>
<tr>
<td>GG</td>
<td>5–7</td>
</tr>
<tr>
<td>GA</td>
<td>5–7</td>
</tr>
<tr>
<td>AA</td>
<td>3–4</td>
</tr>
</tbody>
</table>

*Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, bodyweight, sex, concomitant medication and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1-1639 G>A (rs9923231) variant is used in this table. Other coinherited 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 (>2–4 weeks) to achieve maximum international normalized ratio effect for a given dosage regimen.

Data taken from the US FDA Coumadin (warfarin) label, January 2010 [104].

### DPYD & 5-fluorouracil toxicity

An additional discussion took place regarding polymorphisms of the DPYD and 5-fluorouracil (5-FU) toxicity after the talk by André van Kuilenburg [19] from the Academic Medical Center, Amsterdam, and Ursula Amstutz [20] from the Institute of Clinical Chemistry, Bern. 5-FU and the oral prodrug capecitabine are two of the most frequently prescribed chemotherapeutic drugs for the curative and palliative treatment of patients with cancers of the gastrointestinal tract and breast, as well as head and neck. It has been shown that DPD plays a pivotal role in the metabolism of 5-FU. More than 80% of the administered 5-FU is catabolized by DPD, and patients with a complete or partial DPD deficiency have a strongly reduced capacity to degrade 5-FU. Owing to the fact that 5-FU has a relatively narrow therapeutic index, patients with a complete or partial DPD deficiency may have an increased risk of severe, and sometimes even lethal, drug-induced toxicity. It has been proposed that severe 5-FU toxicity (hematologic, neurologic and intestinal) could be predicted by DPYD polymorphisms [21,22]. However, only a small proportion of severe toxicities in 5-FU based chemotherapy can be explained with the known rare deleterious DPYD mutations resulting in severe enzyme deficiencies [19,23,24]. Contradictory results have been published [25], showing that patients carrying the main deleterious mutation (DPYD IVS 14+1G>A) did not experience severe 5-FU ADRs [23,24]. The positive predictive values of pharmacogenetic/pharmacogenomic tests for the overall 5-FU toxicity range from 46 [23] to 62% [22]. Furthermore, the relationship between genotype and phenotype is not clear [24], possibly owing to the different methods used for the determination of DPD enzyme activity in peripheral blood cells [24,26]. More comprehensive genetic studies are required to identify additional candidates, which may explain – possibly in addition to DPYD variants – 5-FU toxicity. In this

**Box 6. CYP2C19–clopidogrel pharmacogenomics in postmyocardial infarction.**

**Indication**

- Postmyocardial infarction with percutaneous coronary intervention
- Detect clopidogrel poor responders

**Regulatory status of the PG test**

- EMA
  - None
- US FDA
  - Proposed [106]

**Material**

- Blood or saliva sample

**SNPs to be detected**

- CYP2C19*2 (rs4244285); CYP2C19*3 (rs4986893)

**Interpretation of the results**

- Presence of two loss-of-function alleles = poor response to clopidogrel = do not prescribe the drug, choose another non-CYP2C19-dependent thienopyridine such as prasugrel or ticagrelor
- Presence of one loss-of-function allele = intermediate response to clopidogrel; prefer if possible the use of another non-CYP2C19-dependent thienopyridine such as prasugrel or ticagrelor

EMA: European Medicines Agency; PG: Pharmacogenetic/pharmacogenomic.
context different kinds of ADRs (e.g., hematotoxicity, gastrointestinal toxicity and hand–foot syndrome) should be considered. Toxicity risk assessment should also include sex, mode of administration and folinic acid and concomitant drugs as additional predictive factors. In conclusion, routine screening for DPYD polymorphisms only cannot be recommended to identify patients at risk for 5-FU toxicity.

Gastroenterological use of azathioprine & 6-mercaptopurine

- **TMPT & toxicity of azathioprine & 6-mercaptopurine in Crohn’s disease**
  Azathioprine and 6-mercaptopurine (a metabolite of azathioprine) are immunosuppressant drugs used in Crohn’s disease and other conditions. Both drugs are in part metabolized by TPMT, an enzyme that is highly polymorphically expressed and whose enzyme activity can be measured in red blood cells. Three major loss-of-function alleles have been identified and assayed:
  - TPMT*2 (rs1800462, c.238G>C, Pro80Ala)
  - TPMT*3C (rs1142345, c.719A>G, Tyr240Cys)
  - TPMT*3B (rs1800460, c.460G>A, Ala154Thr).
  TPMT*3A combines rs1142345 and rs1800460 variants. There is a close phenotype–genotype relationship, which allows a genotyping strategy to reliably detect TPMT deficiency, which is particularly important for patients receiving red blood cell transfusions [27–29]. Dose reduction or azathioprine/6-mercaptopurine in homozygous variant carriers reduces the risk of toxicity and allows thiopurine therapy without an increased risk for hematological toxicity. Of note, monitoring of laboratory parameters, including hematological parameters and liver enzymes is recommended because TPMT polymorphism explains only up to 60% of the thiopurine hematotoxicity but no thiopurine-induced liver injury (see Box 4).

6-mercaptopurine is the mainstay of maintenance therapy in childhood acute lymphoblastic leukemia and therefore genetic testing for TPMT is being used in clinical routine in several countries.

Cardiovascular drugs

In the cardiovascular session, we focussed our attention on two major drugs: warfarin (as well as other coumarins) and clopidogrel.
Pharmacogenetically adapted dose of warfarin

Mia Wadelius from Department of Medical Sciences, Uppsala, summarized the present knowledge concerning the pharmacogenetic/pharmacogenomic of warfarin [30]. Two major genetic factors are known to explain 35–50% of the interindividual variability of warfarin response and dose requirement [30–33]. CYP2C9 is the most important enzyme involved in warfarin hepatic metabolism. Its two main decreased function allelic variants, CYP2C9*2 and CYP2C9*3 (see Box 5 & Table 1), are responsible for apparent early overdose (as assessed by elevated international normalized ratio [INR]) and bleeding in the days following warfarin introduction [34]. The VKORC1 gene codes for vitamin K epoxide reductase, the target of warfarin treatment. A SNP which tags a decreased expression haplotype (see Box 5 & Table 1) is associated with low warfarin dose requirements [32].

There are several dose models aiming to find the individual warfarin dose by incorporating CYP2C9 and VKORC1 genotypes into an algorithm, for example Warfarin dosing [103] and the International Warfarin Pharmacogenetics Consortium’s (IWPC’s) algorithm [31]. The US FDA updated the Coumadin (warfarin) label in January 2010 [104] with a range of expected therapeutic warfarin doses based on CYP2C9 and VKORC1 genotypes (see Box 5 & Table 1). The EMA has not yet decided whether to include this information in European drug labels.

Anke-Hilse Maitland-van der Zee [35] from Utrecht Institute for Pharmaceutical Sciences, Utrecht described results concerning the pharmacogenetics/pharmacogenomics of other coumarins used in Europe: phenprocoumon and acenocoumarol. CYP2C9 and VKORC1 play a similar role for these drugs and dosing algorithms are under development. A large European randomized trial (European pharmacogenomic approach to coumarin anticoagulant therapy [EU-PACT]) will commence this year to test the benefit of pharmacogenomics preprescription genotyping for warfarin, phenprocoumon and acenocoumarol. This trial together with other trials (such as the Clarification of Optimal Anticoagulation Through Genetics [COAG] trial in the USA) will be able to conclude whether preprescription genotyping is of clinical utility.

CYP2C19-related clopidogrel nonresponse in postmyocardial infarction

Celine Verstuyft from Université Paris-Sud, Paris, gave an overview of the recently discovered clopidogrel pharmacogenetics/pharmacogenomics [36]. Clopidogrel is an antiplatelet drug used in atherothrombotic diseases, such as myocardial infarction and stroke, which is an inactive prodrug that needs to be bioactivated by a liver enzyme, CYP2C19. Several loss-of-function alleles have been previously

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**Box 9. SLC01B1 and statin myopathy.**

**Indication**
- To confirm after a statin myopathy episode its genetic origin
- In high-risk patients to define the maximum dose of statin not to be exceeded

**Regulatory status of the PG test**
- EMA – None
  - US FDA – None

**Material**
- Blood or saliva sample

**SNPs or mutations to be detected**
- SLC01B1 c.521T>C allele Val174Ala (rs4149056)

**Interpretation of the results**
- Maximal statin dose determined according to SLC01B1*5 genotype adapted from [41]
- Statins will be started according to recommendations at the lowest dose and progressively increased according to low density lipoprotein cholesterol levels achieved
- SLC01B1 pharmacogenetic testing does not obviate the monitoring of creatine kinase and transaminase blood levels

EMA: European Medicines Agency; PG: Pharmacogenetic/pharmacogenomic.

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**Table 2. Maximal statin dose determined according to SLC01B1*5 genotype.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>SLC01B1 c.521TT (wild-type) (mg/day)</th>
<th>SLC01B1 c.521TC (mg/day)</th>
<th>SLC01B1 c.521CC (mg/day)</th>
<th>Normal dose range in the USA (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>80</td>
<td>40</td>
<td>20</td>
<td>5–80</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1–4</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>80</td>
<td>40</td>
<td>20</td>
<td>10–80</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>80</td>
<td>40</td>
<td>40</td>
<td>10–80</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>40</td>
<td>20</td>
<td>20</td>
<td>5–40</td>
</tr>
<tr>
<td>Fuvastatin</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>20–80</td>
</tr>
</tbody>
</table>

Data taken from [41].

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identified [102]. CY2C19*2 and CYP2C19*3 are the two most frequent variants in Occidentals and Asians, respectively (see Box 6). A total of 3 and 20% of the Occidental and Asian populations, respectively, carry two-loss-of-function alleles and have no CYP2C19 activity (poor metabolizers). In such patients treated with clopidogrel after myocardial infarction, stent thrombosis and recurrent major cardiovascular events occur two- to three-times more frequently compared with CYP2C19 wild-type patients [36–38]. A gene-dose effect seems to occur with the patients heterozygous for one CYP2C19 variant showing an intermediate clinical response between wild-type patients and patients homozygous for the loss-of-function variants [38]. An increase in the daily dose of clopidogrel is not at the moment an alternative for allelic variant carriers in the absence of convincing data, although the FDA suggests an increased loading dose of 600 mg. Since other antiplatelet drugs are available (prasugrel) or soon will be (ticagrelor), the best advice is to consider changing clopidogrel for a CYP2C19-independent drug (see Box 6). There are no additional available data for the other indications of clopidogrel such as stroke. However, the situation might be the same.

### Pharmacogenomics of adverse drug reactions

#### HLAB*5701 & abacavir hypersensitivity

Since the beginning of this century, HLA-B*5701 has been known to be a powerful predictive biomarker of abacavir hypersensitivity episodes, which occur in 5% of patients treated with this drug during the first weeks of treatment. GlaxoSmithKline (London, UK), in conjunction with several lead investigators, conducted the largest international pharmacogenetic randomized clinical trial ever performed to date, which was released in 2008 [39]. They demonstrated that screening for HLA-B*5701 before introducing abacavir and the exclusion of patients carrying this allele resulted in the disappearance of the hypersensitivity syndrome related to this drug. This pharmacogenetic test is now routinely used in many different countries before introducing abacavir (Box 7).

#### HLAB*5701 & flucloxacillin drug-induced liver toxicity

Ann K Daly from the institute of cellular medicine, Newcastle upon Tyne, UK, recently identified HLA-B*5701 as a potent risk factor for drug-induced liver injury owing to flucloxacillin in the Drug Induced Liver Injury Genetics (DILIGEN) study [40]. This HLA allele confers a 80-fold increased risk to develop severe flucloxacillin cholestasis compared with noncarriers of this allele. However, since severe flucloxacillin-mediated cholestasis is fortunately rare, the genetic testing cannot be proposed for an initial screening before introducing the drug. Conversely (see Box 8), if a patient presents with a severe cholestasis for which different causes are possible, HLA-B*5701 genotyping might be a useful test to implicate whether flucloxacillin is the causative agent (imputability pharmacogenetic test).

### Box 10. CYP3A5*3 and tacrolimus dosing in early renal transplantation.

<table>
<thead>
<tr>
<th>Indication</th>
<th>The dialysis period which precedes renal transplantation or in the first days following transplantation to predict the individualized dose of tacrolimus in order to prevent overdose (risk of nephrotoxicity) or underdose (risk of acute graft rejection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory status of the PG test</td>
<td>EMA: None  &lt;br&gt; US FDA: None</td>
</tr>
<tr>
<td>Material</td>
<td>Blood or saliva sample</td>
</tr>
<tr>
<td>SNPs or mutations to be detected</td>
<td>CYP3A5<em>3 allele: rs776746  &lt;br&gt; Interpretation of the results  &lt;br&gt; Genotype CYP3A5</em>3/<em>3 = introduce tacrolimus at 0.15 mg/kg/day  &lt;br&gt; Genotype CYP3A5</em>3/<em>1 = introduce tacrolimus at 0.20 mg/kg/day  &lt;br&gt; Genotype CYP3A5</em>1/*1 = introduce tacrolimus at 0.25 mg/kg/day  &lt;br&gt; Initial CYP3A5 genotyping also requires the regular monitoring of tacrolimus trough plasma levels to reach the target concentrations</td>
</tr>
</tbody>
</table>

EMA: European Medicines Agency; PG: Pharmacogenetic/pharmacogenomic.
**SLCO1B1 & statin myopathy**

Mikko Niemi from the University of Helsinki, Helsinki, emphasized the role of the OATP1B1 hepatic uptake transporter in statin disposition and as a risk factor for statin muscular toxicity. Several transporters (e.g., OATP1B1, P-glycoprotein, BCRP and MRP2) or drug-metabolizing enzymes (e.g., CYP3A4 and CYP3A5) influence statin pharmacokinetics, but only one variant of SLCO1B1 coding for OATP1B1, has been linked to statin myopathy in a genome-wide association study [42]. This c.521T>C (rs4149056) variant (see Box 9 & Table 2) changes an amino acid residue (Val174Ala) and decreases the activity of the transporter. It provides a 17-fold increased risk of myopathy in homozygous carriers of the allelic variant using simvastatin at the high 80 mg dose [42]. The effects of this variant, however, differ markedly depending on the statin in question [43–45], and the maximum statin dose that should not be exceeded might be dependent upon SLCO1B1 genotype [41]. Interestingly, fluvastatin disposition is not influenced by the SLCO1B1 c.521T>C variant [43] and might be an alternative to other statins in carriers of this variant.

**Pharmacogenomics of organ transplantation**

It has been known for several years that tacrolimus disposition is highly influenced by the presence (CYP3A5*3) or absence (CYP3A5*1) of CYP3A5 expression. Eric Thervet from Paris Descartes University, Paris, presented the results of a prospective randomized trial aimed at determining the usefulness of a priori CYP3A5 genotyping to adapt tacrolimus dose to individual genotype at the beginning of renal transplantation [46]. In one arm, patients received a fixed dose of tacrolimus, and in the second arm the tacrolimus dose was adapted to CYP3A5 genotype. Thervet demonstrated that the tacrolimus trough target concentration (main clinical end point) was reached after 1 week of treatment in 43% of the patients whose dose was pharmacogenetically adapted compared with 29% in the nonadapted arm. A total of 75% of the patients reached the target tacrolimus concentration at day 8 in the intervention arm compared with day 25 in the nonadapted arm. In the adapted arm tacrolimus steady state could be reached with less (30%) dose modifications compared with the non-adapted arm. No differences in organ rejection frequency could be observed but all the patients of the trial received an induction treatment, which prevents acute rejection during the first weeks of treatment. Therefore CYP3A5 genotyping prior to grafting may help physicians to reach steady state plasma tacrolimus concentrations earlier (Box 10).

Evelyne Jacqz-Aigrain from Hôpital Robert Debré, Paris, gave an overview of how both age and pharmacogenetics affect the disposition of immunosuppressants in pediatric renal transplant recipients [47]. A population pharmacokinetic–pharmacogenetic model of tacrolimus was presented based on rich pharmacokinetic sampling data from 50 pediatric kidney transplant patients (ranging from age 2 to 18 years), indicating that the CYP3A5 polymorphism has a major influence on the tacrolimus apparent oral clearance (CL/F) as CL/F was 30% lower in patients with the CYP3A5*3/*3 genotype compared with patients carrying the CYP3A5*1 allele. CYP3A5 polymorphism, weight and haematocrit were central variables for dosage adjustment in the early post-transplantation period [47].

**Conclusion**

The aim of the third ESF–UB Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics was to discuss whether side effects can be avoided and therapeutic effects maximized through pharmacogenetics/pharmacogenomics. This article summarizes these discussions and presents pharmacogenetic tests that may help improve risk stratification or predict outcome. In addition to the ten presented clinical examples, we discussed additional drugs and gene targets, of which the levels of scientific evidence or the magnitude of the genetic effect are currently insufficient to propose any recommendations for routine genotyping. In the future, some of these drugs might be prescribed according to a pharmacogenetic principle and a test yet to be established (see ‘Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels’ [105]). We hope that the synopsis provided from our discussions concerning the ten different settings will help improve the development of pharmacogenetics in routine medical practice in order to avoid side effects, and to choose the best drug and dose according to each individual genotype. Of note, recommendations given at the meeting must be considered with caution as they do not reflect official positions of the respective medical societies in different countries and of the official regulatory agencies (e.g., FDA and EMA). Moreover, a major...
First paper indicating a relationship between Gefitinib or chemotherapy for non-small-cell lung cancer

Pharmacogeneomics was focused on practical applications in routine medical practice.

We identified ten situations illustrating the usefulness of pharmacogenetically guided therapy:

- Tumor EGFR to define the responder status to gefitinib and erlotinib in advanced or metastatic non-small-cell lung cancer.
- Tumor KRAS to define the responder status to cetuximab and panitumumab in metastatic colon cancer.
- TPMT genotyping to prevent azathioprine and 6-mercaptopurine hematotoxicity.
- CYP2D6 to define the responder status to tamoxifen in postmenopausal breast cancer positive for estrogen receptors.
- CYP2C19 to define the responder status to clopidogrel in myocardial infarction.
- CYP3A5 to define the best tacrolimus dose to start with in renal transplantation.
- CYP2C9 and VKORC1 to define the best warfarin dose to introduce.
- HLA-B*5701 to prevent abacavir hypersensitivity in AIDS.
- HLA-B*5701 to attribute a drug-induced liver injury to fluvoxacinil.
- OATP1B1 to define in high-risk patients the maximum dose of statin not to be exceeded.

We propose herein comments that might accompany the results of these tests, indicating the best drug and doses to be prescribed.

**Bibliography**

Papers of special note have been highlighted as:
- of interest
- of considerable interest


5 First demonstration that gefitinib response depends on EGFR tumoral activating mutations.


Clear demonstration that cetuximab response is only present in KRAS wild-type tumors.


** Good very paper with one of the largest patients cohort investigating different genetic risk factors of 5-fluorouracil related adverse drug reactions.

* First demonstration that CYP2C9 polymorphisms are risk factors of bleeding in patients treated with warfarin.

** Clear association of VKORC1 variants and warfarin dose requirements and the functionality of the variants.


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Clear association of VKORC1 variants and warfarin dose requirements and the functionality of the variants.
Genome-wide association study that identified HLA-B*5701 as a risk factor of flucloxacillin mediated drug-induced liver injury.


Excellent review on the topic.


Genome-wide association study that clearly demonstrated that SLCO1B1 is related to statin myopathy.


Only randomized clinical trial demonstrating the usefulness of CYP3A5 screening before tacrolimus dosing in renal transplantation.


Websites

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