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 *KRAS*, cetuximab, panitumumab, *EGFR*–gefitinib, *CYP2D6*–tamoxifen, *TPMT*–azathioprine–6-mercaptopurine, *VKORC1*/*CYP2C9*–warfarin, *CYP2C19*–clopidogrel, *HLA-B*5701*–abacavir, *HLA-B*5701*–flucloxacillin, *SLCO1B1*–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 ■ warfarin

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The 3rd European Science Foundation–University of Barcelona (ESF–UB) Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics was held in Sant Feliu de Guixols, Spain, from 6–10 June 2010. It was focused on practical applications in routine medical practice [101]. When planning this conference 2 years ago, we thought it would be interesting to synthesize some knowledge gained in the field of pharmacogenetics and pharmacogenomics in the last 50 years, in order to identify the current pharmacogenetic/pharmacogenomic tests that could be used in routine medical practice. Our aim was to determine, through daily discussions involving all participants, which pharmacogenetic information might be useful for patient therapy. In addition, we wanted to attempt to make some recommendations on which pharmacogenetic tests should be performed in routine medicine and decide what advice we might give to physicians regarding some of these pharmacogenetic/pharmacogenomic tests. The conference could not cover the whole field of pharmacogenetics/pharmacogenomics. Therefore, we limited the program to examples that we considered the most clinically relevant in the field of oncology, cardiovascular diseases, adverse drug reactions (ADRs) and organ transplantation. This choice is naturally subjective, excluding large parts of pharmacogenetics/pharmacogenomics such as neuropsychopharmacology, pain, addiction and rheumatology. We present herein our conclusions on pharmacogenetic information that might be useful in ten clinical situations: guidance recommendations on which tests to be performed, and advice to physicians concerning these tests.

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 EGF 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

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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

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

EMA: European Medicines Agency; NSCLC: Non-small-cell lung cancer; PG: Pharmacogenetic/pharmacogenomic.

Box 2. *KRAS* pharmacogenomics in colon cancer.

Indication
- Metastatic colon cancer, first- or second-line therapy. Detect the poor responders to cetuximab and panitumumab

Regulatory status of the PG test
- EMA
  - Mandatory for cetuximab and panitumumab
- US FDA
  - Suggested for cetuximab and panitumumab

Material
- Colon tumor

Mutations to be detected
- Activating tumor *KRAS* mutations: mainly exon 2 codon 12 and 13

Interpretation of the results
- Presence of *KRAS* mutations = nonresponse to cetuximab and panitumumab = do not prescribe the drug
- Absence of *KRAS* mutations = response to cetuximab and panitumumab

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

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 its 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

Box 3. *CYP2D6*–tamoxifen pharmacogenomics in postmenopausal early breast cancer.

Indication
- Postmenopausal breast cancer positive for estrogen receptors
- Detect potential poor outcome of tamoxifen

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

Material
- Blood or saliva sample

SNPs or deletion to be detected
- Main *CYP2D6* loss-of-function alleles: *CYP2D6*3* (rs35742686); *CYP2D6*4* (rs3892097); *CYP2D6*5* (gene deletion); *CYP2D6*6* (rs5030655); *CYP2D6*7* (rs5030867)
- Main *CYP2D6* decreased function alleles: *CYP2D6*10* (rs1065852); *CYP2D6*41* (rs28371725); *CYP2D6*9* (rs5030656)

Interpretation of the results
- Postmenopausal women
- 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
- Carriers of two functional alleles including gene duplication are likely to respond to tamoxifen
- Premenopausal women: no data available
- Male breast cancer: no data available

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

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

Indication
- Crohn's disease before the introduction of AZA or 6-MP
- Prevention of hematological toxicity of AZA and 6-MP

Regulatory status of the PG test
- EMA
  - None
- US FDA
  - Recommended (*TPMT* genotyping or phenotyping)

Material
- Blood or saliva sample

SNPs to be detected
- rs1800462, c.238G>C, Pro80Ala (*TPMT*2*)
- rs1142345, c.719A>G, Tyr240Cys (*TPMT*3C*) rs1800460, c.460G>A, Ala154Thr (*TPMT*3B*)
- *TPMT*3A* combines rs1142345 and rs1800460

Interpretation of the results
- Presence of two loss-of-function alleles
  - High risk of AZA or 6-MP hematological toxicity in the first weeks of drug intake using recommended standard dosages
  - Dependent on disease entity, the use of alternative drugs should be considered (e.g., inflammatory bowel disease: anti-TNF monoclonal antibody or methotrexate)
  - 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
  - Therapeutic drug monitoring of thioguanine nucleotides is recommended to guide thiopurine dose escalation
- Carriers of one loss-of-function allele
  - Potential risk of AZA or 6-MP hematological toxicity depending on disease entity and treatment regimens
  - In patients with IBD 50% of standard dose at commencement of therapy is recommended with dose increase being possible during the course
  - Therapeutic drug monitoring of thioguanine nucleotides may be used to guide thiopurine dose escalation

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

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

Indication
- Prevention of bleeding in the first days following warfarin introduction
- Individual dosing

Regulatory status of the PG test
- EMA
  - None
- US FDA
  - Recommended

Material
- Blood or saliva sample

SNPs to be detected
- Main *CYP2C9* loss-of-function alleles: *CYP2C9*2* (rs1799853); *CYP2C9*3* (rs1057910)
- Tag for *VKORC1* decreased expression haplotype: *VKORC1* -1639G>A (rs9923321)

Interpretation of the results
- Warfarin maintenance dose according to the FDA Coumadin label – see below (Table 1) or a dosing algorithm (see in text)
- Initial warfarin dosing also requires the regular monitoring of hemostasis (INR)
- No algorithms presently available for other oral anticoagulants such as phenprocoumon, acenoucoumarol or fluindione

EMA: European Medicines Agency; INR: International normalized ratio; PG: Pharmacogenetic/pharmacogenomic.

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

VKORC1	*CYP2C9*					
	**1/1 (mg)*	**1/*2 (mg)*	**1/*3 (mg)*	**2/*2 (mg)*	**2/*3 (mg)*	**3/*3 (mg)*
GG	5–7	5–7	3–4	3–4	3–4	0.5–2
GA	5–7	3–4	3–4	3–4	0.5–2	0.5–2
AA	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

†*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.* VKORCI-*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* (rs 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.

Box 7. *HLA-B*5701* and abacavir-induced hypersensitivity syndrome.

Indication
- Prevent abacavir-related hypersensitivity syndrome

Regulatory status of the PG test
- EMA
  - Mandatory
- US FDA
  - Mandatory

Material
- Blood or saliva sample

Allele to be detected
- *HLA-B*5701*

Interpretation of the results
- In the absence of *HLA-B*5701* allele, abacavir can be safely prescribed but allergic events can still occur owing the concomitant drugs given to the patient
- In the presence of *HLA-B*5701* the risk of hypersensitivity to abacavir is high = do not prescribe the drugs
- However only 50% of patients carrying *HLA-B*5701* allele will develop a hypersensitivity syndrome. If abacavir has absolutely to be introduced, close medical supervision is essential

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) and *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.

Box 8. *HLA-B*5701* and flucloxacillin drug-induced liver injury.

Indication
- Attribute DILI to flucloxacillin in the presence of different potential disease etiologies

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

Material
- Blood or saliva sample

Allele to be detected
- *HLA-B*5701*

Interpretation of the results
- In the presence of the *HLA-B*5701* allele, there is an 80-fold increased risk to develop a fluoxacillin induced DILI.

DILI: Drug-induced liver injury; EMA: European Medicines Agency.

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.

Box 9. *SLCO1B1* 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
- *SLCO1B1* c.521T>C allele Val174Ala (rs4149056)

Interpretation of the results
- Maximal statin dose detemined according to *SLCO1B1*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
- *SLCO1B1* pharmacogenetic testing does not obviate the monitoring of creatine kinase and transaminase blood levels

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

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

Table 2. Maximal statin dose detemined according to *SLCO1B1*5* genotype.

Drug	*SLCO1B1* c.521TT (wild-type) (mg/day)	*SLCO1B1* c.521TC (mg/day)	*SLCO1B1* c.521CC (mg/day)	Normal dose range in the USA (mg/day)
Simvastatin	80	40	20	5–80
Pitavastatin	4	2	1	1–4
Atorvastatin	80	40	20	10–80
Pravastatin	80	40	40	10–80
Rosuvastatin	40	20	20	5–40
Fuvastatin	80	80	80	20–80

Data taken from [41].

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

Indication
- The dialysis period which preceedes 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)

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

Material
- Blood or saliva sample

SNPs or mutations to be detected
- *CYP3A5*3* allele: rs776746
- Interpretation of the results
- Genotype *CYP3A5*3/*3* = introduce tacrolimus at 0.15 mg/kg/day
- Genotype *CYP3A5*3/*1* = introduce tacrolimus at 0.20 mg/kg/day
- Genotype *CYP3A5*1/*1* = introduce tacrolimus at 0.25 mg/kg/day
- Initial *CYP3A5* genotyping also requires the regular monitoring of tacrolimus trough plasma levels to reach to the target concentrations

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

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).

SLCO1B1 & statin myopathy

Mikko Niemi from the university of Helsinki, Helskinki [41], 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*1*) or absence (*CYP3A5*3*) 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 immunossuppressants 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

limitation in pharmacogenomic research is the lack of sufficiently powered studies including randomized control trials.

Future perspective

Pharmacogenetics/pharmacogenomics has already identified clinically relevant loci which alter the response to several drugs. Such pharmacogenetic/pharmacogenomic information is now taken into account by drug regulatory agencies as evidenced by recent drug label modifications integrating pharmacogenetic-based prescription. Whereas pharmacocogenetic traits influencing drug disposition are now relatively well identified, the genetic variability of drug targets remains to be explored. Oncology will probably be the most promising field in pharmacogenomics for three main reasons: the tumoural genetic variability is far more important than the one of our constitutional genome multiplying the situations in which the response to a drug may be genetically determined. Unlike other medical areas, in oncology there is a constant increase of new targeted anticancer drugs released on the market. New technologies allow an exponential discovery of potent new tumoural drug targets. However, dramatic efforts need to be made first in the selection of pharmacogenetic tests, which might really bring a benefit to patients, and second, in the interpretation of the tests that needs to be consensual, clear and simple to implement in order to help the physicians to adapt their treatment on pharmacogenetics.

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Executive summary

- The 3rd 2010 European Science Foundation–University of Barcelona (ESF–UB) Conference in Biomedicine on Pharmacogenetics and Pharmacogenomics was focused on practical applications in routine medical practice.
- Our aim was to define a limited set of consensual clinically relevant situations that would benefit patients and to define practical advices that might be used in pharmacogenetic counseling.
- 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 flucloxacillin.
  - *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.

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