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## Pharmacogenomics and personalized medicine in clinical practice

The Santorini Conference on prospective biology, genomics and pharmacogenomics occurs every 2 years. On 30 September to 2nd October 2010, the fifth meeting in this series took place in Santorini, Greece. This conference has established a tradition of organizing a workshop each time to address the most recent developments and key issues in pharmacogenomics. This year, the workshop was chaired by Bryan Dechairo and Alain Huriez, and was titled 'Pharmacogenomics and personalized medicine in clinical practice'.

**KEYWORDS:** biomarkers ■ cytochromes ■ personalized medicine ■ pharmacogenetics ■ pharmacogenomics ■ theranostics

The first presentation of the round table was given by Bryan Dechairo (Medco Health Solutions Inc., MD, USA) who introduced the topic of 'Pharmacogenomics in Clinical Practice: Example from the Real World' (Box 1). He provided an overview of Medco's approach to implementing pharmacogenomic testing for warfarin in USA as an example that can hopefully be followed around the world. First he noted that the key point for pharmacogenomics to enter clinical practice is not only to transfer scientific innovation into clinical application, but also to decrease the time that it takes until original discoveries enter clinical practice. He used the case of warfarin as a main example, which saw a total of 17 years before implementation of *CYP2C9* and *VKORC1* genotyping in clinical practice. Dechairo stated that although the scientific knowledge existed, the genome-wide association study (GWAS) applied in the case of warfarin, that confirmed *CYP2C9* and *VKORC1* polymorphisms as contributors to warfarin-prediction dose, boosted confidence in warfarin pharmacogenomics. GWAS have mainly been applied in disease genetics; however, GWAS in pharmacogenomics research are also essential to find new or validate known variations associated with drug response. Furthermore, in the case of warfarin, despite the fact that the US FDA has updated the warfarin insert package, proposing a dose range according to *CYP2C9/VKORC1* genotype, a genotyping test has yet to be reimbursed owing to the fact that there is not a randomized control clinical trial proving the benefit of testing on clinical outcomes.

Medco, a pharmacy benefit manager and mail order pharmacy, delivers drugs directly to people's residence and by this way improves

adherence to pharmacotherapy. Currently, Medco's pharmacy benefit manager covers 65 million people in USA. Since Medco provides coverage for the cost associated with prescriptions drugs, the company is interested in implementing pharmacogenomic tests in clinical practice to limit costs associated with prescribing drugs of reduced efficacy. Towards this direction, Medco focuses on educating both patients and clinicians about available tests. In addition, it is interested in assessing the real lifesaving potential of incorporating pharmacogenetics information into prescription decisions. In fulfilling that goal, Medco has started implementing clinical studies such as the Medco Warfarin Study. In this study, warfarin-treated patients were genotyped for *CYP2C9* and *VKORC1* following warfarin treatment initiation. If patients were on the wrong dose according to their genotype, Medco contacted the doctors, provided the genotyping results which recommended the right dose. A total of 896 patients were included in the study and were monitored for 6 months. When this procedure was followed and doctors were informed of the results, a 28% decrease in patients' hospitalization and a 27% reduction in bleeding or thromboembolism was demonstrated. Medco now offers this test to everyone who starts warfarin and who have signed up for the warfarin testing program. Overall, when physicians are not educated, they are unlikely to order a test. Medco has also observed that when patients are educated, a bigger uptake of pharmacogenetic testing occurs. It appears that there is a major education gap amongst physicians and this leads to lower rates of test adoption. In a Medco survey, although 98% of physicians believed that genetics affected drug

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**Box 1. Pharmacogenomics and personalized medicine in clinical practice round table: list of discussions.****Moderators: Bryan Dechairo & Alain Huriez**

- Changing clinical practice based on evidence generated in the real world. Comparative effectiveness studies: a series of examples
  - Bryan Dechairo (Medco Health Solutions Inc., MD, USA): Pharmacogenomics in Clinical Practice: Example from the Real World
  - Alberto Lazarowski (Buenos Aires University, Buenos Aires, Argentina): Impact of ATP-Binding-Cassette (ABC) Transporters in Epilepsy and Stroke
  - Adrián LLerena (Extremadura University Hospital, Badajoz, Spain): Application of Pharmacogenetics in Psychiatry: Clinical and Technical Aspects
  - Alexander Kühn (Max-Planck Institute for Molecular Genetics, Berlin, Germany): Modeling Cancer using the Monte-Carlo Approach: Individualized Medicine
  - Kiang-Teck J Yeo (University of Chicago, IL, USA): Cardiopharmacogenomics: Application of Pharmacogenomics in Cardiology
  - Ron H van Schaik (Rotterdam, The Netherlands): Clinical Applications: Pharmacogenetics of Immunosuppressants. Tacrolimus, MMF and Cyclosporine
- Development & use of theranostics biomarkers: requirements of guidelines
  - Alain Huriez (EPEMED, Nantes, France): Development and Use of Theranostic Biomarkers. Impact on the Industry Business Model. Needs of Guidelines. Market Access Issues: the European Case
  - Vangelis G Manolopoulos (Democritus University of Thrace Medical School, Alexandroupolis, Greece): Genotype-Guided Dosing of Coumarin Derivatives: The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) Consortium Trial

**Invited panel & discussion participants**

- Antoine Bril (Institut de Recherche Servier, Suresnes, France), Jean Clairambault (INRIA, Paris, France), Tomasz Dylag (European Commission, Unit F.4: Genomics & Systems Biology), Adriano Henney (Obsidian Biomedical Consulting Ltd, Macclesfield, UK), Alexander Kühn (Max-Planck Institute for Molecular Genetics, Berlin, Germany), Adrián LLerena (Clinical Research Center, Extremadura University Hospital, Badajoz, Spain), Vangelis G Manolopoulos (Democritus University of Thrace Medical School, Alexandroupolis, Greece), George Patrinos (School of Health Science, University of Patras, Greece), Wolfgang Sadee (The Ohio State University, OH, USA), Peter Schulz-Knappe (Protagen AG, Dortmund, Germany), Gerard Siest (Université Henri Poincaré, Nancy, France), Ron H van Schaik (Torax Laboratory, Rotterdam, The Netherlands), Kiang-Teck J Yeo (Department of Pathology, University of Chicago, IL, USA)

response, only 10% felt informed about pharmacogenomic testing, and only 12% had ordered at least one pharmacogenomic test for a patient in the last 6 months. After physicians were educated, the percentage ordering a test reached 67%. When both physicians and patients were educated regarding pharmacogenomic testing, 82% ordered a test. Filling this gap in education is a quick way for pharmacogenomics to enter into clinical practice. The speaker concluded that since translation from bench to bedside takes approximately 17 years, there should be a bolus of tests in the near future. Dechairo also noted that acceptance of personalized medicine by patients and regulatory and private payers is greater than that of physicians, government and health plan payers, and that understanding the impact on patient outcomes and the cost of test implementation is essential for reimbursement decisions. Overall, physician education paired with patient empowerment will be the key for future success.

There was a comment made by the audience highlighting the fact that underdosing is one of the reasons for hospitalization during warfarin treatment. Bryan Dechairo agreed with this comment.

The next speaker was Adrián LLerena (Extremadura University Hospital, Badajoz, Spain), who presented the 'Application of

Pharmacogenetics in Psychiatry: Clinical and Technical Aspects'. LLerena opened his talk by mentioning that psychopharmacology is one of the hottest areas of pharmacogenomics and that amongst the drugs that have been studied in pharmacogenetics, psychotropic drugs are second on the list. LLerena also presented a historical overview starting in the early 1980s. Prior to that era, scientists were working with drug metabolic phenotypes and were following adverse reactions across families. They suspected that there was also a genetic background, but at that time, they did not have the tools to investigate further. However, pharmacogenetics was definitely developed when genetics and molecular biology were incorporated into this field. In the last 20 years, huge development has occurred in genetics. Nowadays, genetics is affordable in most clinical environments with new and easy-to-use tools readily available. But what happens with the 'pharmaco' part of pharmacogenetics? Do we have new knowledge? The answer seems to be that it has not grown as much as the field of genetics has. Clinical pharmacology still faces similar problems, including the lack of new drug targets. This is a key issue in psychopharmacology. Most data in this field are released by drug companies and the economical aspect is always a very hot topic in this area. Therefore, there is a need for independent clinical trials,

in particular under real clinical conditions. Nevertheless, the new pharmacogenetic tests are heavily promoted in psychiatry to predict dosages and improve the drug's clinical benefit. But how can we predict unknown effects? The pharmacovigilance system gets spontaneous reports, so this part needs to be improved as it leads to a lack of information regarding drug-response phenotypes. A major issue is that promises made regarding personalized medicine in psychiatric departments cannot be fulfilled. At this point, LLerena introduced the concept of stratified medicine (predicted response for a group) as being more correct than the extensively used concept of personalized medicine (predicted response for a subject). Companies promise that genetic analyses will predict the exact response to a drug, but this is not always true and creates false expectations amongst clinicians, patients and families. Pharmacogenetics can identify risk factors and this is indeed important to improve drug therapy, but to predict individual drug response, other variables may contribute besides potential drug interactions. Therefore, physicians and scientists need to be clear on the promises they make to patients. Most of the tests available in the market are based on the relationship of one single gene during drug monotherapy, normally under clinical trial conditions, whereas most drugs are metabolized by more than one enzyme at a time, and patients are usually under drug polytherapy. In real practice, people take more than one drug and drug interactions are always present. This is a problem that we have to face; in every day practice, we need to predict drug interactions including metabolites. In psychopharmacology, most of the drugs have active metabolites but we do not know their effects or side effects. Environmental factors (e.g., tobacco smoking) also influence the very complex phenotype of drug response. For instance, a great variability exists between smokers and nonsmokers treated with thioridazine. In addition, when adding a second drug metabolized by CYP2D6, the distinguishing line between therapeutic response and cardiotoxicity is significantly narrowed. Overall, the main cause of interindividual variability of drug response in psychiatry is not genetic or environmental, but patient compliance. Moreover, the patient may modulate drug dose or change lifestyle habits such as food intake, water, caffeine and tobacco consumption. To define the genetic aspect of a pharmacological effect we have to study more than one gene under polytherapy in steady-state conditions as well as the relevance

of environmental and endogenous factors. The pharmacologic effect of a drug is only part of its therapeutic effect.

A broad understanding of genetics can improve global health. LLerena presented comparison data on *CYP2D6* genotype-derived phenotypes in Europeans and Latin Americans. Finally, LLerena suggested the creation of a European Society for Pharmacogenetics, the generation of general recommendations and the adaptation of pharmacovigilance programs based on pharmacogenetics knowledge.

Adriano Henney (Obsidian Biomedical Consulting Ltd, Macclesfield, UK) proposed to Adrian LLerena that 'in drug response it is not just genetics. We have to think about physiology but in a completely different way; in an integrating way. Understanding how modeling and simulation of physiology should include the variability of the genetic level between patients is incredibly important'.

Adrián LLerena fully agreed with the relevance of genetic polymorphisms in drug-metabolizing enzymes to endogenous metabolism (CYP2D6 and psychological functioning). The role of pharmacogenetics in the vulnerability of the disease is a key point to be studied.

Gerard Siest (Université Henri Poincaré, Nancy, France) stated his support for this proposition as it is very clear that there are genetic and physiological variations contributing to overall biological variation.

Alexander Kühn (Max-Planck Institute for Molecular Genetics, Berlin, Germany) presented a model of cancer that was developed at the Max-Planck Institute for Molecular Genetics in collaboration with Alacris Theranostics. Kühn discussed how this model can be used to individualize cancer treatment. The background of modeling biochemicals is a translation of biochemical reactions into a mathematical model, for example, as given by an ordinary differential equation system. In these equations, according to the kinetic parameters and initial values that are given, any component of the system can be calculated. To build such kinetic models the systems biology group at the Max-Planck Institute have developed a modeling system called PyBioS [1]. PyBioS makes it easy to build large models such as a cancer model as PyBioS enables the addition of new components and the connection of different components and bioreactions in the system as well as the ability to assign reactions. The system also has tools that enable the importing of data from available databases and the simulation of models.

The cancer model constructed by PyBioS contains several cancer-relevant signaling pathways as proposed by Hanahan and Weinberg [2]. Overall, the up-to-date developed modeling system covers more than 200 genes, almost 1000 paralogs, reflects over 1400 components, and also contains inhibitors, activators and mutated forms of genes. In total, these different components are connected to more than 1800 reactions giving rise to over 2226 kinetic parameters. A main problem in such modeling systems is the lack of kinetic parameters. When there is a lack of knowledge regarding kinetic parameters, the problem is overcome with a Monte-Carlo-based simulation approach. To prove the validity of the Monte-Carlo approach, the system was applied to the EGF receptor (EGFR) signaling. EGF signals were simulated, each model component was calculated and the concentration of Myc and phosphatidylinositol 3,4,5-trisphosphate (PIP3) was observed. The simulation results of the treatment with EGF were compared to that of untreated cells, the model predicted that activation of the EGF pathway leads to an upregulation of Myc compared with unactivated cells, and an increase in PIP3. These results were also compared to simulation results of *RAS*-mutated cells. *RAS* mutation leads to the upregulation of Myc compared with untreated cells, whereas PIP3 remains unchanged. The results were as expected for *RAS* mutations. To demonstrate the power of the model Kühn presented the results of cancer treatment in patients with colorectal cancer (CRC) with erlotinib, a drug that blocks EGFR, and therefore, the proliferation of CRC cells. There are however mutations such as in *KRAS* and *BRAF* that counteract the response to erlotinib. These mutations are often found in CRC patients. Patients carrying these mutations have no improvement in standard of care, but in the absence of these mutations, erlotinib improves survival. Therefore, what a doctor normally does before they treat a patient with erlotinib is to scan for *KRAS* and *BRAF* mutations. This was also predicted by the model. The model does not only find the mutations that are not beneficial for the drug, but also identifies drugs according to carried mutations. The developed model predicts drug response or drug combination to different mutation panels. In personalized cancer therapy, after tumor sampling, next-generation sequencing technologies are applied to initialize a patient-specific mutation/expression model and find

the optimal treatment. This model was used in a melanoma patient who was found to carry 667 mutations; 16 of which were imported in the model. The drug optimization process runs all available drugs and combines drugs according to a patient's genotype. For this patient, the model demonstrated four drugs that could be given in combined therapy. Researchers also validated the model by *in silico* testing drug combinations in patients' tumors. Finally, the model was validated using clinical data, by the sequencing of prostate cancer patients. The simulation of these patients data were compared with clinical profiles of these patients: many correlations were found between real practice and model-predicted drug response.

Kühn summarized noting that the large pathway and signal transduction model that has been developed at the Max-Planck Institute is able to simulate complex cellular processes such as cancer using the Monte-Carlo-based approach. This model can be used for clinical trial stratification, and thus, help in identifying appropriate patient populations for new cancer drugs. By using expression data as well as mutation data based on next-generation sequencing technologies, the model is able to simulate patient-specific tumors and thus to find an optimal drug combination for a patient specific therapy.

■ **Question: did you or anyone from your group see the patients personally?**

**Alexander Kühn:** "No, only their physicians".

**Jean Clairambault (INRIA, Paris, France):** "We are talking about bringing things to clinical practice. What do you think are the steps that you need to take for your discoveries and modeling to be utilized by physicians to take decisions?"

**Alexander Kühn:** "Actually, what we do right now is an ongoing project where we sequence 20 different melanoma patients, in collaboration with oncologists. We hope that we can treat these patients based on model predictions. Of course, all these patients are more or less at end-stage disease therapy".

**Jean Clairambault:** "So, if you use melanoma patients or melanoma tissues then they are highly heterogeneous. Most scientists believe that they have stem cells that have different characteristics, what is actually modeling in them?"

**Alexander Kühn:** "At the moment, we do two things: we do deep sequencing of tumor tissue and of cancer stem cells derived selection by CD133<sup>+</sup> selection and do modeling of them both. This gives us the opportunity to deal with certain stem cell characteristics. Right

now, we do not have any other solutions on this heterogeneity. That is indeed a problem in real life”.

Kiang-Teck J Yeo (Department of Pathology, University of Chicago, IL, USA) presented ‘Cardiopharmacogenomics: Application of Pharmacogenomics in Cardiology’. He started his talk by stating that pharmacogenomics is a very attractive field right now and focused his talk mainly on two drugs of major pharmacogenetic impact that have been relabeled by the FDA: warfarin and clopidogrel. He referred to the updated package insert of warfarin and also to the reasons that genotyping has not yet been reimbursed. He mentioned the results of the Medco–Mayo Warfarin Study [3], appraised the efforts of Medco to promote pharmacogenomic testing and also expressed his disappointment regarding the Centers for Medicare and Medicaid Services (CMS) ruling for pharmacogenomics testing released on 4 May 2009 that are opposite to the results of this study. According to the CMS ruling, available evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries. It was also proposed that pharmacogenomics testing to predict warfarin responsiveness is not reasonable and necessary under §1862(a)(1)(A) of the Social Security Act [101]. Thus, pharmacogenomics testing is covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin and only then in the context of a prospective, randomized, controlled clinical study. Currently, the majority of physicians in the USA are not ready to adopt pharmacogenomic testing, and are also not happy with the efforts of some companies to sell genetic tests directly to consumers. In the case of clopidogrel, Yeo noted that among all factors that contribute to interindividual variability in response to clopidogrel is the lack of patient compliance, other conditions such as obesity and insulin resistance (that may also have genetic basis), the nature of the coronary event, genetic factors in absorption and metabolism and drug–drug interactions (with CYP2C19 inhibitors). The hyporesponsiveness is associated with poorer clinical outcomes, but the precise mechanisms are not known and are likely to be multifactorial. Despite the fact that the clopidogrel package insert was relabeled, information on CYP2C19 variant alleles is not complete since the CYP2C19\*17 allele, which is associated with an ultrarapid metabolism of

CYP2C19 substrates, is not included in revised labels. Yeo presented the results of the study by Mega *et al.* that boosted the field of clopidogrel pharmacogenomics and also noted that recently a study was published demonstrating no effect of CYP2C19 variant alleles on clopidogrel response [4]. However, based on Mega *et al.*, CYP2C19 variant alleles affect both clopidogrel pharmacokinetics and pharmacodynamics.

Finally, Yeo presented novel results on KIF6 polymorphisms predicting who might benefit from high doses of atorvastatin. KIF6 appears to be a good predictor. Carriers of the 719Arg allele are at an increased risk of cardiovascular events, but they seem to benefit from aggressive atorvastatin therapy [5]. Yeo concluded that pharmacogenetic markers will increasingly be used for personalizing drug therapy. The clinical utility of pharmacogenetic testing lies within dose adjustments in the case of warfarin, selection of alternative drugs/dose escalation for loss-of-function carriers in the case of clopidogrel, and the selection of patients for aggressive therapy in the case of statins.

The next presentation was given by Ron H van Schaik (Erasmus MC Rotterdam, The Netherlands), on pharmacogenetics and transplantation. He started his talk with the question of how we can proceed with pharmacogenomics of immunosuppressants. The three immunosuppressant drugs he discussed were tacrolimus, mycophenolic acid and cyclosporine. Pharmacogenetics plays a role in all three compounds and he provided examples for them. Tacrolimus has a narrow therapeutic window: low dose is associated with kidney rejection whereas high dose is associated with nephrotoxicity. Thus, tacrolimus dose is correlated with both acute organ rejection and side effects such as nephrotoxicity. Tacrolimus administration at concentrations below 10 ng/ml are associated with an increased risk on rejection, whereas concentrations above 15 ng/ml are associated with nephrotoxicity. Differences in tacrolimus metabolism between patients is dependent, for a significant part, on polymorphisms of CYP3A5, the principal metabolizing enzyme of this drug. CYP3A5 expressors have lower tacrolimus concentrations on the same dose when compared with nonexpressors. CYP3A5 polymorphisms might thus be of importance, especially in the early phase of tacrolimus treatment. Results from the TacTic pharmacogenetic study [6], a prospective French study in kidney transplant patients taking tacrolimus who were genotyped in advance, demonstrated that an adjusted dose

for CYP3A5 expressors of 0.25 mg/kg instead of the standard dose of 0.20 mg/kg presented a significantly higher proportion of patients within the target tacrolimus concentrations. The same was true for CYP3A5 nonexpressors receiving a dose of 0.15 mg/kg instead of 20 mg/kg. Therefore, if you are a CYP3A5 expressor, you are initially underdosed with the standard dose of 0.20 mg/kg.

During exposure to mycophenolic acid a large number of kidney transplantation patients in the fixed-dose versus concentration-controlled (FDCC) study had levels of mycophenolic acid below the target concentration range of 30–60 ng/ml [7]. Specifically, 18% of the population has had above target levels and 21% had below target levels; the latter group being at risk of losing the transplanted kidney. Therefore, patients have to receive the right dose as soon as possible. Mycophenolic acid catabolism depends on UGT1A9 activity. In the promoter region of the *UGT1A9* gene the polymorphism -275T>A confers higher enzyme activity. Owing to this polymorphism, patients with the polymorphism receiving standard dosing of mycophenolic acid had a significantly lower exposure to the drug (20% lower mycophenolic acid area under the curve) and were at an increased risk of acute transplant rejection. These results were confirmed by another group, demonstrating that patients carrying the -275T>A polymorphism had a 27% lower mycophenolic area under the curve. Logistic regression analysis demonstrated that patients carrying the -275T>A polymorphism are at increased risk by more than 13-times to reject the kidney transplant.

For cyclosporine, there are many efforts to find genetic polymorphisms which would predict the interindividual variation in its metabolism, but the results do not demonstrate a consistent and significant candidate thus far. van Schaik presented the results of a pharmacogenetics study on the acceptors and donors of kidney transplantations. This study demonstrated that there was no correlation between nephrotoxicity and *ABCB1* polymorphisms in transplant acceptors. However, the situation is different with the donors; if the kidney comes from somebody who carries the TT genotype of the *ABCB1* 3435C>T polymorphism, then the odds ratio (OR) of nephrotoxicity is 13.4. van Schaik's conclusions regarding the three drugs are as follows: in the case of tacrolimus, *CYP3A5\*1* carriers have initially lower tacrolimus exposures when given standard dosing and are therefore possibly at increased risk of

acute rejection; in the case of mycophenolic acid, the *UGT1A9* -275/-2152 SNPs are correlated with decreased mycophenolic acid exposure, and present a higher risk of acute transplant rejection (OR: 13 [95% CI: 1.1–162]) in these patients; and in the case of cyclosporine, there is no consistent and significant relationship with genetic polymorphisms in the transplant recipient, but donor *ABCB1* 3435C>T status appears to be correlated with nephrotoxicity.

■ **Question:** in the tacrolimus study in which dose was adjusted based on *CYP3A5* genotype & therefore moved patients in the therapeutic range, did you have any outcomes in that population?

**Ron van Schaik:** “It’s a French study, led by Eric Thervet [6]. They looked at patient outcome and they could not find a correlation with acute rejection. The tricky thing with that particular study is that they have given tacrolimus on the seventh day of the study; the other results that I have shown you are from our own FDCC study where patients started on tacrolimus from day 1 [8]. Thus, in the French study there is a gap of 7 days in which patients did not get tacrolimus. It could be that this particular clinical end point was not significant because they started so much later with tacrolimus dosing. But you could see an effect on the pharmacokinetics and that comes back to the first question of the pharmacogenetic approach here: if you can see an effect on pharmacokinetics, is that sufficient to do the testing or is it necessary to see a significant effect at a pharmacodynamic end point?”

■ **Question:** how do you feel that you are going to operationalize this in a clinical study because difficulties for acute conditions such as this need to get the genotype pretty rapidly to make a decision on dosing unlike areas such as warfarin or clopidogrel where one can adjust things a week or two later & have no major impact? How do you go about getting this into the clinic so that everybody is able to make a decision right away?

**Ron van Schaik:** “We have been doing pharmacogenetic testing for patients’ diagnostics for 5 years. For any genotyping request you’ll have an answer in our hospital in 3 days. If it is from an outpatient clinic it takes a bit longer because our clinical pharmacologists will also give specific advice on dosing for that individual patient.

In any case, for inhouse requests, in 3–4 days you will have the results. So, at this moment it is working pretty well. We would like to do it faster, ideally have the result within the same day. But for that, more requests per day are needed so that it is economically justified to have technicians performing the analyses on a daily basis. So technically, that is not really the problem. With tacrolimus I'm not sure if the clinicians are convinced to already use the genotyping in advance (although we have recently started such a study), but I have noticed that once the test is available and clinicians get familiar with it, they will send their problematic cases: somebody is giving tacrolimus to the patient and then he measures, for instance, too low drug concentrations, there is a need to increase. Sometimes, physicians are a little bit reluctant to do that so then they are asking for the genotyping test to get confirmation that this patient may have a genetic polymorphism that justifies higher drug dosing than normal. If we can help out these clinicians with their problematic cases, there will be a moment when they will want to know this information in advance because they have now experienced the contribution of the genotype themselves”.

Vangelis G Manolopoulos (Democritus University of Thrace Medical School, Alexandroupolis, Greece) gave the next lecture on ‘Genotype-Guided Dosing of Coumarin Derivatives: The European-Pharmacogenetics of Anticoagulant Therapy (EU-PACT) Consortium Trial’. EU-PACT is the first large-scale randomized controlled trial of pharmacogenetic-guided anticoagulation therapy to ever be performed in Europe [9]. The EU-PACT trial is a two-armed, single-blind randomized controlled trial that will test the effectiveness of genotype-guided regimens during anticoagulant treatment with the three coumarin derivatives used in Europe (warfarin, phenprocoumon or acenocoumarol). EU-PACT trial is about to start in seven European countries (UK, Sweden, The Netherlands, Spain, Greece, Germany and Austria) in a total of 13 different centers. Approximately 3000 patients starting anticoagulant therapy with warfarin, phenprocoumon or acenocoumarol will be recruited (1000 for each coumarin derivative). Patients will be randomized to receive the dose of each coumarin derivative calculated either with an algorithm that includes genetic information on *CYP2C9* and *VKORC1* genes (intervention group) or with an algorithm without genetic information. All dosing regimens will be computer assisted. Patients that

are randomized to the intervention group will be genotyped for *CYP2C9*\*2 and *CYP2C9*\*3 variant alleles and for the *VKORC1* -1639G>A polymorphism. A novel feature of the EU-PACT trial is the use of a point of care test developed by LGC Ltd (Middlesex, UK) for rapid genotyping within 90 min in a nonlaboratory environment. Therefore, a patient's genotype will be instantly available prior to their first coumarin derivative prescription. Only newly diagnosed patients with either atrial fibrillation or venous thromboembolism requiring anticoagulation therapy will be included. The primary outcome of the study is percentage of time in range of the International normalized ratio (INR; range 2.0–3.0) during the first 3 months following initiation of anticoagulant therapy. Among secondary outcomes are the incidence of adverse effects, the utility of the rapid genotyping test in daily anticoagulation practice, patient quality of life and cost-effectiveness of pharmacogenetic-guided doses for each of the three coumarin derivatives. It is anticipated that the results of the EU-PACT trial will help persuade clinicians to incorporate pharmacogenetic-based dosing into their clinical practice.

**Comment 1 (Wolfgang Sadee, The Ohio State University, OH, USA):** “I see that in this European Consortium you use the *VKORC1* -1639G>A polymorphism and that is useful because this is the polymorphism that has a functional effect. The Medco study was done with a different polymorphism that is only a survey marker. I have a major concern on all data on what the physical roles of each SNP used are. I think it is really important to make sure that we do not introduce unnecessary genotyping in clinical practice”.

**Vangelis Manolopoulos:** “We had a lot of discussion on this, although *VKORC1* polymorphisms are on linkage disequilibrium, we decided to go with the -1639G>A polymorphism”.

**Comment 2 (Wolfgang Sadee):** “This is a good point. We genotype *CYP450* enzymes and all defective alleles are correlated with pharmacokinetics, but we have to start incorporating other alleles as well to increase predictive value. Even though we cannot predict 100% of warfarin response, we can predict a great percentage and that is very important”.

The last lecture was given by Alain Huriez (President of the European Personalized Medicine Diagnostics [EPEMED], Nantes,

France) on 'Development and Use of Theranostic Biomarkers. Impact on the Industry Business Model. Needs of Guidelines. Market Access Issues: the European Case'. Huriez presented the practical application of personalized medicine and how we can translate the developed markers and all the research carried out so that they are available for patients. However, there are questions regarding guidelines, market access issues and the industry payers involved in the model. Personalized medicine tends to improve cost-effectiveness of medicines for patients. When you look at the therapeutic efficacy of drugs, the response rate is still very variable depending on the treatment and on the patient. Owing to high expenditures in the healthcare system, the authorities are willing to push for cost minimization and better effectiveness. Subsequently, there are constraints on new drug approval. The regulatory agencies and the health technology assessment agencies are pushing to see new diagnostics of personalized treatment being developed. The concept of the biomarker is not new. The first blood biomarker was glycemia for diabetes and clearly the concept of new personalized markers dates back to the late 1980s with the new 'omics' technology. The newest products are Herceptin® and HercepTest™ and Vectibix®/Erbix® and *KRAS* mutations. There are an increased number of examples of drug-associated companion diagnostics. Huriez provided as examples of diagnostics approved by the FDA for clinical practice, the drugs herceptin, cetuximab and imatinib and their respective targets HER2, EGFR and the cell-surface tyrosine kinase receptor. This concept of companion diagnostics is a multidisciplinary issue, it involves academic centers, research centers, biotech companies and pharmaceutical industries. Drug development continues until commercialization and during this phase, the concept of companion diagnostics may influence the attrition rate, the benefit:risk:response ratio as well as the economic perspective. In addition, at the postapproval follow-up of marketed drugs, the concept of companion diagnostics can improve the benefit:risk:response ratio and as for retrospective strategy, it improves drug lifecycle management and brings some competitive advantage to the product. At this point Huriez reminded the audience that for *KRAS* mutations the drug was approved before the development of the test and the identification of the mutations. Huriez passed on the kind of impact that companion diagnostics may have in the future on the industry. Clearly, there are some pros and

cons. The pros include lifecycle management (improved evaluation), differentiation against biosimilars or new entrants without companion diagnostics, and patient stratification during clinical development that allows the patenting of new drug use and application. Among the cons are restricted patient populations and market potential, who actually pays, and what the price is for research diagnostics as well as the way the product will be distributed and the corresponding royalties. Despite promising data we only see a small number of companion diagnostics that have reached the market. There are questions about utility, specificity and validation of biomarkers – prospective trials are the key to demonstrate evidence-based data – and many hurdles associated with regulatory questions, market access and the commercialization business model. In Europe, despite the progresses, the application of molecular diagnostics in personalized medicine is still lacking in comparison to the USA and the main reason for this is the lack of education and training of the various stakeholders. In Europe, there are several differences across member states. Huriez took as an example the differences in five European countries regarding the evaluation system for companion diagnostics. In the final part of his talk, Huriez provided a brief overview of what EPEMED is. EPEMED is a not-for-profit organization bringing together forces in personalized medicine that address issues in personalized medicine that confront the industry, regulators, payers and insurers, as well as governments. EPEMED is aiming to provide a platform for the harmonization of personalized medicine development and implementation across Europe, focusing on the crucial role of diagnostics, to make personalized medicine a reality. Huriez pointed out the mission of EPEMED in development as threefold: to develop a central point of communication for the different parties involved in progressing personalized medicine; optimal regulatory and reimbursement routes for innovators to deliver personalized medicine treatments to patients; and a greater understanding of the clinical development of personalized therapeutics through the creation and application of advanced diagnostic tests. Huriez also defined the near term goals of EPEMED. Therefore, as a centralized European organization, EPEMED will address the following in Europe and worldwide: regulatory guidance on the co-development of diagnostic tests and personalized drug therapy; validation approaches for companion diagnostic tests; value-based

pricing and reimbursement of diagnostic tests; and efforts to improve market access for high-value companion diagnostics. Finally, Huriez provided further information on EPEMED partners and members.

### General discussion

Gerard Siest opened the discussion section of the round table. He noted that he was concerned by the big differences between the fundamental part of the meeting, and the last round table, which was more practical. There is an incredible gap between the discovery of new results with particular genes and the clinical outcome that had been discussed in the afternoon session. Another concern of Siest's was that only genotyping was discussed, they had not mentioned phenotyping expression analysis and miRNA approaches, and they had not discussed much regarding proteomics. So it is very strange that no other 'omics' technologies are used in an attempt to provide more information to the clinicians.

Adriano Henney further commented on this issue. He believes that the problem is that everyone wants to perform metabolomics, proteomics and transcriptomics on patient samples. Whilst these technologies are established at the academic level, in his opinion, the biggest hurdle to advancement in applying them in the clinic is access to patient samples and tissues in sufficient quality and quantity. We have been banking DNA samples for the past 20 years as part of linkage studies and association studies, so thousands of samples exist to link, retrospectively, data on diseases, how they develop over time and how that changes. Biomarker research however does the reverse; using proteomics or metabolomics profiles to predict outcome. Therefore, we need to start by taking samples and linking those profiles prospectively with outcomes. The question is which markers to choose and what profiles to focus on from a huge range of options, and then to link these with these patients to evaluate them for their ability to predict outcomes. As we have seen from GWAS, you need many thousands of samples to deal with the statistics of multiple testing. It is going to be very difficult to achieve that level of knowledge and collect the number of appropriate samples necessary to evaluate these technologies in a prospective fashion.

Henney added that there is an even more pertinent issue to consider. Henney himself is not a clinician but he has a son who is, and he hears of the pressures placed on the normal hospital doctor every single day on what they

have to do in their day job. The daily time and administrative pressures on the hospital doctor is absolutely huge. So when presented with the question by an enthusiastic researcher: "I've got this brand new, promising technique and it is sort of interesting and we believe we should be using it in the clinic with you guys", it is not surprising that the response will be lukewarm. We have to respect and understand the pressures and imperatives on the clinician, and find ways to work within these constraints as scientists to bridge the divide between science and clinic in the application of these new technologies, focusing primarily on the benefit to the patient rather than the scientist. Henney acknowledged that some fantastic science was presented at the meeting, but the question remains: 'where is the added benefit that these techniques bring to clinical practice, over and above the algorithms already in use, that give you the best chance to treat a patient optimally?' That is the key question because nobody is going to pay for an attractive piece of science if it is not going to provide a cost benefit over current practice. In addition, you are not going to be able to do that unless you get together and work it into the clinic with the clinicians in a way that fits their constraints. Henney believes that as scientists we are tending not to do that properly. In many ways, we have forgotten the patient in much of what we are doing in order to progress our own scientific objectives for the quality of science. Now, there is clearly nothing wrong with the pursuit of academic science in its own right, but when it comes to applying it to clinical scenarios, the primary end point for consideration is the delivery to the patient. The final comment he wanted to make was that it is actually economics that will be the driver, not the science. If it becomes clear that there is a test that can segment a treatment group, payers will undoubtedly begin to demand that it is used to justify reimbursement. As a result, that is eventually going to be the driver and that has to be the focus of the research efforts.

George Patrinos (University of Patras, Greece) made a comment about storing genetic information. He stated that we are talking about personalized medicine so we need to improvise a way to store genetic information for the patients. We have companies claiming they can sequence a whole genome for less than US\$10,000, that means the \$1000 genome is just around the corner. We are talking about third-generation sequencing, which will make this a reality, so we also need to seriously sit down and try to

consider ways of storing genetic information so that if somebody goes to the clinician and the clinician wants to know his/her genotype, he should be able to get it very quickly or have this information beforehand.

Bryan Dechairo responded that in the pharmacy world, when they carry out one of the tests (i.e., a warfarin test), they may check for other CYPs as well and store the data in the patient's electronic medical record. Thus, if a patient gets a *CYP2D6* test for tamoxifen and then they are prescribed a selective serotonin reuptake inhibitor such as fluoxetine, a pharmacy alert automatically appears that tells the physician and the pharmacist that actually they should be on a drug not metabolized through *CYP2D6*, so they are recycling the information. Dechairo agrees that there has to be storage of pharmacogenetics information. In his opinion, another issue that this panel should address is the sequencing of the whole-chip approach. The biggest hurdle to this is a regulatory one, and the difficulty is if you can measure 10,000 things and only 500 are clinically meaningful at this point, what do you do with the rest? Do you store? Do you report out additional relevant results later? How do you obtain additional test results from your original data after new tests are approved and previous findings now have additional clinical utility? For regulatory submission there is a process to take one test through at a time, but there is currently not a process to take broad DNA chips through where only some of the data gathered is currently clinically meaningful. In addition, what are the ethics of knowing something but not recording it yet? The data is not completely validated but you are in possession of this data regarding your patient today. Thus, overall we have to be careful with ethics issues on data not used.

Kiang-Teck J Yeo commented that he believes there is a large gap between very innovative science and the very conservative economic environment. Thus, Yeo thinks that very innovative science and clinical practice do not play to the same timelines. In addition, if you look at numerous current standard-of-care biomarkers, it appears that they were adopted into clinical practice with less stringent requirements for evidence of clinical utility. If the same high level of evidence that is required of warfarin is employed for these prior biomarkers, a lot of them would not be approved today for reimbursements by CMS. The second thing is that obviously there is the huge financial investment needed to translate a biomarker from a research concept to a validated clinical product in the marketplace. So there is a gap between

the academic world, some research centers and even some biotech companies, and then the gap for having used prospective validation studies, well-designed studies bringing sufficiently strong evidence-based data to make regulators change a label or decide that this is a product that should be reimbursed. In addition, the reimbursement structure is still unclear, even the coding system is not adjusted to the complexity of the majority of multiparameter molecular tests. So the question of the return on investment as well has made the overall system not optimal yet.

Wolfgang Sadee commented that there are two dependents to drug complications particularly for genotyping and also to all biomarkers. One is the need to order the test, which is a huge problem, and the other one is the current cost/benefit analysis, which is widely moving on. As some people commented we are probably moving to whole-genome sequencing or to other methods that divide into smaller segments, with each test costing up to \$300. In his laboratory or in any other laboratory these data can be produced at a much lower cost. So we must now move forward to the time when a patient comes to the door and the information is already available. Then the only remaining pressure is that the information is useful, owing to the cost of storing the data: storing the data means retrieving the data and learning from the data and that is the cost.

Bryan Dechairo answered that this is going to take more than 2–3 years because the biggest hurdle to this is not the technology, nor the issue of cost effectiveness, but because producing a chip at \$200 is cheaper than one warfarin assay being reimbursed. The real issue is the oversight of ethics on how you store, retrieve, what you see and what you do not see and what is reported when a family mutation is detected or it is found that somebody is not somebody's parent. There are many ethical questions there and so the biggest inhibition to getting this in the marketplace now is governmental regulations and payers' perspectives of this. In addition, if you look at healthcare costs, diagnostic costs are less than 3% of all healthcare costs. So when you start talking to a company who is the payer, they actually do not want to talk to you about diagnostics because they have 97% of other things that are more important to them. Therefore, it is really difficult to have that cost–effectiveness dialogue with that company today.

Kiang-Teck J Yeo noted that one thing people should not forget is the facilities that can translate emerging tests into the clinical routine. While the clinical laboratories play a very

important role, most are presently not ready to adopt making these tests routine for many practical reasons. One practical reason is that some of the variants are not common, so what do you use for a quality control? Are synthetic oligonucleotides containing the particular SNPs acceptable as quality controls for rare and common variants? Some would argue against using synthetic oligonucleotides since they do not reflect the total process of DNA extraction from real sample to detection of the target polymorphism. There is one other aspect that people should know; in the USA there are probably more lawyers than scientists. So with FDA relabeling of drugs, lawyers are advertising on the internet to represent any patient who might have suffered a preventable adverse drug reaction because a physician had chosen not to order the relevant pharmacogenetic test owing to nonreimbursement concerns. Imagine if somebody gets hurt, for instance a bleeding event, especially if this person happens to be politically connected. Even though they may be rare, every one in 1 million of those may sue. If you just look at the internet there are lawyer enterprises with services for Stevens–Johnson syndrome. And yet why isn't everybody screened for that even though it is a rare variant? Another practical issue for the clinical laboratory includes proper interpretation of complex genotypes (e.g. *CYP2D6*). Thus we may not know what it means if you are a carrier of some of these complex variants. So in Yeo's opinion the companion genetic test may need to be complemented by the measurement of drug/metabolite concentrations, perhaps even requiring classical phenotyping with probe drugs for a case with complex genotypic results. This is because the genotype-predicted phenotype relationship is still not well worked out yet for *CYP2D6*. Yeo would say the same thing for *CYP2C19* and Plavix®. At present, Yeo thinks that the implementation of pharmacogenetic testing for resistance to Plavix should include more than the variants mentioned in the FDA relabeling, and should include the *CYP2C19\*17* and possibly the *ABCBI* variants.

Adriano Henney came back to a fundamentally important point, which is the gap between the academic science laboratory, the clinical practitioner and industry. He thinks that is something that needs to be addressed urgently. In this meeting, we got into specific technical details, but not so much focusing on translating the cutting edge science into practice. A lot of this is largely precompetitive. Henney's view is that, especially in Europe, we have the potential

to set up some kind of safe harbor that will offer the opportunity to academic laboratories to test in the real-world some of their science, and offer clinicians the opportunity to look at how things may be applied. Henney proposed a different kind of collaboration that would allow not only the evaluation of biomarkers, but also to study how system approaches might be more effectively adopted to understand the 'omics' signatures in the context of physiological response. Henney thinks that this is the only way to generate the evidence needed to convince people that this is the way forward. We have no alternative. The science that we practice now is very complex. The old traditional routes used by the pharmaceuticals industry will not tackle the challenges of complex diseases effectively; that is now clearer than ever. Henney also added that the major areas of impact on health economics are not cancer, but cardiovascular diseases, diabetes and similar highly prevalent complex, chronic diseases that have significant unmet clinical needs, and that are a major drain of resources. That is where the focus has to be, that is where we need to be focusing our attention. We have great results on targeted therapy in cancer but where the real economic benefit is going to be is on these major diseases and he thinks that we have to be creative in constructing new ideas on how to tackle it.

Bryan Dechairo added to the above comment that one of the things people need to start doing differently is not thinking that pharmaceutical companies are their partners but start looking at healthcare payers, healthcare companies and the government, where there are potential partners for academic groups to work with. Payer organizations can form partnerships in research because we are moving towards electronic medical records at least in the USA and electronic medical records already exist in other parts of the world. You can actually carry out this type of translational research and then the clinicians see the results of their data without having rigorous problems with case-report forms to do this kind of thing because they are using electronic medical records to guide you with the benefit of a test. Dechairo thinks that we have to just change the way we take our grant money and get prospective samples in partnership with the healthcare providers.

Tomasz Dylag from the European Commission (Brussels, Belgium) commented that the majority of outcomes on personalized medicine from available reports are similar with this workshop and he is very happy that there is a

consistency because what we are doing is a better way to inform. He emphasized a few issues that have not been mentioned. He agrees that there are disadvantages in novel technologies. For all technologies, from the start, we have to deal with issues of quality control, standardization, data storing and data collection. The collected data are beyond the comprehension of one person. There should also be a manner to combine data from different technologies. Concerning the 'omics' platforms, Dylag believes that they are very useful for the development of biomarkers and it would be very useful if the development of these biomarkers starts with the development of a new drug. However, they should be developed while always keeping in mind the clinical utility. It is absolutely right that we see plenty of great science, but indeed this is not taken up by the clinicians. There must be someone who supports the development, for this purpose they recently published a call for proposals for development of technological platforms, so that technological development can be applied in personalized medicine. In this round table they observed this process of implementation, but before revolution there should be evolution. Towards this end, the European Commission are trying to organize a big event, maybe a big conference probably next year to better steer the research this way.

Adrián Llerena commented that everyone believes in the clinical utility of pharmacogenetics. We cannot reach personalized medicine without clinicians. The first question is whether we have enough science yet to go directly into clinical problems. Llerena does not think so. He presented as an example the *CYP2D6* gene and the idea people have that drug dosage can be decided according to the number of active alleles. This is not true at least in psychiatry where clinicians face many problems with compliance. It could be a problem for psychiatrists to follow prescriptions according to the genotype and deal with their patients. To solve that problem we need to be humble, we also have to solve the problem of how to use drugs, we need to have science on the top of that, and we need to produce independent academic clinical trials in real conditions (drug polytherapy). Llerena was positive about FP7 even though we have Clinical Research Networks Centers (in Europe ECTIN); the cost of a trial is really a problem and FP7 can be helpful in tackling that. These European Clinical Research Networks Centers however are essential to convert knowledge into practice. Finally, Llerena noted the cost of antipsychotic drugs and commented that new

antipsychotic drugs are more expensive than old antipsychotic drugs; however, they produced clinically important adverse reactions. Llerena used this example to emphasize that we need to produce information on drugs because otherwise we cannot predict anything.

Bryan Dechairo commented on the point made by Adrián Llerena. There are many drugs in the market that may have adverse effects but work very well. Therefore, there is potential for personalized medicine in psychiatry, diabetes and cardiovascular disease to bring back older drugs that are cost effective and look at current pipelines for available drugs. He thinks that we should all work on these areas.

Peter Schulz-Knappe (Protagen AG, Dortmund, Germany) asked what could make the pharmaceutical industry pay for this?

Antoine Bril (Institut de Recherche Servier, Suresnes, France) agreed that the pharmaceutical industry at large has a responsibility in the education of physicians and patients. Patients now have access to much information through the internet so they need to understand all the specifics in the treatments they receive. Therefore, the responsibility of all those involved in the discovery of novel therapeutic solutions, scientists, clinicians and drug companies, is to ensure patients understand the utility of their treatments. This 'education' has to be provided by experts such as physicians, especially because patients have a close relationship with their physicians. A second point is that the pharmaceutical industries have to innovate more. Altogether, scientists and clinicians carry out a lot of research and write good papers, but the key point is to ensure that those discoveries are translated into benefit to the patients. When a drug is approved the patient has to really benefit from it as well as from all the technologies used to ensure a better use of such a drug. Bril considers biomarkers, which could be a biochemical or genetic marker as well as an imaging strategy, as technology and believes that such technologies are required to answer the right questions. A right question is what the benefit is for the patient. The discovery of novel therapeutic solutions will be possible only if we are all working together. It seems that there is no way for one single company to do all the work needed alone. Pharmaceutical companies need to collaborate with biotech and with academic teams for the discovery of therapeutic solutions, including drugs, markers and better ways to define patient populations. Thus, we all have to rethink the way we implement collaborations. It could even be necessary to redefine

what is competitive between various companies to ensure that patients are eventually receiving the best treatments.

Adrián LLerena disagrees with this comment because he claimed a drug company is a company, and ultimately they need to produce money. He believes that drug company marketing does not favor pharmacogenomics.

Adriano Henney agreed with this comment but also believes that companies have now improved in this respect. The point he wanted to make was on ethics. He believes that companies have to be segmenting the treatment of a group of patients and mentions that although this is not ethical, are there any ethical considerations for not developing a test? So, ethics is the first thing to consider when investigating who is going to pay for this. Regulators will require companies to perform the segmentation. We have seen examples of companies that have been reimbursed for a treatment that addresses a certain proportion of the patients when a test was available. So that is already happening, but we must avoid misinterpretation. People have to understand what we can do with the tests and what we cannot do. Another point Henney wanted to make was that we are focusing on markers that can be directly used in the clinic. Henney believes that there is a lot more that can be done in this respect. One way is possibly using nonvalidated clinical markers for decision-making in clinical trials. We have to change the process in order to make better

decisions and bring these markers closer to the market. Improved decisions will ultimately benefit the patients. Tomasz Dylag added that phenotyping is also crucial and Gerard Siest commented that national and European organizations dealing with pharmacogenomics will help in having better defined protocols and filling the gap between clinicians' education and scientists. We need specific supports for improving quality assurance, data treatment and storage such as biobanking. This is not 'high science' but it is essential to improve the quality of the data and their use, that is, the control of preanalytical variability for which no grants are easily available. This is absolutely essential in making practical recommendations in the field. The way of developing pharmacogenomics should be organized perhaps by a systems biology approach, so we should be creative. Finally, some points of the discussion could be developed at a European level by the creation of a European society of pharmacogenomics.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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#### Executive summary

- The hot topics of the round table discussion include the following:
  - The interest of measuring phenotypes in addition to genotypes, as genetic information alone is insufficient
  - The use of models for the different types of cancer
  - The necessity to better define the populations and the biological variations found within them
- Assessing patient benefit is more important than new developments in pharmacogenomics, ethics is also important. The implementation of pharmacogenomics in clinical practice requires understanding the costs and reimbursement possibilities.
- Compliance is often a major problem in nonresponding patients.
- The following drugs are currently the main applications for pharmacogenomics:
  - Warfarin
  - Clopidogrel
  - Tacrolimus
  - Mycophenolic acid
  - Anticancerous drugs
  - Antipsychotropic drugs
  - Statins
- The round table was coordinated by two private organizations (Medco and European Personalized Medicine Diagnostics) and at the conclusion of the meeting it was proposed that a scientific European organization be developed to realize independent studies and clinical trials and to participate in educational efforts (European Society of Pharmacogenomics and Theranostics).

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## Website

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