



Article scientifique

Article

2019

Accepted version

Open Access

This is an author manuscript post-peer-reviewing (accepted version) of the original publication. The layout of the published version may differ .

4th ESPT Conference: pharmacogenomics and personalized medicine - research progress and clinical implementation

Sipeky, Csilla; Llerena, Adrián; Manolopoulos, Vangelis G; Pearson, Ewan; Mlakar, Vid; Gozzo, Lucia; Simmaco, Maurizio; Marchetti, Paolo; Re, Marzia Del; Stankovic, Sanja; Meyer, Urs; Cascorbi, Ingolf; Ingelman-Sundberg, Magnus; Suarez-Kurtz, Guilherme [**and 7 more**]

How to cite

SIPEKY, Csilla et al. 4th ESPT Conference: pharmacogenomics and personalized medicine - research progress and clinical implementation. In: Pharmacogenomics, 2019, vol. 20, n° 15, p. 1063–1069. doi: 10.2217/pgs-2019-0095

This publication URL: <https://archive-ouverte.unige.ch/unige:147157>

Publication DOI: [10.2217/pgs-2019-0095](https://doi.org/10.2217/pgs-2019-0095)

4TH ESPT CONFERENCE: Pharmacogenomics and Personalised Medicine - research progress and clinical implementation

C. Sipeky¹, A. Llerena², V. G. Manolopoulos³, E. Pearson⁴, V. Mlakar⁵, L. Gozzo⁶, M. Simmaco⁷, P. Marchetti⁸, M. Del Re⁹, S. Stankovic¹⁰, U. Meyer¹¹, I. Cascorbi¹², M. Ingelman-Sundberg¹³, G. Suarez-Kurtz¹⁴, J. Marc¹⁵, T. Katsila¹⁶, M. Paulmichl¹⁷, C. Nofziger¹⁸, M. Ansari¹⁹, F. Drago⁶, R.H.N. van Schaik²⁰

¹Institute of Biomedicine, University of Turku, Turku, Finland

²CICAB Clinical Research Center, Extremadura University Hospital and Medical School, Badajoz, Spain

³Laboratory of Pharmacology, Medical School, Democritus University of Thrace, Alexandroupolis, Greece

⁴Division of Cardiovascular & Diabetes Medicine, University of Dundee, Dundee DD1 9SY, UK

⁵CANSEARCH Research Laboratory, Department of Paediatrics, Faculty of Medicine, Geneva University, 1205 Geneva, Switzerland

⁶Dept. of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy

⁷Analytical Laboratory Unit Sant'Andrea Hospital, Sapienza University, Roma Italy

⁸Oncology Unit Sant'Andrea Hospital, Sapienza University, Roma Italy

⁹Clinical Pharmacology and Pharmacogenetic Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy

¹⁰Centre of Medical Biochemistry, Clinical Centre of Serbia, Belgrade, Serbia

¹¹Biozentrum, University of Basel, CH-4056 Basel, Switzerland

¹²Institute of Experimental and Clinical Pharmacology, University Hospital Schleswig-Holstein, Kiel, Germany

¹³Department of Physiology and Pharmacology, Section of Pharmacogenetics, Biomedicum 5B, Karolinska Institutet SE-171 77 Stockholm, Sweden

¹⁴Instituto Nacional de Câncer and Rede Nacional de Farmacogenética, Rio de Janeiro, Brazil

¹⁵Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

¹⁶Department of Pharmacy, University of Patras, Patras, Greece

¹⁷Center for Health & Bioresources, Austrian Institute of Technology, 1210 Vienna

¹⁸PharmGenetix Gmbh, 5081 Anif, Austria

¹⁹Geneva University Hospital, Department of Paediatrics, Oncology and Haematology Unit, Geneva, Switzerland. CANSEARCH Research Laboratory, Department of Paediatrics, Faculty of Medicine, Geneva University, 1205 Geneva, Switzerland

²⁰Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, The Netherlands

Corresponding author:

Csilla Sipeky

Institute of Biomedicine, University of Turku, FINLAND

Email: csilla.sipeky@utu.fi

ABSTRACT

The 4th European Society of Pharmacogenomics and Personalised Therapy (ESPT) biennial conference was organized in collaboration with the Italian Society of Personalized Medicine (SIMeP) and was held at Benedictine Monastery of San Nicolò l'Arena in Catania, Sicily (IT) on 4-7 October 2017. The congress addressed the research progress and clinical implementation in pharmacogenomics and personalised medicine. The 4th ESPT congress brought together leading international scientists and healthcare professionals actively working in the fields of pharmacogenomics and personalised therapy. Altogether, 25 speakers in 15 sessions comprehensively covered a broad spectrum of pharmacogenetics and pharmacogenomics research, clinical applications in different clinical disciplines attended by 270 delegates.

KEYWORDS: ESPT conference, pharmacogenomics, clinical implementation, personalised medicine

INTRODUCTION

The 4th Conference of the European Society for Pharmacogenomics and Personalised Therapy (ESPT) was held in collaboration with the Italian Society of Personalized Medicine (SIMEP), under the auspices of European Federation of Clinical Chemistry and Laboratory Medicine (EFLM), Federation of Clinical Chemistry and Laboratory Medicine (IFCC), SIF (Societa Italiana di Farmacologia) on 4-7 October 2017 in Catania, Italy. The historical Benedictine Monastery of San Nicolò l'Arena, served as congress venue.

After successful events in the previous years (Budapest 2015, Lisbon 2013, Bled 2011), the Catania congress again brought together leading international scientists, healthcare professionals and stakeholders of pharmacogenomics and personalised therapy, striving to enhance the scientific interaction and facilitate diagnostic implementation of pharmacogenomics. The mission of ESPT is to contribute to safer and more efficient use of drug therapy for every patient in Europe, utilizing the potential of pharmacogenomic information.

The Conference was opened by **Prof. Urs Meyer (CH)**, BioZentrum University Basel, giving an overview on seven decades of therapeutic lessons for human individuality, showing where pharmacogenetics and pharmacogenomics have started, and showing the current status as well as the future perspectives, as addressed in challenges and opportunities, and lessons to be learned from history. The opening session was extended by an excellent lecture of **Prof. Ann Daly (UK)**, Newcastle University, Newcastle upon Tyne, focusing on the genetics of drug induced liver injury, showing that idiosyncratic drug-induced liver injury (DILI) is rare (1:10,000-100,000) but can cause serious toxicity, with 5-10% of cases to develop potentially fatal liver failure, requiring transplantation. For flucloxacillin, a DILI GWAS study identified a strong correlation with *HLA-B*57:01*, with the *HLA-B*57:03* as an alternative risk factor. *HLA-A*3301* was significantly associated with DILI for a.o. terbinafine, ticlopidine (Omnibus GWAS). The role of *PTPN22* associated with DILI was described.

Prof. Adrian Llerena (ESP) indicated that pharmacogenetics and personalized medicine are expected to be helpful in clinical decision making for depression in general, and particularly for suicide. The relationship between drug metabolizing genes and suicide can be due to different mechanisms. Prof. Llerena indicated that there does not appear to be clinical trials directly exploring suicide risk, since available information is mostly based on indirect analyses of suicidal events as adverse drug reactions (ADRs) during clinical trials on antidepressant drugs. Pharmacogenes could be helpful to explain suicidal events in relation to the lack of efficacy for a prescribed/standardized antidepressant drugs treatment in an individual vulnerable to suicide.

Prof. Ewan Pearson (UK) opened the session on cardiovascular and antidiabetic drugs stating that pharmacogenetics should be part of mainstream clinical care. He outlined key areas where genetic variants altered drug response in type 2 diabetes, such as *CYP2C9* for sulphonylureas and *SLC2A2* for metformin response. **Prof. Alfredo Ferro (IT)** gave an introduction to computational pathway analysis and presented several examples how this can be applied in pharmacogenomics. **Dr. Chiara di Resta (IT)** presented an overview of the recent developments and challenges of sequencing in cardiopathies. The complexities of the disease make variant interpretation challenging and whilst sequencing offers the ability to evaluate multiple genes simultaneously, it does create challenges with deciding on pathogenicity and when to report variants of uncertain significance. Mutations can be associated with different clinical phenotypes (e.g. both conduction and structural disorders); half of patients have no variants whereas 20% have multiple variants in multiple genes. **Prof. Vangelis G. Manolopoulos (GR)** presented a lecture on the current state regarding pharmacogenomics for cardiovascular drugs, showing a prominent role for genetic variation for anticoagulants, clopidogrel, beta blockers, cholesteryl ester transfer protein (CETP) inhibitors and statins. Open issues and questions blocking wide adaptation of pharmacogenomic testing into routine cardiovascular clinical practice were addressed. The speaker concluded that cardiovascular drug pharmacogenomics and therapy personalization is neither a reality nor a hype,

but rather an uphill long-distance track we must strive to continue successfully for the benefit of our patients and society.

Prof. Laure Elens (BE) presented pharmacogenomics for guiding immunosuppression in solid organ transplantation. The presentation began with a review of tacrolimus for liver and kidney transplantation demonstrating that the drug is highly variable in terms of pharmacokinetics and pharmacodynamics. A case of two patients with highly different pharmacokinetics was presented, highlighting the importance of *CYP3A5*, *CYP3A4* and *ABCB1* in tacrolimus metabolism. In the second part of the talk, the pharmacogenomics of cyclosporine, mycophenolate mofetil (MMF) and inosine monophosphate dehydrogenase (IMPDH) was discussed. **Prof. Sofia Siest (FR)** addressed *VEGF* as a potential biomarker for systems medicine. She demonstrated that four SNPs in *VEGF* gene can explain 50% of heritable variability in gene expression, also showing functional implications of these variations. Lecture concluded by presentation of current activities and future plans within the VEGF consortium. **Dr. Maja Matic (NL)** presented clinical studies on pharmacogenomics and pain. Main drugs used for controlling the pain are opioids and their mode of action with candidate gene approach was extensively reviewed in the beginning of the lecture. Out of ten selected genes investigated for association with codeine, three were significantly associated with efficacy and adverse side effects: *CYP2D6*, *OPRM1* and *COMT*. Next results of studies on cardiac surgery and cancer patients were presented demonstrating *OPRM1* and *COMT* are associated with higher dose requirements for analgesia. In children, tramadol was investigated in conjunction with *CYP2D6*, *OPRM1* and *OCT-1* transporter. The presentation was concluded by a discussion on the importance of variant and gene interaction for explanation of associations with drug efficacy and toxicity.

The Italian Society of Personalized Medicine (SIMeP) session was opened by SIMeP President **Prof. Paolo Marchetti**, from Sapienza University of Rome, who gave an overview on the state of the art and the perspective of personalized medicine in oncology. He highlighted that “Imprecision medicine” leads to drastically high rate of inefficacy or toxicity during treatment with main drug classes. Prof. Marchetti continued stressing the importance to address the problem of patient’s adherence to the therapy. Patient’s non-adherence is a main source of inefficacy and increasing quality, efficacy and tolerability of pharmacological treatment by targeted therapy prescription may represent the key to increase patient’s compliance. Prof. Marchetti presented data showing that a preemptive biochemical functional assay performed on peripheral blood mononuclear cells is able to predict severe toxicity and is probably linked to clinical outcome, and has improved predictive performance compared to currently used pharmacogenetic testing. **Prof. Maurizio Simmaco (IT)** presented the organizational model of the Personalized Medicine service at the Sant’Andrea Hospital of Rome, which is based on integration of genotype and phenotype characterization. Genome based prediction of drug response is flanked by phenotypic evaluation using therapeutic drug monitoring, biochemical functional assays and metabolomics. Prof. Simmaco showed the high potential of liquid chromatography coupled with tandem mass

spectrometry to develop rapid, robust, effective and low cost analytical assay for phenotype characterization. He presented examples for (1) evaluation of intestinal permeability (2) detection of neurosteroids and (3) studying metabolites of the kynurenine pathway. **Prof. Monica Miozzo (IT)** presented the concomitant detection of chromosome 1p/19q codeletion and *IDH1*, *IDH2* and *TERT* mutation status by Mass Array approach in glioma. The talk addressed the recently revised glioma diagnosis WHO guidelines which integrates molecular parameters and demonstrated the development of a reliable, accurate, rapid, and cost-effective MassARRAY (MS)-based test that can identify 1p/19q codeletion using quantitative SNP genotyping and, simultaneously, characterize hotspot mutations in the *IDH1*, *IDH2*, and *TERT* genes in tumor DNA. Furthermore, this MS approach could be similarly exploited in evaluation of loss of heterozygosity (LOH) in other tumors for clinical and/or research importance (1). **Prof. Marianna Nuti (IT)** explained that immune cells can shape the outcome of various anticancer therapies. Accumulating data suggest that antitumor activity of conventional cancer therapy results in part from its ability to harness the innate and adaptive immune systems by inducing immunologically active tumor cell death. Pre-existing immunity against tumor cells is the factor that influences the response to standard and target therapies. Immune checkpoint inhibitors (ICI) have recently been introduced as novel therapeutic strategy in the treatment of cancer. Pre-existing natural or induced anti-tumor immunity is one of the variables that has been associated with increased response and the concomitant elimination of immune-suppressive cells are also dominant mechanisms of enhanced antitumor activity. Immunoncology is entering the field of precision medicine and a number of emerging biomarkers are now been validated in the different clinical settings.

Dr. Patricia Curtis (CH) opened the Pharmacogenomics in Oncology session with DNA repair genes associated with chemotherapy and stem cell bone marrow transplantation. Acute graft versus host disease (aGvHD) is one of the main reasons of mortality and conditioning regimen as important factor for success of hematopoietic stem cell transplantation (HSCT). Phases of aGvHD were described by focusing on DNA damaging mechanisms of busulfan and latter release of damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) by damaged cells and their activation of immune system. *MGMT* was a gene that exhibited significant association with aGvHD. **Prof. Thomas Muerdter (GE)** presented pharmacogenomics of tamoxifen. The intracellular metabolism through *CYP2D6*, the generation of endoxifen and the implication for clinical practice and current pharmacogenomics guidelines for tamoxifen administration were addressed. LOH was demonstrated to be an important factor determining tamoxifen treatment effect. Three possible options for translating current knowledge into the clinical practice were discussed: dose escalation, high dose endoxifen treatment or supplementation of tamoxifen with low doses of endoxifen. **Dr. Linda Henricks (NL)** showed the clinical value of *DPYD*-guided dosing of fluoropyrimidines. Results of a prospective clinical trial on 2,035 patients demonstrated a significant risk of toxicity for slow metabolizers. This toxicity risk could be reduced from 73% to 30% in case of genotype-based dose adjustment. In addition, appropriate plasma concentrations were achieved significantly faster when using

pretreatment genotyping leading to significantly economic benefits by improving patient's safety. Lecture was concluded by presentation of new project focused on implementation of new screening tests for dihydropyrimidine dehydrogenase (*DPD*) pretreatment phenotyping.

Prof Romano Danesi (IT) highlighted the use and clinical utility of cell free DNA analysis using digital droplet PCR (ddPCR) to detect the *EGFR* T790M mutation in lung cancer patients. Detection of this mutation will drive a change of therapy towards the use of osimertinib, because of associated tyrosine kinase inhibitors (TKIs) resistance. **Dr. Marzia del Re (IT)**, continued on the use of exosomal derived AR-V7 for the detection of prostate cancer resistance, again using ddPCR. This approach showed a better discrimination between AR-V7 positive and AR-V7 negative patients compared with the paper of Antonarakis, who showed a progression free survival of 6.2 months for Ar-V7 negative patients as determined using circulating tumor cells (CTCs), against a progression free survival of 20 months using AR-V7 detection through exosomes. This suggested that the AR-V7 negative patients in the Antonarakis study may have been missed due to the lower sensitivity of CTCs versus exosomal AR-V7 analysis. **Prof Winand Dinjens (NL)** presented Next Gen Sequencing (NGS) with Unique Molecular Identifiers (UMIs) for the sensitive detection of mutations in *EGFR* in cell free DNA from lung cancer patients. By using UMIs, a very high sensitivity could be obtained, comparable to the digital droplet PCR approach. The advantage of NGS being that multiple mutations can be monitored than just T790M, Exon19del, L858R or C797S, as done with ddPCR.

Helen Gautschi (SA), from DNalysis Biotechnology, presented the practical application of nutrigenomics and nutrigenetics. Mrs. Gautschi analyzed how dietary improvement (vitamins B12 and B6, folic acid and omega-3 fatty acids) may provide an efficacious and accessible treatment strategy for the management of highly prevalent mental disorder, including depression. She showed beneficial effect of adjunctive l-methylfolate 15 mg among inadequate responders to selective serotonin reuptake inhibitors (SSRIs) in depressed patients who were stratified by biomarker associated with inflammation or metabolism levels and genomic markers associated with l-methylfolate synthesis and metabolism. The presentation continued with outline of research studies that explored SNPs that alter IL-1 activity (*IL-1A* 4845 G>T & -889 C>T, *IL-1B* 3954 C>T & -511 A>G, and *IL-1RN* 2018 C>T) and the course of certain chronic diseases, followed by presenting how specifically formulated botanical mixture targeting IL-1 production and response was able to significantly reduce *IL-1* gene expression and C-reactive protein (CRP) in healthy individuals carrying gene variations associated with *IL-1* overexpression. **Carlos Malpica (USA)**, from Metabolon Inc. gave a lecture about adding precision metabolomics applied to personalized medicine. In the introduction, he explained that metabolomics improves understanding of health and the influences of diet, drug treatment, genes and lifestyle. Dr Malpica presented the main principle of the patented technology that automatically compares the generated data against an extensive chemical library to isolate relevant metabolites in minutes, giving accurate, and reproducible result. In the second part of the talk Meta IMD™ - comprehensive analysis of

hundreds of metabolites associated with a wide range of inherited metabolic disorders using Metabolon's proprietary technology and informatics was presented. It simultaneously surveys individual metabolites and pathways across amino acids, carbohydrates, organic acids, fatty acids, neurotransmitters, nucleotides and bile acids to detect biochemical abnormalities associated with a wide range of Inherited metabolic disorders, and may also spot disorders for which there is presently no biochemical testing available. The metabolic signature consistent with early signs of disease conditions and drug effects associated with efficacy and toxicity was explained. Lecture concluded by presentation of metabolomics as an effective approach to complement NGS for disease risk assessment, disease monitoring, and customized drug therapy in clinics.

This year, aiming to provide an inspirational platform for young scientist, ESPT board introduced a new session focusing on young investigators. The ESPT Poster Committee selected the three best abstracts for oral presentation. **Dr. Matthias Samwald (AT)** from the Medical University of Vienna gave a lecture about establishing multi-lingual, multi-modal pharmacogenomic decision support. The Ubiquitous Pharmacogenomics (U-PGx) project is an international, multidisciplinary effort aiming to implement pharmacogenomics-guided drug dosing across seven European countries. Advantages of the developed system are safe use of patient data and adoption to local languages. **Irene Dapia (ES)**, INGEMM Hospital Universitario La Paz in Madrid, presented on the implementation of pharmacogenetics (PGx) in the Spanish National Health System. She revealed that the most relevant barriers for the implementation of PGx in the clinical practice are low institutional promotion, lack of clinical guidelines and economical aspects. Therefore, they created a PGx Unit aiming to provide consultation and genotyping of 180 SNPs (PharmArray®). As an outcome, in the clinical recommendation both the predicted phenotype and the clinical information are individually integrated for each patient. **Dr. Sylvie Quaranta (FR)** explained the levels of evidence and recommendations developed at the French Network of Pharmacogenetics (RNPGx) aiming for pharmacogenetics-based personalized therapy in four major therapeutic domains. The RNPGx classification integrates the functional impact of genetic variations, the nature of the phenotype concerned, the clinical evidences available, and the existence of non-genetic options for treatment personalization. Based on this, three levels of evidence were developed: (i) 'essential' in the case of unpredictable clinical phenotype of major importance by a non-genetic approach; (ii) 'advisable' in the case of intermediary phenotypes or for clinical phenotypes of major importance, but predictable by non-genetic methods; (iii) 'possibly useful' in case of intermediary phenotypes with less robust evidences but useful case-by-case.

Prof. Ingolf Cascorbi (DE) opened the session on PGx on drug transporters talking about new SNPs and clinical applications of *CYP3A4* genetic variants. He emphasised the clinical importance of *CYP3A5**3 contributing to variability of drug response of tacrolimus. *CYP3A4**22 significantly affected trough/dose concentration ratios, whereas variants in related genes such as *NR1/2*, *POR* or *PPAR alpha* have only minor impact. Hence, combination of *CYP3A5**3 and *CYP3A4**22 explains best interindividual variability of tacrolimus pharmacokinetics. Of major clinical

importance are rare but functionally inactive specific SNPs creating a premature stop-codon like in *CYP3A4*20* and *CYP3A4*26*. It can be expected that wider application of NGS technologies will lead to the discovery of more rare variants contributing to the explanation of overall variability of *CYP3A4* activity. **Dr. Charity Nofziger (AUT)** talked about in depth analysis of *CYP2D6*. This locus is extremely complex containing variable number of structurally similar pseudogenes and accurate sequences cannot be obtained using standard NGS methods, but long read methods are required. In particular this laboratory has identified many novel *CYP2D6/CYP2D7* hybrids. In her lecture she gave examples of the most complex gene arrangements and pinpointed the necessity of careful validation of the methods used for identification of the genetic variants. **Dr. Jos Kleinjans (NL)** talked about miRNAs as pharmacogenomic biomarkers for drug safety. He gave an overview of acetaminophen-induced miRNAs and their target mRNAs which were to a great extent related to immune response, and apoptosis/DNA damage. The miRNAs could be clustered in relation to type of liver injury. He concluded that these miRNAs could be examined as novel biomarkers for drug injury and disease. **Prof. Magnus Ingelman-Sundberg (SWE)** talked about sequencing rare variants as the next step in pharmacogenetics. He gave an overview about the current pharmacogenomic biomarkers and then presented a study where the *CYP2C19* genotype was analysed in 2,087 patients taking escitalopram (2). It was found that 40% of the patients carrying preferentially *CYP2C19*17* did not receive a therapeutic plasma dose during standard regimen and that 30% of patients carrying **2/*2* or **17/*17* genotypes switched medication within 1 year as compared to 12% in the other genotype groups. He stressed the importance of pre-emptive genotyping before starting escitalopram therapy. He presented data showing that the extent of rare genetic variants is very different between different pharmacogenes and that the overall contribution of rare variants to the variability in drug pharmacokinetics is 20-30%. Analyses of 204 pharmacogenes from 60,706 individuals (ExCAC) revealed 73,998 genetic variants of which 83% were novel and 98% were rare. In fact, 50 % of the variants were only seen in one individual.

Dr. Scott Megill (USA) from Coriell Life Sciences, a commercial spin out of the Coriell Institute for Medical Research, providing pharmacogenetics services to hospital systems, clinics and individual practitioners in the U.S., Asia, Europe and South America, discussed what is needed for pharmacogenomics implementation from the perspectives of the population, health providers, patients and caregivers and then introduced GeneDose^{LIVE}, a physician and pharmacist tool for pharmacogenomic decision support. He emphasized that decision support tools can dramatically reduce the time required to produce individualized medication recommendations and serve as key educators for physicians in the proper use of genetic testing. **Prof. Guilherme Suarez-Kurtz (BRA)** discussed the impact of population diversity on the conceptual development and clinical implementation of pharmacogenetics. Data from Brazilians and Mexicans were used to highlight the diversity and complex admixture pattern of Latin American populations, in which the individual proportions of Native, European and African ancestry vary widely and, most importantly, in a continuous pattern, that is not captured by race/color/ethnic categorization, and

must be recognized in the design, interpretation and reporting of pharmacogenomic trials. **Dr. Robin Everts (USA)**, from Agena Bioscience, showed data from a new copy number variation panel that allows a better overview of the *CYP2D6* gene. The panel detects variations in 5 different sites throughout the *CYP2D6* gene and could therefore detect samples containing hybrids such as *13 and *36. The data showed that 5% of the samples tested contained a *CYP2D6-CYP2D7* (*68) or *CYP2D7-CYP2D6* (*13) hybrid allele that could potentially alter the phenotype. Due to the multiplexing of the assays in a single well, high throughput screening of many samples at the same time is possible and obsoletes the use of different techniques to test for these hybrid alleles. **Prof. Adrian LLerena (ESP)** Americans/Hispanics (588 million of people) that are product of Post-Columbian admixture between the autochthonous Amerindians, Europeans, and African slaves and their descendants. This study is aimed at characterize the frequencies of *CYP2D6*, *CYP2C9* or *CYP2C19* alleles, as well as genotype-predicted poor or ultrarapid metabolizer phenotypes (gPMs or gUMs), in different populations from Latino and IberoAmerica, in a total of 6,060 individuals. A high interethnic variability has been described in several of *CYP2D6*, *CYP2C9* and *CYP2C19* alleles, as well as *CYP2D6* or *CYP2C19* gPMs and gUMs.

Dominique Dewolf (BE), affiliated to Life Technologies, opened this session presenting pioneering pharmacogenomic assays and technologies that may serve as pre-emptive pharmacogenomics strategies. **Dr. Jari Forsström (FIN)**, an expert in health informatics at Åbomics, shared his experience towards the implementation of pre-emptive pharmacogenetic screening and reporting in the clinic. Opportunities and challenges were presented, considering the paradigm of the establishment of the Atuline Virtual Hospital. **Dr. Daniella Steinberger (GER)**, CEO of bio.logis, acknowledged the current status of implementing genetic information for clinical use, reviewing the clinico-genomic tools and databases available. She introduced the Genetic Information Management Suite (GIMS) of bio.logis, an IT-based solution for the efficient management of genetic information and notably, after raising the question on what is still missing, Dr. Steinberger introduced the term “clinical interpretome” as the means to pave the way towards an actionable pharmacogenomics analysis. **Dr. Theodora Katsilla (GR)**, affiliated to the University of Patras, emphasized on decision- and sense-making in genomic medicine and presented the potential of a human – artificial intelligence synergy to avoid biases.

Prof. Sir Munir Pirmohamed (UK) underlined that despite recent Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines demonstrating the economic benefit of pre-emptive genotyping of both HLA-A*31:01 and HLA-B*15:02 for carbamazepine therapy (CBZ), regulatory efforts lag behind and no change in the summary of product characteristics (SmPC) for CBZ is foreseen. **Prof. Markus Paulmichl (AT)** followed with an underpinning message relevant to all stakeholders within the field of PGx - the genotyping results need to be right! The complexity of the *CYP2D6* gene and surrounding locus was used to demonstrate how easy genotyping errors can be made. He highlighted the current EMA initiative to make the requirements related to the choice of appropriate genomic methodologies transparent, presented in the form of a guideline

entitled "Good Pharmacogenomic Practice" (see <http://www.ema.europa.eu>). **Prof Mario Pazzagli (IT)** rounded out the session with an overview on the aims and activities of the joint EFLM-ESPT (EFLM, European Federation of Clinical Chemistry and Laboratory Medicine) working group named "Personalized Laboratory Medicine", the main goal of which is to develop documents and disseminate knowledge on the implementation in the clinical laboratory of the personalized laboratory medicine approach in European countries.

The symposium was concluded with a discussion session, started by a presentation of Prof Ron van Schaik on the European Pharmacogenetic Implementation Consortium (Eu-PIC, www.eu-pic.net), which consists of 106 participants in 38 institutes in 19 (mostly) European countries, involving The Netherlands, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Luxemburg, Lithuania, Portugal, Serbia, Slovenia, Sweden, Switzerland, Turkey and the United Kingdom. A collaboration with the US Pharmacogenomics Research Network (PGRN) was recently established. The need for harmonization and exchange of experiences is the basis of this network, which focusses on clinical laboratories performing PGx analysis for diagnostics. The network has decided to collaborate with ESPT, and is now joining the Clinical Implementation Division of ESPT. Eu-PIC/ESPT are now involved in setting up PGx in Lithuania, Turkey, Serbia and Italy. After this, the new call in HORIZON2020 was addressed, and opportunities to submit a proposal there, discussed, especially project SC1-BHC-25-2019: demonstration pilots for implementation of personalized medicine in health care. A discussion session followed with the panel Sir Munir Pirmohamed, Markus Paulmichl, Guilherme Suarez-Kurz, Magnus Ingelman-Sundberg, Filippo Drago, Mario Pazzagli (EFLM) and Romano Danesi, addressing the barriers and potential solutions to move the implementation of PGx in Europe. Filippo Drago pointed out that lack of knowledge on physicians as well as lack of access to testing were barriers. Whereas on one hand the need for solid evidence prior to implementation was acknowledged by the panel, the example of clopidogrel and *CYP2C19* was put forward to show that the phrase "sufficient evidence" could still be interpreted rather broad: whereas the FDA has put a boxed warning on *CYP2C19* in the drug label of clopidogrel, the European Society for Cardiology in their guidelines still indicated that "insufficient prospective evidence" was there to recommend genetic testing of *CYP2C19*. The apparent position of genetic testing was discussed, and whether this special position was justified. PGx is a lab test, and not a new drug. In that respect, it was remarked that the requested randomized controlled trials fitted better with the introduction of a new drug, than the implementation of a new laboratory test. The difference in uptake of the *DPYD* genotyping for capecitabine was highlighted: whereas in The Netherlands, this test is now commonly used before starting therapy, the European Society for Medical Oncology (ESMO) does not recommend this test (yet), Prof Romano Danesi remarked. Conclusion was that still more knowledge and implementation projects were needed to drive the implementation of PGx.

The ESPT congress closed on Saturday Oct 7, 13:00.

REFERENCES

1. Pesenti C, Paganini L, Fontana L, Veniani E, Runza L, Ferrero S, et al. Mass spectrometry-based assay for the molecular diagnosis of glioma: concomitant detection of chromosome 1p/19q codeletion, and. *Oncotarget*. 2017;8(34):57134-48.
2. Jukić MM, Haslemo T, Molden E, Ingelman-Sundberg M. Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. *Am J Psychiatry*. 2018;175(5):463-70.

Conflict of interest

CN is employed by Pharmgenetix GmbH, an independent laboratory offering pharmacogenetic testing and reporting services.