Conference Report

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Pharmacogenomics

The Sixth European Society of Pharmacogenomics and Personalised Therapy Congress

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On 8–9 November 2022, the European Society of Pharmacogenomics and Personalised Therapy organized its sixth biennial congress, in Belgrade, Serbia (congress website: www.sspt.rs). The congress aimed to address the current status and future perspectives of pharmacogenomics, share latest knowledge in the field of precision medicine and showcase the implementation of clinical applications in pharmacogenomics/pharmacogenetics. The 2 day congress consisted of 17 lectures given by key-opinion leaders and included a poster session plus discussions. The meeting was a great success by generating an informal environment and enabling the exchange of information between 162 participants from 16 different countries.

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The European Society of Pharmacogenomics and Personalised Therapy (ESPT) (www.esptsociety.eu) was created in 2011, aiming to contribute to safer and more efficient use of drug therapy for every patient in Europe, utilizing the potential of pharmacogenomic information, by sharing knowledge and creating interactions between experts and stakeholders. The main goal of ESPT is to facilitate clinical implementation of pharmacogenomics/pharmacogenetics (PGx) in Europe. To achieve this, ESPT organizes an international congress biannually. Previous meetings were held in Bled, Slovenia (2011); Lisbon, Portugal (2013); Budapest, Hungary (2015); Catania, Italy (2017) and Seville, Spain (2019). The sixth congress, reviewed here, took place in Belgrade, Serbia, 8–9 November 2022, having been delayed 1 year by the COVID-19 pandemic.

Clinical implementation of PGx

Participants were welcomed by ESPT President, Professor Vangelis Manolopoulos (University of Thrace, Greece), who explained the mission and vision of ESPT.

In the first lecture, A Daly (Newcastle University, Newcastle upon Tyne, UK) explained the latest developments on drug-induced liver injury (DILI), a rare but serious toxicity. New risk factors for DILI by genome-wide association study refinement, such as *ERAP2* genotype as a predictor for DILI due to amoxicillin clavulanate therapy [1], were addressed. Daly also presented a more complex polygenic risk score predictive for amoxicillin clavulanate, fasiglifam and flucloxacillin DILI [2]. The second lecture, by G Patrinos (University of Patras, Patras, Greece; United Arab Emirates University, Al Ain, UAE), covered the U-PGx Horizon 2020 project, focusing on the psychiatry arm of the study. He showed that implementation of a pre-emptive 12-gene pharmacogenetic panel for psychoactive drugs resulted in a decrease of adverse drug reactions (ADR) in psychiatric patients in Greece. An important aspect is the application of economic evaluation to assess the feasibility of reimbursement for pharmacogenetics testing [3]. Subsequently, B Zukic (University of Belgrade, Belgrade, Serbia) discussed the Pharmacogenomics-HUB in the Balkans, another European Horizon project. This collaboration between the universities of Belgrade, Patras, Ljubljana and Trieste aims at a pharmacogenomics population analysis and will apply a web-based information system (ePGA-WB) as a clinical decision-support tool [4].

Perspectives on PGx testing in Europe

The second day started with the keynote lecture of D Primorac (St Catherine Specialty Hospital, Zagreb, Croatia), addressing his views on pharmacogenomics being at the center of precision medicine, and identifying challenges and perspectives in an era of big data [5]. St. Catherine's individualized medicine model, focusing on 27 genes, 111 SNPs and affecting over 300 medications, resulted in the identification of 43.6% significant gene–drug interactions. Primorac also addressed the need for a multi-omics model, in which PGx is one of the components, as well as the future of PGx, including next-generation sequencing (short and long reads). Next, J Swen (Leiden University Medical Center, Leiden, The Netherlands), highlighted the European U-PGx Horizon 2020 PREPARE study, in which pre-emptive pharmacogenetic analysis of 12 genes, based on the Dutch Pharmacogenetics Working Group dosing advice, was performed in seven European countries, with the frequency of ADRs as the primary outcome [6]. Swen indicated that the study showed significantly reduced ADRs by using PGx; study results are expected to be published shortly. M Ingelman-Sundberg (Karolinska Institute, Stockholm, Sweden) addressed the missing heritability in pharmacogenomics. Based on twin data, up to 50% of the genetic variation in absorption, distribution, metabolism and excretion genes remains unknown, and the explanations include a plethora of rare genetic variants [7] in regulator genes like *NFIB* and as-yet unidentified haplotypes of common alleles. An example of the latter is the identification of the new *CYP2C:TG* haplotype, which causes ultrarapid CYP2C19 activity [8]. In the last lecture in this session, T Morris (Illumina, Cambridge, UK), focused on pharmacogenomics for precision dosing, highlighting opportunities for broad-panel pre-emptive pharmacogenetic testing as compared with single-gene reactive testing. Increasing evidence on the economic benefits of pre-emptive PGx testing regarding rehospitalizations, long-term care in psychiatry and in cardiology was addressed.

Psychiatry & childhood leukemia

The session was opened by E Molden (University of Oslo, Oslo, Norway), presenting on the relationship between PGx and drug concentrations in psychiatry. Molden showed correlations between *CYP2C19* genotype and escitalopram drug concentrations between *CYP2D6* genotype and concentration/switching on vortioxetine, and between

CYP2D6 genotype and efficacy of risperidone and aripiprazole treatments [9]. For clozapine, a genome-wide association study identified *NFIB* and *CYP1A2* as important genetic markers [10]. Lastly, Molden reflected on the potential use of solanidine as a dietary *CYP2D6* biomarker. D Müller (University of Toronto, ON, Canada) then highlighted the medical perspective on PGx implementation in psychiatry. He reviewed findings which consistently showed that adults and children with actionable *CYP2C19* and *CYP2D6* profiles were more likely to discontinue antidepressant and antipsychotic medications [11]. Data from the IMPACT study showed much higher than expected frequencies of variant *CYP2D6* genotypes among 12,000 patients being referred to the Center for Addiction and Mental Health, a specialized tertiary care center [12]. Müller reflected on Clinical Pharmacogenetics Implementation Consortium, US FDA and Dutch Pharmacogenetics Working Group guidelines for PGx and differences between them. S Pavlovic (University of Belgrade, Belgrade, Serbia) highlighted PGx in childhood leukemia, with *NR3C1, ABCB1* and *GST*s as promising markers for glucocorticoid response [13]. She gave an overview on PGx for vincristine, methotrexate, asparaginase, anthracyclines and thiopurines. The session was concluded by S Russmann (Zurich, Switzerland) showing that PGx-guided pharmacotherapy can be expanded from drug–gene to drug–drug–gene interactions. The role of *HLA* genes with respect to DILI was addressed, and he showed the clinical relevance of a 16-gene pharmacogenetic panel test for medication management in a cohort of 135 patients [14]. In addition, *CYP2C19*/clopidogrel and *SLCO1B1*/statin combinations were highlighted.

Oncology & cardiology

M Ansari (University of Geneva, Geneva, Switzerland) reflected on PGx in pediatric oncology, focusing on sinusoidal obstruction syndrome of the liver in hematopoietic stem cells. Using a candidate-gene approach as well as whole-exome sequencing for busulfan therapy, an association between *GSTA1* diplotype groups and busulfan metabolism was found. *UGT2B10* and *KIAA1715* were retained in a multivariable model as significant genetic factors [15]. A systematic review of genetic predictors for sinusoidal obstruction syndrome was published recently by Ansari and his group [16]. A large multicenter pediatric prospective randomized clinical trial is ongoing to validate these results (Bugenes). L Henricks (Leiden University Medical Center, Leiden, The Netherlands) presented on PGx for *DPYD* in capecitabine therapy. In a randomized controlled trial, Hendricks and colleagues showed that adjusting the dose based on four *DPYD* SNPs – *2A (1905+1G>A, rs3918290), *13 (c.1679T>G (rs55886062), 2846A>T (rs67376798) and 1236G>A (rs56038477) – significantly reduced capecitabine toxicity [17]. Henricks further reflected on the use of uracil as a measure for DPD deficiency, indicating that uracil levels showed poor correlation with DPD enzymatic activity and were influenced by pre-analytical factors, and thus should only be used with great caution to guide capecitabine therapy [18]. Wout van den Broek (St. Antonius Hospital, Nieuwegein, The Netherlands) discussed *CYP2C19* genotyping for clopidogrel in the acute coronary syndrome setting. Clopidogrel is less effective in patients with *CYP2C19* nonfunctional (loss-of-function) alleles. In the POPular GENETICs study (a genotype-guided $P2Y_{12}$-inhibitor study), therapy with clopidogrel for noncarriers and ticagrelor for *CYP2C19* nonfunctional allele carriers was found to be noninferior regarding net clinical benefit and reduced bleeding risk, as compared with standard care (ticagrelor for all) [19]. The last presentation was by F Florindi and C Valsecchie (Thermo Fisher Scientific, Brussels, Belgium), addressing the potential and possibilities of both genome-wide and custom-designed microarrays for the future of pharmacogenomics.

New directions

In this last session, N Božina (Zagreb University, Zagreb, Croatia) looked beyond PGx, addressing the clinical utility of drug–drug–gene interactions. For lamotrigine, an impact of the *ABCG2* 421C>A appeared to be specific for valproate. D Akin (Bahesir University, Istanbul, Turkey) addressed the unmet need regarding methylphenidate therapy and presented an update on the status of PGx regarding this drug for treating attention-deficit/hyperactivity disorder (ADHD). To investigate the association with methylphenidate therapeutic outcomes in childhood ADHD, Akin performed *CES1* and *LPHN3* genotyping, with outcomes to be validated. The final presentation was by L Louring Christrup (University of Copenhagen, Copenhagen, Denmark), representing the Danish Society for Pharmacogenomics and Personalised Therapy, addressing the Danish approach to personalised medicine. She finished her presentation by announcing the seventh ESPT Congress, which will take place in Copenhagen on 25–27 October 2023.

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References

1. Nicoletti P, Dellinger A, Li YJ *et al.* Identification of reduced *ERAP2* expression and a novel HLA allele as components of a risk score for susceptibility to liver injury due to amoxicillin-clavulanate. *Gastroenterology* 164(3), 454–466 (2023).
2. Koido M, Kawakami E, Fukumura J *et al.* Polygenic architecture informs potential vulnerability to drug-induced liver injury. *Nat. Med.* 26(10), 1541–1548 (2020).
3. Simeonidis S, Koutsilieri S, Vozikis A, Cooper DN, Mitropoulou C, Patrinos GP. Application of economic evaluation to assess feasibility for reimbursement of genomic testing as part of personalized medicine interventions. *Front. Pharmacol.* 10, 830 (2019).
4. Lakiotaki K, Kartsaki E, Kanterakis A, Katsila T, Patrinos GP, Potamias G. ePGA: a web-based information system for translational pharmacogenomics. *PLOS ONE* 11(9), e0162801 (2016).
5. Primorac D, Bach-Rojecky L, Vadunec D *et al.* Pharmacogenomics at the center of precision medicine: challenges and perspective in an era of big data. *Pharmacogenomics* 21(2), 141–156 (2020).
6. Swen JJ, van der Wouden CH, Manson LE *et al.* A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet* 401(10374), 347–356 (2023).
7. Ingelman-Sundberg M, Mkrtchian S, Zhou Y, Lauschke VM. Integrating rare genetic variants into pharmacogenetic drug response predictions. *Hum. Genomics* 12(1), 26 (2018).
8. Braten LS, Haslemo T, Jukic MM *et al.* A novel *CYP2C*-haplotype associated with ultrarapid metabolism of escitalopram. *Clin. Pharmacol. Ther.* 110(3), 786–793 (2021).
9. Jukic MM, Smith RL, Haslemo T, Molden E, Ingelman-Sundberg M. Effect of *CYP2D6* genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. *Lancet Psychiatry* 6(5), 418–426 (2019).
10. Lenk HC, Lovsletten Smith R, O'Connell KS *et al.* Impact of *NFIB* and *CYP1A* variants on clozapine serum concentration – a retrospective naturalistic cohort study on 526 patients with known smoking habits. *Clin. Transl. Sci.* 16(1), 62–72 (2023).
11. Aldrich SL, Poweleit EA, Prows CA, Martin LJ, Strawn JR, Ramsey LB. Influence of CYP2C19 metabolizer status on escitalopram/citalopram tolerability and response in youth with anxiety and depressive disorders. *Front. Pharmacol.* 10, 99 (2019).
12. Herbert D, Neves-Pereira M, Baidya R *et al.* Genetic testing as a supporting tool in prescribing psychiatric medication: design and protocol of the IMPACT study. *J. Psychiatr. Res.* 96, 265–272 (2018).
13. Gasic V, Zukic B, Stankovic B *et al.* Pharmacogenomic markers of glucocorticoid response in the initial phase of remission induction therapy in childhood acute lymphoblastic leukemia. *Radiol. Oncol.* 52(3), 296–306 (2018).
14. Niedrig DF, Rahmany A, Heib K *et al.* Clinical relevance of a 16-gene pharmacogenetic panel test for medication management in a cohort of 135 patients. *J. Clin. Med.* 10(15), 3200 (2021).
15. Ansari M, Petrykey K, Rezgui MA *et al.* Genetic susceptibility to hepatic sinusoidal obstruction syndrome in pediatric patients undergoing hematopoietic stem cell transplantation. *Biol. Blood Marrow Transplant.* 26(5), 920–927 (2020).
16. Waespe N, Strebel S, Jurkovic Mlakar S *et al.* Genetic predictors for sinusoidal obstruction syndrome – a systematic review. *J. Pers. Med.* 11(5), 347 (2021).
17. Henricks LM, Lunenburg C, de Man FM *et al. DPYD* genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. *Lancet Oncol.* 19(11), 1459–1467 (2018).
18. de With M, Knikman J, de Man FM *et al.* Dihydropyrimidine dehydrogenase phenotyping using pretreatment uracil: a note of caution based on a large prospective clinical study. *Clin. Pharmacol. Ther.* 112(1), 62–68 (2022).
19. Claassens DMF, Vos GJA, Bergmeijer TO *et al.* A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. *N. Engl. J. Med.* 381(17), 1621–1631 (2019).