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PP149— THE CEIBA COCKTAIL FOR DRUG HYDROXYLATION PHENOTYPING IN HISPANIC POPULATIONS

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Introduction: Interethnic variability of drug metabolism has been demonstrated across Iberoamerican populations by the CEIBA Consortium. Drug-metabolizing enzymes genotype just predicts actual drug metabolic activity (phenotype) in the cases of poor metabolizers. For example, only 30% of ultrarapid metabolizers can be predicted from genotyping (Llerena et al., 2012). Moreover, according to EMA recommendations, development of phenotyping procedures for drug interactions studies and clinical research recommended (EMA, 2013). Therefore, a novel cocktail approach to measure metabolic activity (metabolic ratios) of the main CYP enzymes in just one experiment is developed and validated to be used in the study of Latin-American populations.
Patients (or Materials) and Methods: Subjects were given low oral doses of 100-mg caffeine, 25-mg losartan, 20-mg omeprazole, and 30-mg dextromethorphan. Blood samples were taken 4 hours after administering the drugs to assay the following metabolic ratios in plasma: CYP1A2 (caffeine/paraxanthine), CYP2C9 (losartan /E-3174), CYP2C19 (omeprazole/5-hydroxyomeprazole), CYP2D6 (dextromethorphan/ dextrorphan), and CYP3A4 (dextromethorphan/3-methoxymorphinan). Solid phase extraction was utilized for analyte extraction and LC-MS/MS to quantify the probe drugs and metabolites.
Results: Recovery values >80% were obtained for all analytes, and no carryover or relative matrix effects were observed. The analytes were separated and detected in 9 minutes and the method was fully validated, with lower limits of quantification ranging from 0.3 ng mL–1 for 5-hydroxyomeprazole to 3.2 ng mL–1 for paraxanthine. The correlation coefficient (r2) values obtained were over 0.995 for all analytes. According to the EMA guideline on bioanalytical method validation, precision and accuracy values below 15% were achieved.
Conclusion: The method was proven to be useful to measure targeted analytes for the evaluation of CYPs hydroxylation capacity in just a single experiment.
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Disclosure of Interest: None declared.

PP151—PREVALENCE OF CARRIAGE CYP2C9, VKORC1 AND CYP4F2 POLYMORPHISMS IN RUSSIAN PATIENTS WITH HIGH THROMBOTIC RISK PRESCRIBED WARFARIN COMPARED WITH OTHER ETHNIC GROUPS

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Introduction: *VKORC1*, *CYP2C9*, and *CYP4F2* responsible for the metabolism of warfarin. Personal and ethnic differences in the genetic profile reveals in determining the outcome of a drug therapy. *Aim*: to explore the frequencies of *CYP2C9, VCORC1*, and *CYP4F2* genotypes in Russians, compare results with ones for other nations
Patients (or Materials) and Methods: A total 91 Caucasian subjects were recruited into the study. Forty (48.2%) patients were male and age was 66.17 (10.9) years. All patients had indications to receive warfarin. Medical records for the patients group were reviewed for the relevant clinical data. 5 ml of blood was taken from each subject, and DNA was isolated and used for identification of the *CYP2C9* allele *1, *2, *3; G-1639A *VCORC1*; *CYP4F2* V433M rs2108622 C > T using real-time polymerase chain reaction-restriction fragment length polymorphism assay. Results were compared with other ethnic groups and statistically analyzed with chi-square test.
Results: We described the prevalence of *CYP2C9* polymorphisms *1/*1 (67%), *1/*2 (9,9%), *1/*3 (11%), *2/*2 (2,2%), *2/*3 (8,8%), same for *VKORC1* GG (49,5%), GA (28,6%), AA (22,%) and *CYP4F2* CC (57,1%), CT (34,1%), TT (7,7%). No significant deviantions from Hardy-Wainberg equilibrium were observed ($p < 0.05$). Polymorphisms' frequency of *CYP2C9* ($P < 0.001$) and *VKORC1* GG, AA ($P < 0.05$) in Russian distinguish from Asian. There are no significant interethnic variations for *CYP4F2* between Russian, Asian and Caucasian ($P > 0.05$).
Conclusion: Prevalence of carriage of *CYP2C9, VKORC1* polymorphisms in Russian patients with high thrombotic risk is closed to Caucasians and distinguish from Asians but no for CYP4F2.
Disclosure of Interest: None declared.

PP152—TENDENCY TO HIGHER ACTIVITY OF CYP3A5 IN WOMEN WITH STILLBIRTH

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Introduction: CYP3A5 is an enzyme known to be involved in metabolism of human hormones – progesterone and testosterone, which metabolism may play a role in either disease origin or treatment efficacy in women with stillbirth. There is a common genetic polymorphism leading to its increased activity (6986*>G). Our aim was to investigate possible role of this polymorphism in stillbirth.
Patients (or Materials) and Methods: All women admitted to gynecology department of university clinics with verified diagnoses of still birth were considered for recruitment to the study. At the same time women who attended routine pregnancy registration were screened and recruited at the same time as the study group being matched by their age and concomitant diseases. All women who gave informed consent were recruited. Peripheral venous blood samples were drawn into EDTA tubes. Dna was extracted. Polymerase chain reaction in real time was performed to detect genetic variants of CYP3A5 *3/*1 (6986*>G). Chi-square test was used for frequency comparisons using statistical software Graphpad Prizm 5.0.
Results: Fifty-three women with stillbirth were recruited to the study. Control group consisted of 92 matched women. Frequency of the minor

allele A in the study group was 8%, in the control group – 4% (p = 0.1; chi-square). The following genotypes distribution was observed in the study group: AA – 0.02; AG – 0.13; GG – 0.85. In the control group the following genotype distribution was observed: AA – 0.01; AG – 0.05; GG – 0.94. Distributions corresponded to Hardy-Weinberg equilibrium.
Conclusion: In our prospective study, we observed tendency to genetic predisposition to higher activity of CYP3A5 in women with stillbirth compared with matched women with normal pregnancy. The results, however, did not reach statistical significance, which may demonstrate either lack of real association or insufficient number of subjects recruited. The observation needs to be proved or disproved in a larger population.
Disclosure of Interest: None declared.

PP153—EVALUATION OF THE RELATIONSHIPS BETWEEN ABCB1 C3435T AND G2677T/A POLYMORPHISMS AND CLINICAL RESPONSE TO VENLAFAXINE IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Introduction: Venlafaxine, as a substrate of p-glycoprotein, is a widely used serotonin-noradrenaline reuptake inhibitor (SNRI). The aim of the study is to investigate the influence of *ABCB1* G2677T/A, C3435T polymorphisms on efficacy of venlafaxine.
Patients (or Materials) and Methods: Patients (n = 52) who met the *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition-IV* criteria for major depressive disorder (MDD) were enrolled the study. All patients had affirmed for once a day administration of venlafaxine at 8:00 to 9:00 AM during the study. Protocol visits were completed at baseline, 1st, 2nd, 4th, and 6th weeks. The clinical response to venlafaxine was evaluated by psychiatrists with 17-item Hamilton Rating Scale for Depression (HAM-D17). Blood samples were taken for genotyping at 4th week of the study. Genotyping for the ABCB1 gene 3435C>T and G2677T/A polymorphisms was performed by PCR/RFLP assays.
Results: Our results showed that there is no correlation between efficacy and tolerability of venlafaxine and *ABCB1* G2677T/A, C3435T polymorphisms. But carriers of the TT genotype for 3435C>T polymorphism and carriers of the TT/TA genotype for G2677T/A polymorphism could be tended to be poor responder (Table).

Table. $HAMD_{17}$ scores according to *ABCB1* G2677T/A, C3435T genotypes.

	3435C>T		2677G>T/A	
	CC-CT	**TT**	**GG-GT-GA**	**TT-TA**
n	**41**	**11**	**41**	**11**
$HAMD_{17}$, baseline	21.56 ± 0.695	22.45 ± 2.077	21.78 ± 0.737	21.64 ± 1.865
$HAMD_{17}$, 1st week	14.93 ± 0.851	16.73 ± 2.195	15.34 ± 0.852	15.18 ± 2.252
$HAMD_{17}$, 2nd week	13.76 ±0.939	15.64 ± 1.820	13.59 ± 0.907	16.27 ± 1.978
$HAMD_{17}$, 4th week	11.27 ± 0.968	11.54 ± 1.883	11.24 ± 0.931	12.36 ± 2.125
$HAMD_{17}$, 6th week	9.63 ± 1.11	10.09 ± 2.095	9.54 ± 1.038	10.45 ± 2.577
	F = 0.41, *P* = 0.741		F = 0.672, *P* = 0.563	

Conclusion: Although our results showed that there is no correlation between efficacy of venlafaxine and *ABCB1* G2677T/A, C3435T polymorphisms, we couldn't reach the sufficient patient number. There is need for studies with sufficient patient number and haplotype analysis including also *ABCB1* C1236T polymorphism in MDD patients.
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PP154—PERSONALISING HEALTH CARE: FEASIBILITY AND FUTURE IMPLICATIONS FOR ALL STAKEHOLDER GROUPS INCLUDING AUTHORITIES, PHYSICIANS AND PATIENTS

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Introduction: The promise of personalized care has not always translated into improvements in patient care. There are concerns among payers that advice for certain genetic tests has been revoked, diagnostic tests can be costly, and there is fragmentation of funding of care including tests. In addition, pharmaceutical companies are seeking high prices for new targeted drugs through designating them as orphan drugs. Consequently, there is a need to integrate current knowledge about the value of genetic, biomarkers, prognostic tests and targeted drug therapies from a health authority perspective to provide future guidance.
Patients (or Materials) and Methods: This will be achieved by (1) reviewing the current literature regarding personalized medicine; (2) appraising key funding, organizational, and health care issues that need to be addressed especially from a health authority perspective; and (3) suggesting future avenues for all key stakeholder groups to enhance future funding and utilization of new personalized approaches to improve future patient care. The latter will be achieved through an iterative process.
Results: Multiple findings are consolidated under headings. These include (1) general considerations incorporating definitions and the need for different approaches to progress personalized medicine; (2) knowledge about the influence of pharmacogenomics on response and toxicity of drug therapies using current examples including cases where recommendations have recently been revoked; (3) knowledge of the value of biomarker tests to target treatment approaches; (4) challenges and concerns including the potentially high cost of tests and targeted therapies and current fragmentation of funding; and (5) key issues for health care funding bodies to address to enhance funding for new diagnostic/prognostic tests as well as new targeted therapies. Guidance is given on potential ways forward for all key stakeholder groups including reviewing key medical, ethical, legal,