PREEMPTIVE PHARMACOGENOMIC TESTING FOR PREVENTING ADVERSE DRUG REACTIONS (PREPARE): STATE OF ART AND PRELIMINARY RESULTS ON GENOTYPE ACTIONABILITY

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Introduction: In the last decade several studies have demonstrated that genetic variants in genes involved in drug metabolism and transport affect inter-individual variability in drug efficacy and safety. Since the 1st of January 2016an unique initiative has been launched in Europe with the financial support of Horizon 2020 program, Ubiquitous Pharmacogenomics (U-PGx), under the coordination of Leiden University Medical Center. The core of the project is the PREPARE randomized clinical trial that will be conducted in seven healthcare environments (The Netherlands, Spain, UK, Italy, Austria, Greece, Slovenia).. Primary aim of the study is to evaluate the effect of a pre-emptive pharmacogenomic approach on the prevention of toxic events and the improvement of patients quality of life.

Material and methods: The PREPARE study has a total duration of three years. Countries were randomized to starteither with the control arm phase, in which enrolled patients received the therapeutic standard dose without taking into account the pharmacogenomics profile; or with the study arm phase, in which the enrolled patients were preventively genotypedand the analysis results were used to personalize the therapy. Recruitable patients for the study must be drug-naive or have been free from treatment for at least twelve months before enrolment. Once enlisted, they had to donate either a blood or a saliva sample for PGx analysis. The analysis was performed on a panel of forty-five genetic variants in twelve genes (CYP2C9, CYP2C19, CYP2B6, CYP3A5, CYP2D6, DPYD, UGT1A1, F5, HLA-B, SLCO1B1, TPMT, VKORK).

Results: A total of 4,907patients has been enrolled from March 2017until today: 3,581patients during the first 18months phase of the study and the remaining 1,326after the 1stOctober 2018arm switch. AtExperimental and Clinical Pharmacology Unit CRO Aviano, coordinating enrolment also in San Filippo Neri (Rome) and Cà Foncello (Treviso), 904patients were enrolled in total, 302after the switch to the study arm.Patients were immediately genotyped using an allelic discrimination based method designed to provide a result for all the 45genetic variants within a 2-days turnaround time. A clinical decision support system (GIMS) developed by one of the project partners allowed the production of a pharmacogenetic report that is forwarded to the prescribing physician. A preliminary analysis performed among CRO study arm patients pointed out that only 4% of the genotyped patients have no actionable variants, while 96% have one or more.The preliminary data analyses focused on the DPYD, UGT1A1and CYP2D6genes, encoding for metabolizing enzymes of the most commonly drugs prescribed at the CRO Center (fluoropyrimidine, irinotecan and tamoxifen).Regarding DPYD gene, four variants were analysed (rs3918290, rs67376798, rs55886062, rs56038477) and only 4.3% of patients showed an actionable genotype which results in a recommendation of dose reduction for capecitabine and fluorouracil. UGT1A1(rs8175347)occurred in 14.2% resulting in a clinical recommendation for irinotecan treatment. CYP2D6definition of the metabolizer phenotype (poor, extensive, rapid or ultrarapid) was based on the analysis of 14Genetic variants. It resulted 42% of the patients presented a genetically affected metabolizer phenotype resulting in clinical therapeutic recommendation for tamoxifen treatment.

Discussion and conclusions: A huge international effort is ongoing to demonstrate that a pre-treatment pharmacogenetic approach is feasible in the clinical practice across 7European countries and could benefit patients and health practitioners as well as save economical resources. Preliminary data showedthat themajority of the patients has at least one actionable genotype in their genome demonstrating the high impact of pharmacogenomics especially in those drugs where the therapeutic window is small, such as antineoplastic drugs.