PREPARE (PRE-EMPTIVE PHARMACOGENOMIC TESTING FOR PREVENTING ADVERSE DRUG REACTIONS), A PHARMACOGENOMIC RANDOMIZED CLINICAL TRIAL WITHIN THE U-PGX H2020 PROGRAM, TO DRIVE PHARMACOGENOMICS INTO CLINICAL PRACTICE IN 7 EUROPEAN CLINICAL ENVIRONMENTS, TO IMPRO

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Although the clinical validity of a number of pharmacogenetic markers is nowadays a matter of fact and led authoritative scientific consortia to publish pharmacogenetic guidelines, the clinical implementation in the real life remains challenging, due to the lack of convincing cost-effectiveness data, the difficulty for the clinical practitioners to deal with patients genetic information, the lack of proper infrastructures.

Great efforts are ongoing worldwide to push the routinely application of pharmacogenomics in the clinical practice, with six medical centers in the United States carrying on specific programs for the use of pre-emptive genotyping to optimize pharmacotherapy (Dunnenberger 2015).

Since the 1st of January 2016 a 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. U-PGx is a challenging research program with the aim to “make effective treatment optimization accessible to every European citizen” (www.upgx.eu) (van der Wouden 2017; Cecchin 2017).

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). 4,050 patients, pre-emptively genotyped for 50 actionable variants for 43 drugs, and treated accordingly, will be compared with 4,050 controls treated with the standard of care. 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.

The Centro di Riferimento Oncologico (CRO) of Aviano is the coordinator of the study for Italy with a specific focus on anti-cancer drugs (5-fluorouracil, capecitabine, tegafur, irinotecan and tamoxifen), with a requested enrollment of 1,200 patients. Other participating centers in Italy are San Filippo Neri in Rome, and Ca Foncello in Treviso.

In the first year of the project all the infrastructures required for the clinical trial have been set up. Specifically, an array based genetic platform has been provided, allowing the simultaneous analysis of all the genetic variants in the panel. An electronic clinical decision support system was developed to alert physicians and pharmacists about patients with risky genotypes. A set of questionnaires were developed to collect clinical-demographic information, quality of life (including adverse drug reactions), pharmacoeconomic parameters, and the individual perception

of the pharmacogenomic issues. An online eCRF system has been developed to allow a centralized patients data collection.

Since March 2017, patients enrollment has started. Italy was randomized to start with the standard of care arm until June 2018, when it will switch to the intervention arm. The most compelling eligibility criteria is that the patient will receive a first prescription for one of the 43 drugs included in the U-PGx guidelines. Once a patient accept to participate in the study a blood sample is drawn and a baseline data collection questionnaire is administered. Follow up questionnaires are collected at 4 and 12 weeks after treatment initiation, and at the end of the study. Up to date 20 patients were enrolled in CRO and 10 in San Filippo Neri. Of these, 14 were enrolled for 5-fluorouracil, 13 for capecitabine, 2 for tamoxifen, and 1 for irinotecan. An electronic safety code card with the patients genetic profile and pharmacogenetic information is provided to each patient.

The project will hopefully demonstrate the clinical benefit to patients of the PGx approach, and the feasibility to set up a common international infrastructure allowing accessibility to a personalized treatment to all the European citizens.

Dunnenberger (2015). Annu Rev Pharmacol Toxicol. 55: 89–106

Van Der Wouden (2017). Clin Pharmacol Ther. 101(3):341-358

Cecchin (2017). Curr Pharm Biotechnol. e-pub