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REVIEW ARTICLE

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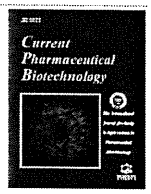
Ubiquitous Pharmacogenomics (U-PGx): The Time for Implementation is Now. An Horizon2020 Program to Drive Pharmacogenomics into Clinical Practice



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Abstract: Although the clinical validity of a number of pharmacogenetic markers is nowadays a matter of fact, and led authoritative scientific consortia as the Dutch Pharmacogenetic Working Group (DPWG) and the Clinical Pharmacogenomics Implementation Consortium (CPIC) to publish pharmacogenetic guidelines, the clinical implementation in real life remains challenging. Ubiquitous Pharmacogenomics (U-PGx) program is a coordinated effort that put together scientific and clinical expertise in the pharmacogenomic field, to implement the pre-emptive pharmacogenomic approach in the clinical practice in Europe, and to demonstrate its benefit in both patients' clinical outcome and quality of life, with an economic advantage for the healthcare system. The project is conceived as a clinical trial that will compare 4,000 patients, pre-emptively genotyped for a panel of pharmacogenes included in the DPWG guidelines, and treated accordingly, with 4,000 controls treated with the standard of care. All the genetic data will be prospectively collected and fully embedded into the patient's clinical record. An electronic clinical decision support system will be developed to alert physicians and pharmacists when a drug is being prescribed or dispensed to a patient with a risky genotype. U-PGx will test and harmonize this approach in seven healthcare environments (The Netherlands, Spain, UK, Italy, Austria, Greece, Slovenia) to set the basis for a future European healthcare system where an 'effective treatment optimization will be accessible to every European citizen' (www.upgx.eu).

Keywords: Europe, implementation, pharmacogenomics, precision medicine, pre-emptive testing.

1. INTRODUCTION

Precision medicine based on the patient's pharmacogenomic (PGx) profile is among the ultimate goals of the Human Genome Project, holding the promise of a genotype-driven therapeutic strategy to personalize the pharmacological treatment. At the time of writing, the U.S. Food and Drug Administration listed more than 130 drugs with a PGx warning in their label, and about 100 of these are affected by host genetic polymorphisms with an acknowledged impact on the drug pharmacokinetics or pharmacodynamics [1].

Despite the publication of authoritative guidelines providing clear suggestions for drug prescription, by scientific consortia for PGx clinical implementation such as CPIC (Clinical Pharmacogenomics Implementation Consortium) in the U.S. [2] and DPWG (Dutch Pharmacogenetic Working Group) in Europe [3], the majority of patients are still treated according to the standard clinical practice, unaware to be potential carriers of risk genetic variants. The debate about the opportunity to implement PGx markers in the clinical practice is no longer focused on the scientific evidence of the clinical validity of the approach, which has been widely acknowledged. Indeed, a number of randomized clinical trials have shown improved outcome of PGx-adjusted prescribing [4-6]. However, major concern on implementation is its clinical utility [7], defined by the Centers for Disease Control and Prevention [8] as "how likely the test is to significantly improve patient outcomes", but the even definition of "clinical utility" of a PGx test is still controversial [9]. As a matter of fact, PGx is only sporadically applied as a pre-treatment tool for therapy tailoring in clinical practice, and, usually, instead of a pre-emptive systematic approach, only gene-specific PGx tests are prescribed by the clinicians in the prevision of an at-risk prescription such as DPYD polymorphisms when prescribing a fluoropyrimidine. Among the

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most widely acknowledged barriers to PGx implementation there is the lack of convincing cost-effectiveness and cost-consequences data, issues that have never been properly addressed by previous studies. In many cases there is also the difficulty for the clinical practitioners to deal with patients genetic information due to the low awareness of the pharmacogenetic issues, or to the lack of proper infrastructures, such as genotyping platforms with a satisfactory turn-around time, or IT tools for genetic data handling.

In 2015 president Obama himself has announced the launch of new initiatives for providing precision medicine benefit to improve citizens health, witnessing the high attention and expectation in the field [10]. In fact, great efforts are ongoing to push the routine 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 [11]. Specifically, St. Jude Children's Research Hospital in Memphis started in 2011, a clinical research protocol called PG4KDS to transfer an array-based pharmacogenetic testing as a pre-emptive routine diagnostic tool [12]. Other similar implementation projects are ongoing at Vanderbilt University School of Medicine in Nashville (PREDICT) [13]; at the Mayo Clinic in Rochester (eMERGE) [14]; at Ichan School of Medicine at Mount Sinai, New York (CLIPMERGE PGx Program) [15]; at the University of Florida and Shands Hospital (Personalized Medicine Program) [16]; and more recently at the University of Chicago (1200 Patients Project) [14, 15]. The common objective of all of these programs is not to establish the opportunity of transferring PGx implementation in the clinical practice, but instead to demonstrate what is the best way to do that, in term of choosing the best genotyping platform, the right panel of markers, the most user-friendly IT technologies to support the implementation process [17, 18].

Since the 1st of January of 2016 a unique initiative has been launched in Europe with the financial support of Horizon 2020 granting program, under the coordination of Leiden University Medical Center, in Leiden, Netherlands. U-PGx is a challenging research program with the aim to "make effective treatment optimization accessible to every European citizen" [19] (Fig. 1). The implementational character of U-PGx is reflected in its multidisciplinary consortium that include clinicians, human geneticists, IT experts to experts in Health Technology Assessment (HTA), communication, ethical, legal and societal issues. Fifteen research centers from 10 European countries (Netherlands, United Kingdom, Germany, Sweden, France, Spain, Slovenia, Greece, Italy, Austria) will be involved in 5 years' program in the development of this ambitious research program.

The U-PGx is conceived as a European coordinated effort that through frequent virtual and person meetings will take advantage of the multidisciplinary and country-diversity within the consortium. In addition, a scientific advisory board made of clinicians and scientists that are experts in the field, and are directly involved in implementation projects in the U.S. will further guarantee a high standard of research and monitor the progress of the project, providing advice for a continuous improvement of the process [19].

2. UBIQUITOUS PHARMACOGENOMICS (U-PGX): A RANDOMIZED CLINICAL TRIAL

Large randomized clinical trials are usually claimed as the only approach that could finally clear up the real value of implementing a pre-emptive PGx strategy in the everyday clinical practice. U-PGx is conceived as a randomized clinical trial with a cross-over design that will be set up, for the first time, with the aim to compare a standard of treatment strategy with a personalized PGx-based treatment approach in a total of 8,000 patients across seven different European countries. The main objective of the project is to test the effectiveness of implementing pre-emptive PGx testing in a real world clinical setting, to primarily provide evidence of its value in improving patients' outcome, being easy to be used in the clinical practice, and cost-effective. The concept of a pre-emptive genotyping of a comprehensive panel of actionable genetic variants at the first drug prescription is already implemented in some US medical centers, as mentioned above, but is quite unique in Europe. The embedding in the patients clinical record of a panel of genetic polymorphisms that can be analyzed just once, and be usable for a lifetime, would probably be the most practical and cost-effective strategy for PGx implementation [20]. This kind of approach certainly requires a broad set of shared enabling

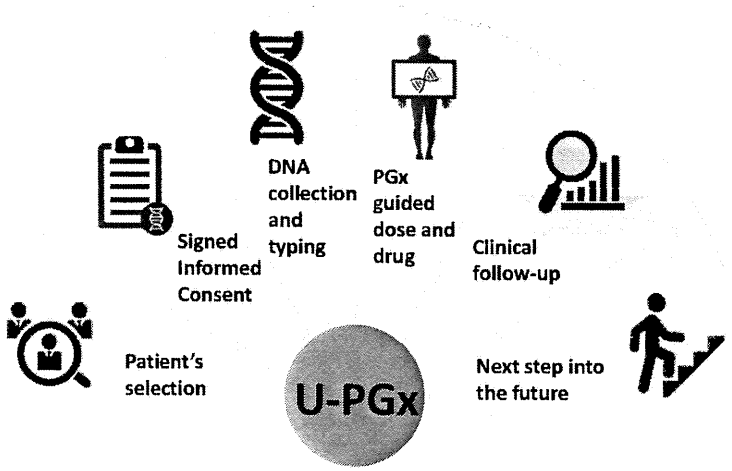

Fig. (1). Workflow of Ubiquitous Pharmacogenomics (U-PGx) program.

tools, and one of the main challenges of U-PGx is to harmonize the implementation process in countries with sharp differences not only in the healthcare systems organization but also in some cultural, social and economic aspects. The ultimate goal will be to create a common model of PGx implementation effective in each of the seven implementation countries that, after the 5-year project timeframe, will be extendable to all the rest of Europe. Seven European centers have been selected as clinical implementation sites for their long-standing commitment in the clinical pharmacogenetic field such as Leiden University Medical Center (The Netherlands), Royal Liverpool University Hospital (United Kingdom), San Cecilio University Hospital of Granada (Spain), Medical University of Vienna (Austria), University of Patras (Greece), Centro di Riferimento Oncologico- National Cancer Institute of Aviano (Italy), University of Ljubljana (Slovenia). After a first year of preparation of the enabling infrastructures for the trial, the patients enrollment in the implementation program should start at the beginning of 2017.

DPWG guidelines [21] will be the cornerstone of the U-PGx project and will be shared and applied to all participating countries. Patients receiving a first prescription for at least 1 drug for which a clinical recommendation is available in the DPWG guidelines will be eligible for inclusion. Included patients will be pre-emptively genotyped using DNA obtained from blood or saliva for a broad (more than 80 genetic variants) panel of variants in a list of 13 actionable pharmacogenes. PGx test results will become part of the patients' medical record and the physicians or clinical pharmacists responsible for drug prescription will be warned whenever a relevant drug is prescribed or dispensed to the patient. Drug and dose selection will be modified consistently with the DPWG guidelines. The pre-emptively determined panel will be used during the entire 18 months' intervention period to drive any pharmacological prescription of drugs included in the DPWG guidelines. Among the 8,000 patients estimated to be enrolled in the U-PGx trial, 4,000 patients will receive the PGx-based treatment (intervention) and another 4,000 patients will serve as controls. The order of intervention and control at the seven U-PGx implementation centers will be randomized to minimize the influence of time dependent variables. To avoid bias and account for differences per country, centers will serve as their own controls by comparing results of the U-PGx intervention with results from an 18 months standard care period in the same center. Clinical outcome will be evaluated during a 3-year follow-up period both by patient reported outcomes and clinical evaluation.

2.1. Shared Guidelines

The lack of clear and up-dated guidelines has been for a while among the major barriers to PGx implementation. In 2005 the Royal Dutch Pharmacists Association (KNMP) established the Dutch Pharmacogenetic Working Group with the aim to provide unambiguous recommendation for a rational drug choice or dose adjustment based on the patients' genotype. In 2011 a comprehensive list of 163 gene-drug interactions including 53 drugs with specific recommendations was published by DPWG [3], and these guidelines were made available in the PharmGKB website [21]. DPWG guidelines now include polymorphic variants in *CYP1A2*, *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *TPMT*, *DPYD*, *UGT1A1*, *SLCO1B1*, *VKORC1*, *HLA-B*, and factor V Leiden (*FVL*) genes and represent the background of U-PGx. The guidelines are curated by KNMP and will be continuously integrated during the project time-frame and afterwards by systematic review of the literature, providing updated therapeutic recommendations for physicians and clinical pharmacists. For the purpose of the project DPWG guidelines will be also harmonized with existing local guidelines available across other European countries, and compared with CPIC recommendation, to provide a shared list of gene-drug interactions, translated in local languages of each clinical implementation site that will be applied in the clinical trial. The project will make the PGx guidelines of DPWG accessible to the participating countries, becoming a valuable resource for further studies and clinical collaboration and dissemination.

2.2. Study Objectives and Measurement of the Outcome

The final objective of U-PGx is to assess the improvement of the clinical outcome by introducing PGx strategy in the everyday clinical practice. The challenge here is that the U-PGx will enroll patients with a multitude of different diseases, treated with a variety of drugs and with a series of pharmacogenes involved, by implementing the U-PGx approach versus standard of care practice. The issue of such a complex and heterogeneous clinical environment will be addressed by the adoption of an innovative clinical end-point aimed at globally measuring the clinical effect of a drug.

This composite end-point was previously adopted for scoring the phenotypic effect of the genetic variants included in the DPWG guidelines and is reported in detail in the PharmaGKB website [21]. In brief, for each drug included in the DPWG guidelines specifically related clinical events (adverse events or events related to lack of efficacy) will be systematically scored on a seven-point scale from changes of scarce impact on the patient quality of life, via clinical effects with different discomfort, up to the extreme phenotype (death).

As an implementation project, U-PGx has also several secondary aims not strictly related to the patients clinical outcome but more focused on measuring those process indicators of the real up-take of a PGx-directed treatment in the clinical practice of each implementation site. Commonly used metric parameters such as the number of tests ordered, the correct application of the guidelines based on the patients genotype, average turnaround time from patients blood/ saliva sampling and report availability for treating physicians will be monitored. To determine the clinical utility of a PGx guided treatment in routine care, health economic evaluation will be carried out in the seven participating implementation sites to provide the basis for implementation of PGx in the different healthcare systems and to inform decision and policy makers. A specific section will be in fact dedicated to the evaluation of cost-effectiveness (including Quality of Life assessment and HTA) of pre-emptive PGx testing. The diversity of healthcare systems will be related to the extent of successful implementation of PGx and described qualitatively.

3. PROJECT ENABLING INFRASTRUCTURES

U-PGx implementation program will need, as specified above, a wide harmonization activity of enabling infrastructures in the wide range of healthcare systems covered by the project in the 7 implementation sites. Some of them are focused on a specific disease area, whereas others will enroll patients in a primary care general medicine setting (Table **1**).

The first enabling tool will be as already specified above the definition of shared PGx guidelines that will be made available to each implementation country in their own local language and will represent the backbone of the project. A common genotyping platform will be selected and installed at each implementation site to simultaneously and rapidly analyze the entire panel of polymorphisms selected for therapy adjustment. Most implementation sites, already active in the PGx field, already have their own genotyping solutions, but the idea is to build up a common platform with high quality standard for international diagnostic accreditation. The selected platform will be activated in each of the seven implementation sites to harmonize the genotyping process providing a cost-effective solution with a suitable turnaround time to be easily usable in the real world clinical practice.

An important barrier for an effective implementation process is the different level of experience of the medical practitioners on the PGx based treatment in the different countries as well as the patients' knowledge on precision medicine and individualized treatment. Great attention will be placed on the monitoring of patients and physicians awareness and perception of the pre-emptive PGx testing. Specific surveys will be spread among PGx stakeholders and specific training and education programs will be set up in each participating country. Through education and experience, health care providers and patients knowledge on individualized therapy will be significantly improved, as well as their understanding of the unique opportunity provided by PGx testing.

The lack of user-friendly and integrated IT solutions for the support of the decision process in the drugs prescription is a crucial obstacle to an effective implementation process. Improvement in the IT infrastructure for PGx testing and its incorporation into the workflow of physicians and pharmacists will greatly facilitate its application in routine patient care. In this field the dis-homogeneities among the European countries participating in the project are very sharp, where only the coordinator country (The Netherlands) presents an interruptive PGx clinical decision support system already integrated in the electronic clinical records, providing alerts during the drug prescription process. Even the use of an electronic clinical records is not widespread across the involved European countries, and therefore a plethora of IT solutions with different levels of automation will be provided to the implementation sites in order to standardize the storage, exchange, interpretation, and implementation of PGx data. The barrier-free, clinically validated computer- based decision support systems developed in this project will ensure that PGx can be easily and seamlessly integrated into clinical practice. To deliver also a unique and innovative tool that will be tested in every national context, a complementary mobile-based PGx Medication Safety Code System, developed at the University of Vienna, partner in the project, will be implemented to facilitate the transfer of PGx results to external health care professionals. This is a portable card with a 2D barcode readable through a widely available smart phone application providing also to a non-trained medical practitioner information on the management of the patient genetic profile from a pharmacological point of view [22].

On completing the establishment of the pre-emptive PGx according with the U-PGx project, its continuity will be granted by a strong dissemination of such initiative for future implementation in other European countries. The inclusion of the medical society, policy and decision makers including European and national academic societies represented by individual U-PGx members will allow rapid and widespread dissemination across Europe. Golden Helix Foundation [23], an international non-profit scientific organization aimed at developing educational activities in the field of genome medicine, partner in the project, will be in charge of organizing dissemination events among the scientific community of the emerging results of the project. In addition, a public-domain web-based PGx information portal (www.upgx.eu) has been designed and developed [19]. It provides up-to date

Table 1. Overview of the PGx implementation sites and their specialties.

Site	State	Specialty	Reference
Department of Clinical Pharmacy & Toxicology of the Leiden University Medical Center	Netherlands	Primary Care	https://www.lumc.nl/
Department of Pharmacy & Cardiology of San Cecilio University Hospital	Spain	Cardiology	http://www.juntadeandalucia.es/servicioandaluzdesalud/hsc/web
Division of Nephrology and Dialysis at the Medical University of Vienna	Austria	Transplantation	http://transplantforum.meduniwien.ac.at/
Department of Pharmacy at the University of Patras	Greece	Psychiatry	http://www.pgnp.gr/
Pharmacogenetics Laboratory of the Faculty of Medicine	Slovenia	Rheumatology	http://www.kclj.si/ http://zd-lj.si/en/
Royal Liverpool University Hospital	UK	Primary Care	http://www.rlbuht.nhs.uk/
Experimental and Clinical Pharmacology Unit at the National Cancer Institute of Aviano	Italy	Oncology	http://www.cro.sanita.fvg.it

information in scientific and lay language, both for specialized scientists and healthcare professionals as well as for the general public and patients, to maximize the impact of the project results. The website will provide links to various PGx knowledge and databases, and to websites of various regulatory agencies.

CONCLUSION AND THE NEXT STEPS INTO THE FUTURE OF U-PGX

Even if a PGx-based treatment has been demonstrated to improve patients outcome, the problem of unpredictable toxicity occurrence and of inter-individual variability in drugs metabolism is far from being solved. Despite its primary implementation nature, U-PGx project is also aimed at expanding the knowledge on PGx in more exploratory and previously uninvestigated fields. The advancement of the next generation sequencing technologies points out the emerging role of rare genetic variants. A recent revision of the 1K genome project results highlighted that about 30 to 40% of the functional variability in drugs ADME (adsorption, distribution, metabolism, and excretion) and nuclear receptors genes is imputable to rare variants not commonly included in the genetic screening panels [24] and can account for the observed variability among individuals in the drug toxicity and pharmacokinetics. One of the next steps into the future, that will be taken in U-PGx, will be the discovery by next generation sequencing of new rare variants potentially impacting the patients clinical phenotypes. In addition, new approaches of system pharmacology, combining genetic and non-genetic information such as patients clinical pathological determinants, will be applied to develop pharmacometric models predictive of the treatment outcome. An extensive study of the drug-drug and drug-drug-gene interactions will be also undertaken.

In conclusion, it is nowadays undisputable that the host genetic polymorphisms have a role in the response to drugs, and current available PGx guidelines are available, but do not provide indications or suggestions on whether to test or not for risk genotypes but how to adjust the treatment accordingly. For sure the adoption of a pre-emptive genotyping approach of a panel of relevant genetic variants embedded in the patients clinical records, have important advantages from practical and economical points of view, lowering both the cost of the test and the turnaround time to get the genotype information. Since 2005 the DPWG prepared over 80 PGx guidelines based upon a comprehensive systematic review of the literature and on this background, 95% of the patients are carriers of at least one actionable genotype [11], underlying the great impact of a PGx based treatment on the global patients health and healthcare system economics.

U-PGx is a clinical trial based in the European healthcare setting that will enroll, genotype, treat, and follow-up at least 8,000 patients from seven different countries in the next few years to demonstrate the validity and utility of PGx in the clinical practice in Europe. The concept of this EU funded U-PGx project is to settle, during the project time frame of 5 years, the background for a real PGx revolution that will accomplish the delivery of a precision medicine based on the pre-emptive PGx implementation as a routine clinical care practice also beyond the project conclusion. This would strengthen the position of the European healthcare community, providing also opportunities of cooperation and dialogue with other stakeholders in Europe. Importantly, it will convincingly demonstrate the clinical benefit to patients of the PGx approach, and the feasibility to set up a common international infrastructure that will allow the same accessibility to a personalized treatment to all the European citizens, setting the base for a future global PGx implementation process.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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