

Harnessing pharmacological knowledge for personalized medicine and pharmacotyping: Challenges and lessons learned

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Abstract

The contribution of the genetic make-up to an individual's capacity has long been recognized in modern pharmacology as a crucial factor leading to therapy inefficiency and toxicity, negatively impacting the economic burden of healthcare and restricting the monitoring of diseases. In practical terms, and in order for drug prescription to be improved toward meeting the personalized medicine concept in drug delivery, the maximum clinical outcome for most, if not all, patients must be achieved, *i.e.*, pharmacotyping. Such a direction although promising and of high expectation from the society, it is however hardly to be afforded for healthcare worldwide. To overcome any existed hurdles, this means that practical clinical utility of personalized medicine decisions have to be documented and validated in the clinical setting. The latter implies for drug delivery the efficient implementation of previously gained *in vivo* pharmacology experience with pharmacogenomics knowledge. As an approach to work faster and in a more productive way, the elaboration of advanced physiologically based pharmacokinetics models is discussed. And in better clarifying this topic, the example of tamoxifen is thoroughly presented. Overall, pharmacotyping represents a major

challenge in modern therapeutics for which pharmacologists need to work in successfully fulfilling this task.

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Key words: Pharmacology; Pharmacogenomics; Personalized medicine; Pharmacokinetics; Pharmacodynamics; Pharmacotyping; Translational medicine; Drug delivery; Education; Curricula

Core tip: Drug prescription in order to be improved, the drug delivery process needs to confront the challenges of genomics knowledge translation to ensure the maximum clinical outcome for most, if not all, patients, *i.e.*, achieving pharmacotyping. The practical clinical utility of personalized medicine decisions needs to be documented and validated in the clinical setting. Physiologically based pharmacokinetic models represent an approach by which the faster and more efficient implementation of pharmacogenomics knowledge in evidence-based medicine could be achieved. Pharmacotyping represents a major challenge in modern therapeutics for which pharmacologists need to work both in academia and research in successfully fulfilling this task.

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INTRODUCTION

Unanimously nowadays, nanotechnology and nanomedicine in parallel with pharmacology and pharmacogenomics (PGx) contribute knowledge and methodologies permitting individualized treatment decisions to enter

in everyday clinical practice. The personalized medicine concept along with the interdisciplinary efforts needed to achieve the desired practical clinical utility for personalized medicine decisions worldwide is extensively and thoroughly described elsewhere^[1]. The latter also implies that PGx by bridging pharmacology with genetics/genomics provides additional advantage for translational medicine to positively impact drug development and delivery outcomes. This means that the molecular etiology of drug response variability, by clinically assessing the genetic factors that contribute to pharmacokinetics (PK) and pharmacodynamics (PD), is now considered an integral part of modern pharmacology and therapeutics. As a consequence, the drug administration has been changed allowing for pharmacotyping (PTx) to emerge in the prescription process *e.g.*, the individual patient (personalized) specific medicine selection and administration scheme, as proposed earlier^[1-4]. From a historical point of view, pharmacogenetics as a term has been introduced by Friedrich Vogel (1959), whereas the first example of pharmacogenetics described ever is flavism disorder by Pythagoras (580-500 BC; ancient Greek mathematician). By following-up chronologically until nowadays such pharmacogenetics-related scientific breakthroughs for pharmacology, it is obvious that these focused efforts have been successful by efficiently translating multidisciplinary-based experimental data that enabled pharmacological improvements both in research and the clinical setting (for such a detailed chronological description of pharmacogenetics/PGx breakthroughs see elsewhere^[1]). However from the experience gained thus far, it needs considerable effort and, more importantly, to invent focused as well as interdisciplinary-oriented “smart and sophisticated” experimental approaches to move all the way through establishing personalized medicine decisions of broader practical clinical utility. The molecular etiology of illness pathophysiology and the elucidation of genetic factors contributing to pharmacological profiles of drugs in the body are hardly experimentally approachable, especially in being thoroughly understood for all marketed therapeutics. Moreover, the interplay of genes with therapeutics implies that their interaction is also modulating drug delivery outcomes, since the mutational status of genes (gene polymorphism) and drug-regulated gene expression profiles contribute to drug response variability (Figure 1). The latter, it leads to patient phenotypic (pharmacological) response modulation, or alternatively into pharmacological response heterogeneity. Complementary, in trying to minimize the emergence of drug response variation amongst population and in order to achieve improved profiles of administered drugs worldwide, a new interdisciplinary infrastructure needs to be created and integrated in clinical practice^[4]. The latter, will also help in adjusting the regulatory environment to improve drug development productivity by minimizing the emergence of adverse drug reactions (ADRs), avoiding drug interactions and thus finally improving the clinical outcome.

Moreover, by considering the issue of education in

pharmacy and medicine, the better training in pharmacology will be achieved through the development of new curricula aiming to advance skills of medical and pharmacy students in implementing *in vivo* pharmacology experience with PGx information. But how this task could be attainable and productive? Already, academics in relevant disciplines confront with obstacles in trying to integrate knowledge from PGx and personalized medicine concepts into teaching curricula and enrich the skills of students toward better handling modern therapeutics issues of practical clinical utility. The previously well-established background bridge between pharmacology and other disciplines (*e.g.*, physiology/pathophysiology, chemistry) created in order future practitioners to understand drug behavior and actions in the body is being expanded by incorporating translational information extracted (*e.g.*, biochemical, biological, molecular) including that from bioinformatics and also material sciences and nanotechnology. Unanimously, the molecular approaches applied to predict and/or assess the behavior of therapeutics in the living organisms enrich the knowledge of students and also strengthen their capacity in drug prescription for better dosage-scheme selection of administered medicines in the clinical setting. And for sure, the better education by covering the concept of PGx as well as personalized medicine will be the maximum positive impact for both academics involved and healthcare practitioners would happen; the latter, however, further necessitates the proper adjustments in academia to restructure and organize relevant innovative medical and pharmacy curricula worldwide^[4-6].

DEVELOPMENT OF ADVANCED PK/PD MODELS TO IMPLEMENT MOLECULAR PHARMACOLOGY FOR ENRICHING TRANSLATIONAL MEDICINE CAPACITY IN DRUG DELIVERY

Nowadays, it has been evidenced that mechanism-based PK/PD modeling has been a necessity in modern pharmacology toward speeding up early achievements in drug discovery and ensuring improved efficacy and safety profiles of candidate molecules before their final clinical development. The latter, implies that improved prediction capabilities of crucial drug-related parameters can be documented by extrapolating *in vitro* experimentation data into *in vivo* clinical variables across species^[7,8]. Importantly, however, PK/PD modeling in order to contribute greatest benefits at the preclinical and the clinical era, it also needs to be embraced across regulatory bodies and pharmaceutical industrial sector, as well as the educational process in academia^[1,9]. The recent advancement of genomic medicine and systems pharmacology, however, forms the baselines for multidisciplinary translational approaches by crossing the borders between molecular pharmacology with pathophysiology,

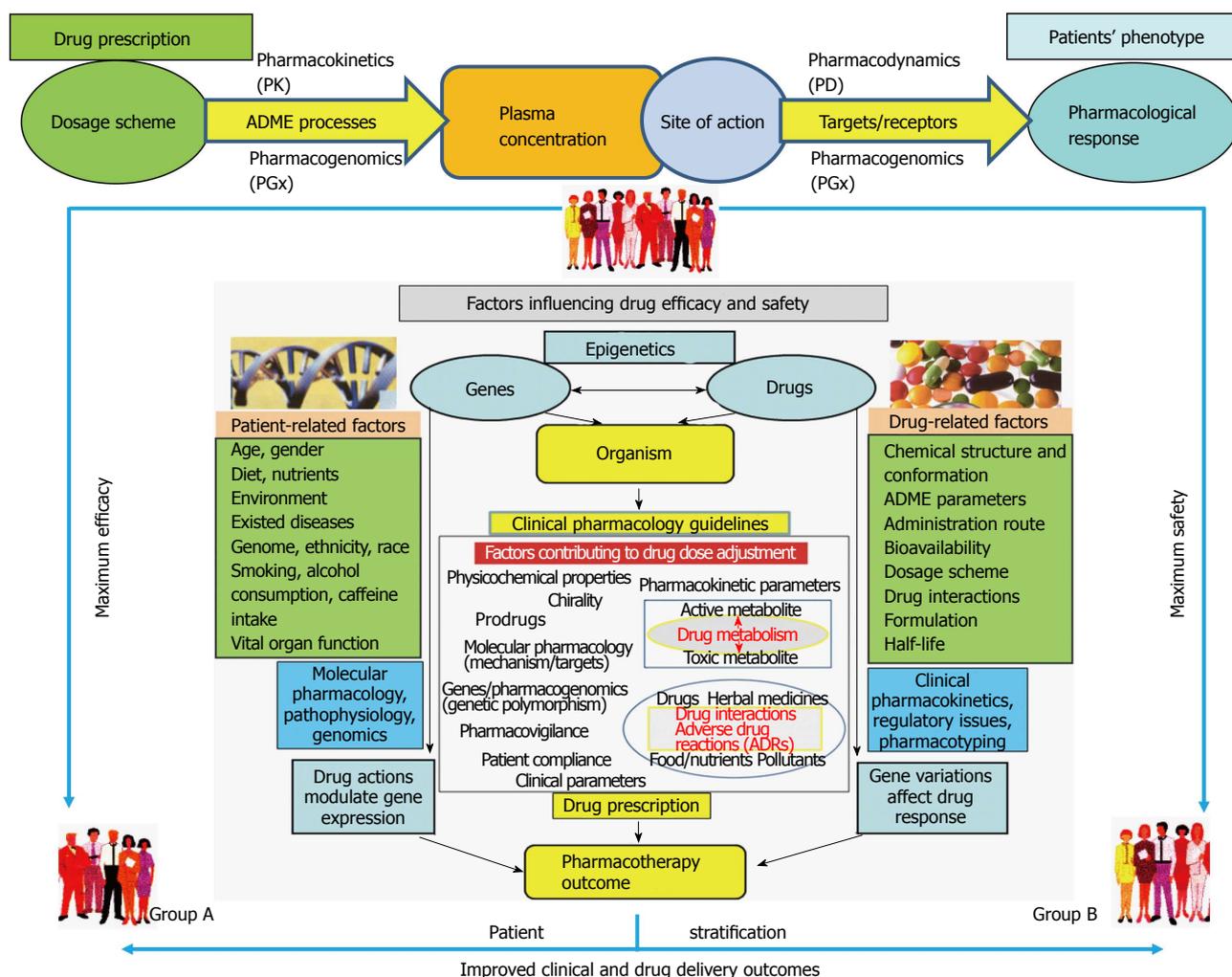


Figure 1 A roadmap of pharmacological response stages to efficiently address the pharmacotyping concepts in drug prescription. The processes and the factors related to pharmacological effects along with the scientific environment contributing to drug delivery outcomes in terms of efficacy, safety are depicted above. The need for enriching pharmacological knowledge to advance personalized medicine decisions in the clinical setting through drug dosage scheme adjustment (*i.e.*, PTx) is exemplified. The *in vivo* pharmacology experience gained thus far and it already appears in the drug regulatory environment is stressfully demanded to be empowered by pharmacogenomics knowledge in terms of PD/PK drug parameters assessment methodologies, the clinical pharmacology guidelines development and the prescription process. Complementary to this, the development of information-based workflow platforms in clinical practice incorporating algorithms to assess the efficient translation of clinical, biological, genomic and chemical information is also eagerly expected. Such a direction of major pharmacological importance permits the maximum efficacy and safety outcomes to be reached in a timely and worldwide basis for everyday healthcare (see text for more details). PTx: Pharmacotyping; PGx: Pharmacogenomics; PK: Pharmacokinetics; PD: Pharmacodynamics.

clinical sciences and genomics. In particular, systems pharmacology aims to understand the effects of drugs including ADRs in terms of pharmacological targets and within the molecular networks context that evidently has been allowing the integration of the systems biology-level in understanding the behavior of drugs in the body^[10]. This direction could be proven helpful especially for complex and multifactorial illnesses where the more thorough elucidation of their molecular pathophysiology is needed; complementary, such task in turn it represents a crucial prerequisite parameter upon attempting to improve pharmacotherapy outcomes in these diseases. By enabling network analyses of interactions mediated both pathophysiological and PD/PK drug responses through the different organization levels, (from the molecular level through organ and tissue into finally the entire organism), in an integrated approach, the faster and more

cost-affordable manner to empower the practical clinical utility of personalized medicine decisions will be clearly achieved^[1,11-14].

It is evident, that the improved translational medicine capacity means the successful adjustment of clinical pharmacology guidelines toward personalized medicine concepts. Complementary to this point, the issue on how the already gained *in vivo* pharmacology experience can be adjusted by being enriched with relevant systems pharmacology approaches and methodologies clearly emerges in a way that the implementation in real time with the PGx knowledge could happen^[15-17]. Alternatively, what it has been already established through the previously gained experience of *in vivo* pharmacology approaches, is the fact that drug pharmacological responses are evidenced by two dynamic processes being interrelated, that of PD and PK. PD describes what medicines do to the body (*i.e.*, drug-

receptor interactions), whereas PK is associated with what an organism does to therapeutics (*i.e.*, absorption, distribution, metabolism, excretion; ADME processes). As a consequence, a question then rises; on how in the new drug delivery era, maximum benefits could be ensured for all patients in terms of drug efficacy and safety? The latter task can be fulfilled only if the molecular mechanisms underlying PD/PK drug effects could decipher issues addressing either the emergence of idiosyncratic (genetic/genomic) toxic effects and ADRs in a given individual, or the involvement of environmental and epigenetic factors^[1,18,19] (Figure 1). The application of predictive bioinformatic approaches and computational methodologies in evaluating PK and PD profiles of drugs represents an established approach, especially the last few decades, throughout the drug development as well as delivery processes^[20]. *In silico* methods use and application of technologies to enhance the predictive capacity to ultimately improve productivity and drug delivery safety and efficacy profiles is now considered a major advancement^[20-23]. In parallel, specific information-based workflow computerized healthcare systems are being developed to contribute in the exploitation of knowledge coming from interdisciplinary resources with an affordable for the end-user manner^[24]. The latter, also implies the proper application of the translated knowledge into information standing types being capable to be simultaneously used in everyday healthcare approaches upon illness prognosis, diagnosis and administration of therapeutics (Figure 1).

Undoubtedly, the development of suitable translational medicine-enriched clinical pharmacology guidelines for providing instructions upon drug prescription (*e.g.*, dosage scheme adjustment, disease prognosis/diagnosis profile improvement) will efficiently facilitate the successful implementation of PGx concepts into everyday clinical practice. The latter, also refers to the information systems applied in routine patient care. Moreover importantly as it has been proposed recently, by working within this direction the maximum benefits from both nanomedicine and personalized medicine efforts is expected to happen empowering clinical outcome through the advent of personalized nanomedicine concepts at both the research and the clinical setting^[25]. Complementary to this, personalized medicine is paving the way toward broader practical clinical utility of translational advancements, thus contributing toward PTx in drug prescription as well as medicine and pharmacy in general. The latter, refers to the development of clinically-applied algorithms in drug prescription regarding the genetic variables being able to affect PK and PD behavior of marketed therapeutics. The use of information-based systems into everyday healthcare has clearly shown the need of developing such unified information systems with adherence to various healthcare environments worldwide (Figure 1). To this end, the more successful development of quantitative PGx models for translation medicine is being achieved then the best benefits in PTx-based drug delivery from genetically-guided drug dose adjustment is expected^[1,26,27].

In fulfilling this task of practical clinical utility, the close collaboration of clinicians with pharmacologists will pace PTx in drug prescription in a faster and more efficient manner.

HARNESSING PHARMACOLOGICAL AND TOXICOLOGICAL GENOMICS KNOWLEDGE FOR ADVANCING THE SKILLS OF FUTURE HEALTHCARE PROFESSIONALS TO IMPLEMENT PTX CONCEPTS IN DRUG PRESCRIPTION

The use of PD/PK tools implemented with biostatistics approaches in courses related to pharmacology, model-based drug development as well as predictive modeling and simulation upon pharmacological assessment empower the teaching process and ensure greatest benefits for researchers, educators, as well as students. Alternatively, in order to achieve this task for strengthening students' knowledge and skills in clinical and molecular pharmacology, PGx expertise as well as personalized medicine decision-making means of being capable to simultaneously: (1) assess and predict clinically relevant drug interactions, thus minimizing ADRs emergence risk; and (2) advance the profiles of drugs in terms of efficacy and safety for individual patients by inter-correlating clinical data, drug properties and genetic/genomic characteristics^[1-6]. Moving forward in this manner for education, future healthcare practitioners will be instructed on how to more efficiently and in real time apply personalized medicine approaches in clinical practice, a fact that impose health and societal benefits in general. In addition, the successful implementation of systems pharmacology and pathophysiology approaches with *in vivo* pharmacology experience better ensures both productivity and clinical outcome for innovative molecularly-targeted therapeutics, "smart/genius" drug delivery systems, translational medicine efforts, as well as nanomedicine applications (Figure 1).

Although PGx advancements contribute clinically relevant genomics knowledge, it is also obvious however, that modern pharmacology is gaining major benefits in experimenting with new sophisticated technological methodologies in drug development and delivery era. By projecting such changes that are expected to happen for therapeutics in the near future, it is important mainly for pharmacologists in academia to be actively engaged in providing their students with strong background and skills of *in vivo* pharmacology enriched with PGx knowledge. Since the latter represents a dynamic knowledge module and an ever changing scientific environment, it means that personalized medicine concepts must be taught to allow therapeutic decisions in real time and for all pharmacological drug classes. In such case, young healthcare practitioners will be trained in getting capable for individualized prescription of drug dosage schemes,

thus minimizing the risk for toxicity, the emergence of interactions and ADRs in clinical practice. It is thus crucial for pharmacologists to prioritize the steps and the process needed to be considered in pharmacology curricula, as well as to set-up a pharmacology-focused roadmap for achieving broader utility of personalized medicine decisions.

Nowadays, laboratory medicine techniques have received major impact from genomics methodologies and experimentation. The availability of methodologies and tools allowing the simultaneous assessment of various source data of clinical relevance (*e.g.*, drug-related, genomics-focused, clinical measurements) clearly contribute toward individualized therapeutic decisions in routine healthcare. Moving forward and in order to improve pharmacology-related productivity and clinical outcome issues, this means that the creation of platforms where the pharmacological assessment and the clinical exploitation of PK/PD-related molecular targets is happening throughout the drug discovery and development process; for example, the improvement of PK/PD behavior of the designed molecularly-targeted therapeutics in the body will be better served and secured^[28]. Moreover, the beneficial implementation of functional mapping framework in pharmacology by smoothly addressing PGx data integration into PK/PD processes will be greatly benefited, as proposed^[29]. In that case, the already applied PK/PD-related mathematical models could be effectively coupled with PGx data referring to specific pharmacology-focused molecular networks and signaling pathways. The interdisciplinary nature of the framework and infrastructure needed represents, however, tedious and long-standing processes that obviously also rely on elucidation of illness etiology and drug behavior profiles. Besides, the establishment of selective molecular biomarkers with broader clinical validity and utility for most, if not all, pathological disorders and marketed therapeutics have to be clearly addressed. Moreover upon formulating personalized medicine decisions, the developed genomics-related methodology profiling (*e.g.*, genome-wide linkage analysis including proteomics-, genotyping-, gene array-, transcriptomics- and/or metabolomics-related data) must exhibit broader advantages in laboratory medicine applications for all patients worldwide^[28-33]. The latter, means that the capability of molecular diagnostics to help addressing routine therapeutic decisions in real time is the most desirable goal nowadays for PTx and personalized medicine concepts.

ESTABLISHMENT OF NETWORK AND SYSTEMS PHARMACOLOGY METHODOLOGIES IN ENRICHING *IN VIVO* PHARMACOLOGY EXPERIENCE TOWARD FORMULATING PTX-BASED CLINICAL PHARMACOLOGY GUIDELINES

Unanimously, the availability of predictive tools to effec-

tively address issues related to safety and efficacy profiles of therapeutics within the body represent a major task toward improving productivity and clinical outcomes of drug candidate molecules. Especially by considering the whole drug discovery and development process, that need is even more stressful at preclinical-clinical phase of development; such capacity in predicting safety and efficacy therapeutic outcomes very early is considered crucial toward establishing focused personalized medicine decisions of broader clinical utility. To do so, the implementation of clinical pharmacology guidelines has to be achieved through the knowledge coming from the use of cost-affordable PGx molecular diagnostics^[3,34]. For example, the organization and development of evidence-based PGx guidelines in clinical practice represents an obstacle hindering translational medicine efforts in drug discovery and development from bench to bedside^[35-37]. To this end and although various issues (*e.g.*, reimbursement, social, cost-benefit and ethical) should be simultaneously addressed, specific efforts for formulating PGx guidelines for dose recommendation schemes in specific pharmacological drug classes has been initiated and proposed^[38-43].

The development and application of physiologically based pharmacokinetic (PBPK) modeling for key PK-related processes have been greatly appreciated in drug delivery and development era. The PBPK models capacity also permits to assess, predict and evaluate in a quantitative basis the potential clinical effect of drug interactions along with any impact related to disease status, genetic make-up, environmental factors and/or drug formulation properties^[44,45]. Such an effort is presented in more detail elsewhere^[34]. As far as the PGx data exploitation is concerned, it is crucial for example to understand that only in the circumstances where the genetic variation represents the rate-limiting PK/PD step it would be possible to directly inter-correlate such molecular knowledge with the predictability profile in drug plasma concentration; and then beneficial for the practical utility of personalized medicine to proceed toward adjusting dosage scheme for individual patients based on their genetic variation (Figure 1). Such a direction upon drug prescription, in order not to be restricted in clinical pharmacology guidelines have to also effectively integrate and address issues related to the PGx concepts, the drug interactions knowledge, as well as the emergence of ADRs^[46]. For having PTx success, this relies on the ability to use drug interactions knowledge being efficiently inter-correlated with PGx knowledge for genes mediated the PK/PD behavior of therapeutics. Moving ahead, such direction necessitates a structure where suitably constructed PGx models assembling large cohort studies will be established to better serve: (1) the interdisciplinary data assessment; (2) the dissemination and broader clinical utility of personal genetic information upon illness risk prevention; and also (3) the use of PTx-based concepts upon medicines prescription^[1,34]. Moreover, the importance of having in these scientific attempts expert pharmacologists to participate is crucial,

since pharmacologists would be capable to verify: (1) the enrichment of *in vivo* pharmacology experience; (2) the efficient translation of PGx information to implement therapeutics decisions; and last, but not least, (3) the adjustment of drug dosage schemes, thus making personalized medicine decisions to benefit routine clinical practice, or alternatively, to achieve PTx for individual patient populations, if not all patients.

PBPK MODELING APPROACHES TO IMPLEMENT *IN VIVO* PHARMACOLOGY EXPERIENCE WITH PGX KNOWLEDGE FOR ENSURING PTX IN CANCER THERAPY: THE CASE OF TAMOXIFEN

PGx of anticancer drugs is now considered an integral part of cancer therapy^[47]. Indeed, a number of predictive PGx biomarkers to assess the safety and efficacy clinical profiles of individual marketed anticancer drugs has been validated by drug regulatory agencies (*e.g.*, the FDA and EMA) and are shown in Table 1. As mentioned above, however, the development of PBPK models implemented with systems pharmacology approaches, (assessing predictive PGx biomarkers), represents a platform where in real time the assessment of both patient-related and drug-related factors can be intercorrelated to achieve maximum efficacy and safety outcome for individual populations, *i.e.*, PTx (Figure 1). Alternatively, the latter means the elaboration of a multidisciplinary environment in order both the assessment of drug interactions and PGx data to be effectively incorporated to guide drug prescription. To better clarify this issue by analyzing the complexity existed and the hurdles needed to be overcome, the example of tamoxifen and serotonin reuptake inhibitors (SSRIs) will be further considered.

Accumulated evidence over the previous years have clearly postulated the contribution of genetic polymorphic variants of CYP2C19 and CYP2D6 (drug metabolizing enzymes) to the pharmacological response of psychotropic drugs in clinical practice^[48-50]. To this end, a specific guideline for psychiatrists providing practical recommendations upon the prescription of psychotropic drugs based both on clinical drug-related as well as CYP2D6 and CYP2C19 PGx data for individual patient populations has been proposed. Although, the broader clinical applicability of such instructions is still elusive, however, the improvement of PK and PD profile toward achieving personalized medicine decisions for psychotropic drug coincides with the capacity to simultaneously assess CYP genes variants in routine healthcare^[51-54].

The fact that metabolism of psychotropic drugs including antidepressants represents a rate-limiting step in their pharmacological profile means that specific CYP polymorphic variant forms (*e.g.*, CYP2D6) contribute either to toxicity and/or drug inefficiency in specific individual populations. Moreover, since some antidepressants

are also CYP2D6 inhibitors, clinically-relevant drug interactions are expected upon their co-administration with other drugs whose pharmacological activity is based on CYP2D6 function like tamoxifen^[55]. The clinical efficacy of tamoxifen varies widely among breast cancer women depending on their CYP2D6 genotype. Tamoxifen is a pro-drug which means that its active metabolite 4-hydroxytamoxifen and endoxifen being produced through the function of CYP2D6 mediates the pharmacological anti-estrogen action in the body. At the same time, co-administration of SSRIs antidepressants had previously been a common routine clinical practice and prescribed to treat hot flashes in women who take tamoxifen^[56-61]. But at what extent, however, would be clinically validated the predictive capacity in dosage scheme to ensure tamoxifen efficacy (active metabolites plasma concentration) and safety (toxicity, *i.e.*, hot flashes) based on CYP2D6 function affected by genotypes and SSRIs inhibitory behavior? Moving ahead, it has been proven that either women exhibiting polymorphic null-activity for CYP2D6 (PMs; CYP2D6 poor-metabolizers), or patients under tamoxifen chemotherapy co-prescribed with potent CYP2D6 inhibitors (*e.g.*, antidepressant drugs fluoxetine and paroxetine) show a greater risk of breast cancer recurrence and mortality due to decreased levels of active tamoxifen metabolites formed in their organism. That knowledge now proposes that personalized dosage schemes of tamoxifen administration to individual or population of patients are achieved through: (1) for CYP2D6 PM women by avoiding the co-prescription of tamoxifen with SSRIs or other medicines acting as potent CYP2D6 inhibitors; (2) Alternatively, similar improvement can be achieved through the proper dose adjustment of tamoxifen, or alternatively by switching into another hormonal therapy drug class (*e.g.*, aromatase inhibitors); and (3) For breast cancer patients exhibiting normal CYP2D6 metabolism (phenotype of CYP2D6 extensive metabolizers) by selecting the co-administration of an antidepressant that exhibits no inhibitor activity for CYP2D6 (*e.g.*, venlafaxine which represents a weak CYP2D6 inhibitor). But even in this case, the clinical effectiveness and the cost-effectiveness of CYP2D6 genotyping for the management of women with breast cancer treated with tamoxifen still needs to be validated^[62]. However, having this knowledge in mind one can further consider the possibility of developing advanced PBPK models in order to: (1) more thoroughly exploit clinical, pharmacological and PGx data of drugs; (2) develop proper algorithms to implement drug prescription; and (3) to facilitate new drug development productivity through predicting PD/PK behavior and reduce attrition rates in potential drug candidate molecules. Recently, the successful PBPK model development for tamoxifen delivery and for the evaluation of PK of patients with cancer clearly shows the dynamics of such scientific approaches^[63,64]. And more importantly this dynamics of PBPK modeling is further strengthened from research efforts reshaping the field of PD/PK modeling by enhancing the capacity to efficiently predict drug

Table 1 Genes used as predictive pharmacogenomics biomarkers to assess the safety and efficacy clinical profiles of individual marketed anticancer drugs^{1,2}

| Drug | Gene | Safety/efficacy profile |
|------------------|---------------------|--|
| Anastrozole | <i>ER</i> | Lower efficacy; no response in cancer patients with tumor <i>ER</i> -negative expression |
| Capecitabine | <i>DPYD</i> | Lower safety; ADRs; Orodigestive neutropenia |
| Cetuximab | <i>EGFR</i> | Lower efficacy; no response in cancer patients with tumor <i>EGFR</i> -negative expression |
| | <i>K-RAS</i> | Lower efficacy; no response in cancer patients with tumor specific <i>K-RAS</i> mutations |
| Cisplatin | <i>TPMT</i> | Lower safety; ADRs; cytotoxicity associated with hearing loss in children |
| Crizotinib | <i>ALK</i> | Efficacy; indication only in patients bearing <i>ALK</i> gene rearrangement positive tumors (<i>EML4-ALK</i> translocation) |
| Dabrafenib | <i>BRAF</i> | Efficacy; indicated only in melanoma patients with <i>BRAF</i> V600E mutation |
| | <i>G6PD</i> | Safety; ADRs; toxicity in <i>G6PD</i> deficient patients |
| Dasatinib | <i>Ph+</i> | Efficacy; indicated only for <i>Ph</i> ⁺ tumors |
| Erlotinib | <i>EGFR</i> | Lower efficacy; no response in cancer patients with tumor <i>EGFR</i> -negative expression |
| Everolimus | <i>Her2/Neu</i> | Efficacy; indicated in <i>HER2</i> protein overexpression negative in breast cancer women |
| | <i>ER</i> | Efficacy; indicated for breast cancer women bearing <i>ER</i> positive tumors (<i>ESR1</i> ⁺) |
| Exemestane | <i>ER</i> | Lower efficacy; no response in cancer patients with tumor <i>ER</i> -negative expression |
| Imatinib | <i>Ph+</i> | Efficacy; indicated only for <i>Ph</i> ⁺ tumors |
| | <i>PDGFR</i> | Efficacy; indicated in myelodysplastic- myeloproliferative syndromes with <i>PGFR</i> gene rearrangements |
| | <i>FIP1L1-PDGFR</i> | Efficacy; assessment of <i>FIP1L1-PDGFR</i> translocation -fusion kinase in tumors |
| | <i>c-kit</i> | Lower efficacy; no response in cancer patients with absence of tumor activating <i>c-Kit</i> mutations |
| Irinotecan | <i>UGT1A1</i> | Lower safety; ADRs; diarrhea, increased risk for severe neutropenia in high doses of irinotecan |
| Lapatinib | <i>Her2/Neu</i> | Efficacy; indicated for over-expressing <i>Her2/Neu</i> advanced or metastatic breast cancer |
| Letrozole | <i>ER</i> | Lower efficacy; no response in cancer patients with tumor <i>ER</i> -negative expression |
| Nilotinib | <i>Ph+</i> | Efficacy; indicated only for <i>Ph</i> ⁺ tumors |
| | <i>UGT1A1</i> | Safety; increased risk of hyperbilirubinemia in patients with <i>UGT1A1</i> *28 genotype |
| 6-Mercaptopurine | <i>TPMT</i> | Lower safety; ADRs; neutropenia |
| Panitumumab | <i>EGFR</i> | Lower efficacy; no response in cancer patients with tumor <i>EGFR</i> -negative expression |
| | <i>K-RAS</i> | Lower efficacy; no response in cancer patients with tumor specific <i>K-RAS</i> mutations |
| Pertuzumab | <i>HER2/Neu</i> | Efficacy; indicated only for <i>HER2/Neu</i> ⁺ breast cancer |
| Tamoxifen | <i>ER</i> | Lower efficacy; no response in cancer patients with tumor <i>ER</i> -negative expression |
| | <i>CYP2D6</i> | Lower efficacy; loss of therapeutic benefit for PMs and/or upon co-administration with <i>CYP2D6</i> inhibitors; lower plasma levels of active metabolite endoxifen achieved |
| | <i>FV</i> | Safety; ADRs; risk for venous thromboembolism in breast cancer women also bearing factor V Leiden (FLV) mutations |
| | <i>F2</i> | Safety; ADRs; risk for venous thromboembolism in breast cancer women also bearing factor II (prothrombin) mutations |
| Thioguanine | <i>TPMT</i> | Lower safety; ADRs; Neutropenia |
| Trastuzumab | <i>HER2/Neu</i> | Lower efficacy; no response in cancer patients with tumor <i>HER2/Neu</i> -negative expression |
| Vemurafenib | <i>BRAF</i> | Efficacy; indicated only in melanoma patients whose tumors has a mutation at amino acid 600 of the B-raf protein (V600E and/or V600K <i>BRAF</i> mutations) |

¹See also the table of PGx biomarkers in drug labeling at the FDA that can be accessed at: <http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm> (Accessed on June 27, 2014); ²Additional data can be seen in "The Pharmacogenomics Knowledge Base (PharmGKB) at: <https://www.pharmgkb.org/> (Accessed on June 29, 2013). ADRs: Adverse drug reactions; G6PD: Glucose-6-phosphate dehydrogenase deficiency; PM: Poor metabolizers; ER: Estrogen receptor; TMTP: Thiopurine methyltransferase gene; DPYD: Dihydropyrimidine dehydrogenase gene; Ph: Philadelphia chromosome; FV: Factor V; F2: Factor II (prothrombin).

effects in the body^[65-68]. This is an example for PTx on how the pharmacological knowledge of drug interactions covering both clinical and biochemical knowledge can be efficiently inter-correlated with PGx information of genes mediating the PK/PD behavior of therapeutics to improve delivered medicines clinical outcomes. The need for well-educated physicians and pharmacists, the proper clinical pharmacology/PGx guidelines development and adjustment, as well as healthcare infrastructure organization equipped with suitable clinically-validated technological methodologies is now, more than ever, stressful and demanding.

The analysis presented above for tamoxifen and SSRIs imply that the broader clinical utility of personalized medicine as well as PTx will be also strengthened by developing pharmacology-focused functional mapping

frameworks for most, if not all, specific pharmacological drug classes. In such a case, additional benefits for translational medicine will be gained; alternatively, this refers to the successful implementation of PD/PK data and the new drug development environment with PGx knowledge^[34]. Such modeling approaches clearly strengthen healthcare efforts toward the establishment of PTx as a new drug prescription "philosophy" in drug delivery. The latter, means that the practical utility of genomics information is conceptually exploited to ensure maximum safety and efficacy profiles. This way toward achieving PTx represents a very complex task that is clearly documented in the case of tamoxifen prescription where the *CYP2D6* pharmacogenomics assessment by healthcare decision makers well documented the steps still needed to be addressed^[69,70]. In the meantime, however, the

proper education of healthcare professionals has to be adjusted to fulfill expectations for the PTx roadmap in personalized medicine. Importantly, to highlight education needs and also to facilitate the teaching process in the revised curricula of various professionals engaged in this topic, a recently edited book volume has been organized and released as a first attempt to fill the gap in terms of the multidisciplinary perspective for personalized medicine^[1].

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