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EDITORIAL



# Predictive biomarkers and personalized pharmacotherapy

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## 1. Introduction

Inherent variability among patients significantly affects the outcomes of pharmacotherapy. Patients with apparently the same diagnosis often respond differently to the same pharmacological intervention, both with respect to efficacy and/or safety. Despite this knowledge, a large part of pharmacotherapy is still based on a 'trial and error' approach, which can have a severe negative impact on the patient [1]. The inability to predict which patients will respond to which drugs affects the efficacy and value of pharmacotherapy. However, the past 30 years of progress in molecular medicine has provided us with a better understanding of the underlying pathophysiology and mechanism of action of drugs, which is a prerequisite for making pharmacotherapy more predictable and efficient [2]. For some diseases and drugs, this understanding has led to the development of different types of predictive biomarkers, which can help to identify patients who are more likely to benefit from the drug in question and make pharmacotherapy more personalized.

According to the FDA-NIH Biomarker Working Group, a predictive biomarker is defined as a biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent [2]. These biomarkers most often represent patient characteristics such as molecular changes related to somatic and germline DNA, receptor proteins, cytochrome P450 enzyme phenotype, HLA type, etc. If a biomarker is predictive for a specific drug, its presence will indicate that the patient will have a higher probability of a positive outcome. For the past couple of decades, two types of predictive biomarkers have found their way into the clinic: companion diagnostic (CDx) and pharmacogenetic (PGx) biomarkers. In this editorial, we briefly discuss different aspects related to these two types of predictive biomarkers and their role in patient care.

## 2. Companion diagnostics

For more than 20 years, CDx has played an increasingly important role in the treatment of patients with oncological and hematological diseases. The first drug developed together with a CDx assay was the monoclonal antibody trastuzumab (Herceptin), indicated for the treatment of HER2-postive breast cancer [3]. In 1998, when the FDA approved trastuzumab, the immunohistochemical assay HercepTest for the detection of HER2 expression in the breast tumor tissue obtained concomitant approval. Since then, the number of targeted drugs with a CDx assay linked to their use have increased significantly, and by June 2022, the FDA has approved more than 50 drug-diagnostic combinations [4]. In addition to the drugs listed in Table 1, several CDx assays are also available for drug combinations. For these drugs or drug combinations, it is stated in their Prescribing Information that testing with an FDA-approved CDx assay should be performed before they are prescribed to patients. To date, CDx assays are almost exclusively found within drugs used for the treatment of oncological and hematological diseases. For the drugs listed in Table 1, only two are for diseases outside these disease areas, namely deferasirox (Jadenu) and setmelanotide (Imcivree), which are used for the treatment of patients with thalassemia and for chronic weight management, respectively [5].

Although the first CDx was approved before the turn of the century, it took more than 15 years for the FDA to issue an official definition. In 2014, the FDA defined this type of assay as an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product [6]. For most CDx assays, the clinical validation is performed using an enrichment trial design in which only biomarker-positive patients are treated with the drug. This is important to have in mind, as the clinical outcome data cannot be extrapolated to any patient population other than those defined by the CDx assays. In fact, the FDA emphasize this as a remark to the definition of a CDx assay and thereby also address the issue of off-label prescriptions [6].

Oncological and hematological diseases are areas with great unmet medical needs, and for the past 20 years, a number of new and more effective drugs have been developed, as listed in Table 1. These drugs have been developed for molecular subsets of patients using the drug-diagnostic co-development model [7]. In this model, the clinical documentation is generated based on data from different types of enrichment trials. If such a trial demonstrates a link between the CDx assay result and the outcome following treatment with the investigational drug, the likelihood of concomitant regulatory

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Table 1. List of the FDA-approved drugs and their CDx biomarkers.

| CDx Biomarkers | Drugs |
|---|---|
| ALK/*ALK* | Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib |
| *BCR-ABL1* | Nilotinib |
| *BRAF V600E or V600K* | Binimetinib, cobimetinib, dabrafenib, encorafenib, trametinib, vemurafenib |
| *BRCA1/BRCA2* | Niraparib, olaparib, rucaparib, talazoparib |
| dMMR | Dostarlimab, pembrolizumab, nivolumab |
| *EGFR* | Amivantamab |
| *EGFR* | Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib, mobocertinib |
| *EZH2* | Tazemetostat |
| *FGFR2* | Pemigatinib, infigratinib |
| *FGFR3* | Erdafitinib |
| *FLT3* | Midostaurin, gilteritinib |
| HER2/*HER2* | Trastuzumab, pertuzumab, trastuzumab emtansine, trastuzumab deruxtecan |
| *HRR* | Olaparib |
| *IDH1* | Ivosidenib |
| *IDH2* | Enasidenib |
| Ki-67 | Abemaciclib |
| *KIT*/c-KIT, *PDGFRB* | Imatinib |
| *KRAS G12C* | Sotorasib |
| Software for MRI | Deferasirox |
| *MET* | Capmatinib |
| MSI-H | Pembrolizumab, nivolumab |
| *NTRK1/2/3* | Larotrectinib, entrectinib |
| PD-L1 | Atezolizumab, cemiplimab, nivolumab, pembrolizumab |
| *PIK3CA* | Alpelisib, olaparib |
| *POMC, PCSK1* and *LEPR* | Setmelanotide |
| *RAS (KRAS/NRAS)*/EGFR | Cetuximab, panitumumab |
| *RET* | Pralsetinib |
| *ROS1* | Crizotinib, entrectinib |
| TMB-H | Pembrolizumab |
| *TP53* | Venetoclax |

approval will be high. After approval, when these drugs are going to be used in the clinic for routine patient care, it is crucial to have access to a validated assay, which, unfortunately, is not always the situation [8]. It is important to note that a CDx assay acts as a gatekeeper for the prescribing process; hence, an analytical and clinically validated assay must be available for regulatory approval at the same time as the drug.

## 3. Pharmacogenetics

In pharmacotherapy, PGx biomarkers address aspects other than those of CDx biomarkers. Whereas CDx biomarkers are most often linked directly or indirectly to a specific mechanism of action, PGx biomarkers are frequently linked to the metabolism of drugs. Cytochrome P450 (CYP450) drug-metabolizing enzymes are the major enzymes that catalyze the oxidative biotransformation of a large fraction of drugs used in daily clinical practice to either inactive metabolites or active substances (pro-drugs) [9,10]. Polymorphism of genes encoding the CYP450 family of enzymes, particularly CYP2C9, CYP2D6, and CYP2C19, has attracted considerable attention as a major target for PGx testing because they are highly polymorphic and thereby determining drug response and adverse drug reactions (ADR) [11]. In addition, single-nucleotide polymorphisms (SNP) in the solute carrier organic anion transporter 1B1 (SLCO1B1), responsible for the uptake of statins into the liver, correlates with an increase in plasma exposure to statins. This can lead to muscle toxicity (myopathy), a common statin-related ADR occurring in 1–5% of the exposed patients in a dose-dependent fashion [12]. Because statins are some of the most commonly prescribed drugs, many patients could potentially be affected by muscle-related ADR [12].

The pharmacogenetic impact on the interaction between drugs and CYP450 isozymes, referred to as drug–gene interaction (DGI), has been incorporated into clinical actionable dosing guidelines (AG) for specific DGIs (see https://www.pharmgkb.org/) [13]. Accordingly, a person can be scored as 'poor metabolizer' (PM), 'intermediate metabolizer' (IM), 'extensive metabolizer' (EM, normal activity) and 'rapid or ultra-rapid metabolizer' (RM and UM), with UM having faster metabolic activity than RM. For statins, PGx-based AGs are now available for the intermediate (IM) or low function (LF) phenotypes of SLCO1B1 [12]. Table 2 shows the phenotypic distribution of PGx biomarkers among Caucasians. It should be noted that the percentage distribution of phenotypes varies among ethnicities [10]. Based on the phenotype score, the guidelines provide clinical recommendations such as dose adjustment, dose monitoring, or use of alternative drugs. In 2020, the FDA issued the 'Table of Pharmacogenetic Associations,' which is based on the current medical evidence for DGI for a large number of drugs, together with considerations and actions to be taken from a PGx perspective [14].

The term phenoconversion introduces an additional complicating factor, which could potentially give rise to 'genotype-phenotype' mismatches; a person scored as, e.g. EM or RM can be phenoconverted to a PM by co-medications, i.e. drug–drug interactions [9]. This means that the 'true' number of PMs could be significantly higher than the number of PMs measured by PGx testing alone. This term also refers to drug–drug–gene interactions (DDGI) [9]. In polypharmacy patients, phenoconversion has been shown to alter a person's drug

Table 2. Distribution of phenotypes (%) among Caucasians.

| | CYP2C9 | CYP2C19 | CYP2D6 | | SLCO1B1 |
|---|---|---|---|---|---|
| EM | 64,0 | 39,1 | 84,2 | NF | 72,3 |
| IM | 20,8 | 26,9 | 6,2 | IF | 25,5 |
| PM | 15,2 | 2,6 | 5,4 | LF | 2,3 |
| UM | 0,0 | 31,5 | 4,2 | | |

Note: CYP450-genotypes: EM, extensive metabolizer; (normal activity) IM, intermediate metabolizer; PM, poor metabolizer; UM, rapid/ultra-rapid metabolizer.
SLCO1B1 genotypes: NF, normal function; IF, intermediate function; LF, low function.
Data modified from [10]

metabolizing status, and a recent comprehensive review emphasizes the importance of assessing and accounting for both DGI and DDGI [9]. The guidelines provided by the PharmGKB webpage do not incorporate drug–drug interactions (DDI/DDGI) in the assessment of dose adjustments. However, this issue has been recognized, and initiatives have been taken to incorporate DDI/DDGI in clinical decision tools. Here, PGx testing is integrated with comprehensive DGI and DDI/DDGI information to assess the cumulative impact of a patient's genetics and drug regimen on efficacy and ADR [15]. Taking clopidogrel as an example, PharmGKB recommends the use of an alternative antiplatelet agent for the treatment of CYP2C19 PM and IM patients. The FDA states that these genotypes have lower plasma concentration of the active metabolite (clopidogrel is a pro-drug) and consequently lower inhibition of antiplatelet activity, which may result in a higher risk of cardiovascular events [16]. Based on this information, alternative antiplatelet therapy should be considered. Table 2 shows that around 30% of clopidogrel patients could be affected, and thereby potentially benefit from having a PGx test. A recent Danish study showed that the prevalence of use (users/1000) of clopidogrel was 22.1 in the general population and 84.1 in persons with diabetes, which emphasizes the widespread use of clopidogrel [16]. In addition, clopidogrel is associated with an increased risk of gastrointestinal (GI) bleeding [16]. Consequently, clopidogrel is commonly prescribed in combinations with proton pump inhibitors (PPIs) to prevent GI bleeding. PPIs have been reported to be inhibitors of CYP2C19, and both the FDA and EMA have published safety concerns regarding the concomitant use of clopidogrel and PPIs due to potential risk of phenoconversion. This warrants special caution when it comes to the use of clopidogrel in combination with PPIs to balance overall risk and benefits [16].

## 4. Conclusion

Predictive biomarkers play a central role in our attempt to personalize pharmacotherapy. Currently, the FDA have approved more than 300 drugs, where the labeling includes different types of biomarker information that can affect patient care. For drugs with a CDx assay linked to their use, testing is required before they can be prescribed to patients. However, this is different when it comes to PGx testing, which is optional in most cases. Despite many initiatives and advances in PGx implementation, significant barriers remain to the proactive use of these tests. This includes improvement of physicians and pharmacists' awareness and understanding of PGx testing, as well as documenting the clinical evidence and cost-effectiveness of PGx biomarkers in the optimization of pharmacotherapy. Despite the relatively slow implementation of PGx, its use seems to gain more and more foothold in clinical practice, as more convincing evidence appears. Finally, for any type of biomarker data used to guide pharmacotherapy, it is important to ensure that they are generated based on assays that have been sufficiently validated analytically and clinically, including the preanalytical aspects such as biopsy acquisition. Inadequate assay performance may have serious therapeutic consequences for individual patients, as erroneous results could lead to incorrect dosage of a drug or to withholding an appropriate therapy or administration of an inappropriate treatment.

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