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Pharmacogenomics – the key to personalized medicine.

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Abstract

Different rates of drug metabolism and the effect of commonly prescribed drugs are often seen in clinical practice. Some of these differences can be predicted if the patient's genetic profile is known by pharmacogenomic analysis, which done once, provides lifetime benefits. In the United States, adverse drug reactions are the fourth leading cause of death, costing their healthcare system about $136 billion annually. By implementing pharmacogenomic testing early in clinical algorithms, debilitating and potentially life-threatening side-effects can be predicted and avoided, which is particularly important in settings of pain therapy and anesthesia. In St. Catherine Specialty Hospital, this approach is readily advocated for our patients. Through the use of the RightMed panel, 25 genes coding for enzymes and other proteins important for drug function, are analyzed, and a pharmacogenomic-driven approach is taken by selecting the right drug, in the right dose, for the right patient.

Keywords: *pharmacogenomics, individualized medicine, personalized medicine, analgesia*

Introduction

Personalized medicine, considering the genetic profile of the patient, lifestyle, and environmental factors, has the potential to add new value to patient care and to change the current one-size-fits-all approach by utilizing pharmacogenomic data. Pharmacogenomics focuses on identifying genetic variants that influence the metabolism and effects of drugs, their pharmacokinetics and pharmacodynamics, with the ultimate goal of understanding individual patient's drug and dose requirements based on their own genetic profile. The terms pharmacogenetics and pharmacogenomics appear similar at first, however, pharmacogenetics explains a single gene-drug interaction, whereas pharmacogenomics is a broader field in which multiple genes are considered [1]. Genetic polymorphisms were first associated with different rates of substrate drug metabolism back in the 1970s in CYP2D6 research [2]. Nowadays, custom single nucleotide polymorphism assay chips are commercially available for anyone who wants to learn their pharmacogenetic profile, and for those clinicians who want to use this approach to tailor their patient's therapy. The latest data from the United States indicates that adverse drug reactions (ADRs) account for up to 7% of all hospital admissions, up to 20% of re-admissions and are the fourth leading cause of death. Their total estimated cost is $136 billion annually [3-6]. Genetic factors can account for up to 95% of an individual's drug response and are estimated to contribute to as much as 20% of the total number of reported ADRs [3,4,7]. These numbers call for a reconsideration of current healthcare strategies and the development of new treatment tools that would reduce the risk for patient's health and the additional treatment costs that predictable ADRs generate.

Background

It is well known that carriers involved in drug transport through different physiological barriers and enzymes that metabolize drugs are proteins, as well as most drug target receptors. This core principle is used in pharmacogenomics, as the variety of observed end-protein activity is influenced by underlying genetic polymorphisms. Therefore, there cannot be a one-size-fits-all drug for a single condition [8]. In pharmacogenomic studies, different alleles are analyzed to find single nucleotide polymorphisms (SNPs) [9]. SNPs make the difference in observed drug effect by modeling the activity of their protein product (metabolizing enzyme, transporter protein, drug-receptor, or other proteins not directly related to the drug). The end protein product can therefore be of normal, increased or decreased function/phenotype, based on various allele combinations. The results of these molecular analyses can be challenging for a clinician to understand, as the integration of genetics in clinical medicine is a new, interdisciplinary field. Therefore, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has established a standardized method for molecular pharmacogenomic analysis report terminology in order to ease the introduction of report interpretation for clinicians and patients. The standardized reporting should be oriented toward indicating the end-protein function, depending on the detected genotype [10].

For a proper introduction of pharmacogenomic guided therapeutic interventions, comprehensive guidelines are needed. CPIC has published 25 clinical guidelines designed to help clinicians optimize drug therapy according to pharmacogenomic analysis [11] (Table 1).

Table 1. Genes-drugs interaction with the highest level of clinical relevance (Clinical Pharmacogenetics Implementation Consortium guidelines recommend a change in prescribing of the affected drug based on evidence that include consistent results from well-designed, well-conducted studies).

Classification of genes	Example of genes	Drug examples	Effect
I. Genes involved in the first phase of drug metabolism – cytochrome P450 enzymes	*CYP2C9*	Phenytoin, warfarin	Certain genotype may influence drug substrate metabolism – consequent changes in drug efficacy and safety
	CYP2C19	Amytriptiline (es)citalopram, sertraline, clopidogrel, voriconazole	
	CYP2D6	Tricyclic antidepressants, atomoxetine, codeine, tramadol, fluvoxamine, paroxetine, ondansetron, tropisetron, tamoxifen	
	CYP3A5	Tacrolimus	
	CYP4F2	Warfarin	
II. Genes involved in the second phase of drug metabolism	*UGT1A1*	Atazanavir	Safety – risk of hyperbilirubinemia
III. Other genes involved in drug metabolism	*TPMT/NUDT15*	Azathioprine†, mercaptopurine†, thioguanine†	Efficacy and safety
	DPYD	Capecitabine, tegafur, fluorouracil	Safety – increased drug toxicity
IV. Genes for drug transporters	*SLCO1B1*	Simvastatin	Safety – risk of myopathy
V. Genes for drug targets	*VKORC1*	Warfarin	Efficacy
	CFTR	Ivacaftor‡	Efficacy
VI. Genes for other proteins important for drug action and safety	*HLA-A*	(Ox)carbamazepine	Safety – increased risk of SJS/TEN
	HLA-B	(Ox)carbamazepine‡, abacavir‡, fosfo(phenytoin), allopurinol	Safety – increased risk of SJS/TEN
	IFNL3	Peginterferon-alfa2a and 2b, ribavirin	Efficacy
	G6PD	Rasburicase‡	Toxicity – risk of hemolysis
	CACNA1S/RyR1	Inhalational anesthetics/suxamethonium	Toxicity – increased risk of malignant hyperthermia

†Testing recommended (according to FDA).
‡Testing required (according to FDA).

Therefore, there is a growing need for high-quality studies that would reinforce current concepts and possibly provide new insight into the combined effect of multiple drug-metabolizing enzymes and receptors on a given drug.

Pain therapy

In daily clinical practice, pain is one of the most commonly treated symptoms. It can be provoked by a plethora of underlying medical conditions that require different treatment strategies. However, successful pain management requires the delivery of analgesia with minimal risk of ADRs. It is often observed that patient's responses to pain medications vary, with almost 50% of patients experiencing inadequate pain relief and serious ADRs with commonly used perioperative analgesics [12]. The direct and indirect cost of chronic pain management ranges from $560 to 635 billion annually in the United States [13-15]. Some of the most commonly used analgesics have available pharmacogenomic information in their FDA label or in CPIC/ Dutch Pharmacogenetics Working Group (DPWG) clinical guidelines, including opioids (codeine, oxycodone, tramadol), anti-inflammatory (celecoxib) and neuropathic pain drugs (tricyclic antidepressants). It should be stated that knowing the genetic profile alone is not enough to completely alleviate pain in patients suffering from various painful conditions. Other factors such as environmental, age, sex, previous medical conditions and lifestyle greatly contribute to the individual sensation of pain [16]. Therefore, a combined approach that includes both the clinical assessment on a patient-to-patient basis and genetic testing is needed to precisely select the optimal strategy for analgesic therapy. Pain therapy is also one of the cornerstones of safe anesthesia. General anesthesia commonly combines various drugs such as volatile anesthetics, hypnotic-sedative agents, muscle relaxants, and opioid analgesics. Although efficient and safe anesthesia is grounded on clinical protocols, which take into consideration relevant procedure-, patient- and drugs-related factors, direct drug levels monitoring and automatic closed-loop control; various polymorphisms of genes encoding for anesthetic drug molecular targets, as well as their transporters and metabolic enzymes, might change a drug pharmacodynamic or pharmacokinetic characteristics, thus influencing the clinical features of anesthesia [17]. Some of the most dangerous complications, like malignant hyperthermia, have a clear genetic background for which a clinical guideline has been established by CPIC [18].

Opioids

Moderate quality evidence has shown that the variability of the analgesic effect is affected by genetic variants in opioid receptors M1 (OPRM1) and catechol-O-methyltransferase (COMT). Polymorphisms of the gene encoding for COMT, an enzyme that degrades catecholamines, are most frequently linked to divergent pain processing [19]. The most studied functional SNP of COMT is rs4680, where A to G transition results in a Val to Met amino-acid substitution, and lower enzymatic activity, as demonstrated in several studies where AA genotype carriers had increased sensitivity to the analgesic effects of opioids compared to AG and GG genotypes [20-22]. Over 100 allele variants in the OPRM1 gene encoding for the M opioid receptor (MOR) have been identified. SNP rs1799971 (118A>G) was related to reduced analgesic effect and requirements for higher doses of morphine [23]. The frequency of the OPRM1 188A>G variant differs between ethnic populations: 35–50% in individuals of Asian descent, 15.4% in individuals of European descent, 14% in individuals of Hispanic descent and 4.7% in those of African descent [24]. A member of the cytochrome P450 family of metabolizing liver enzymes, CYP2D6, is responsible for metabolizing a number of opioid analgesics, including codeine, oxycodone and tramadol. In regard to detected allelic variants, its function/ phenotype can be categorized as poor, intermediate, rapid or ultrarapid [25]. The analgesic effects of codeine and tramadol which are metabolized by CYP2D6, are attributed to their O-demethylation to a more potent MOR agonist, therefore they are "activated" when they undergo CYP2D6 metabolization. Thus, the effect of different phenotypes is reciprocal, where poor metabolizers are at an increased risk of inadequate therapeutic response and ultrarapid metabolizers have a higher risk of adverse effects and overdose. This observation is influenced by changes in their pharmacokinetics, altering the concentration of their active metabolites. A pharmGKB guideline was developed to aid in clinical interpretation and decision-making of CYP2D6 phenotype for tramadol and codeine. For ultrarapid metabolizers, alternative analgesics are suggested [26]. Previous reports warned of respiratory depression and death in children taking codeine who were identified as CYP2D6 ultrarapid metabolizers [27]. Because of the risks associated with CYP2D6 ultrarapid metabolism, breastfeeding is not recommended during treatment with codeine or tramadol. Opioids are commonly used in clinical practice and they have a well-known side-effect profile that can, however, be predicted and reduced if the pharmacogenomic guided approach is used.

Non-steroid anti-inflammatory drugs (NSAIDs)

NSAIDs include two big groups of drugs: non-selective cyclooxygenase inhibitors and selective cyclooxygenase-2 inhibitors, such as etoricoxib and

celecoxib. Both of these groups have analgesic and anti-inflammatory effects. The side effect profile of NSAIDs includes gastrointestinal and cardiovascular ADRs, therefore it is important to use them with care as they are readily available over-the-counter. It is particularly important to consider their side-effect profile in older populations since they are at an already increased risk for gastrointestinal and cardiovascular disease [28-31]. Different bioavailability based on CYP2C8 genotype was shown to have a role in patients developing potentially serious adverse drug reactions with prolonged use of NSAIDs [32]. SNPs of another member of the cytochrome P450 enzyme family, CYP2C9, have been found to influence the metabolism rate of celecoxib and flurbiprofen. For patients who have a determined poor metabolizer phenotype (CYP2C9 *3/*3) a 50% reduction in starting dose has been suggested to avoid potential side effects, however, it is not a part of any official guideline [33]. Another study found an increase in gastrointestinal tract bleeding risk in patients carrying CYP2C8*3 and CYP2C9*2 alleles when using NSAIDs that are the substrate of both of those enzymes, such as ibuprofen and diclofenac [34]. This evidence still needs to be reinforced by more robust clinical studies. But, considering the potential detrimental effect that NSAID ADRs can have on the elderly population the changes in their metabolism induced by these SNPs should be considered if available.

Malignant hyperthermia

In anesthesiology, the most important pharmacogenetic influence on the safety of volatile anesthetics and succinylcholine is the prediction of malignant hyperthermia risk. Influenced by SNPs in RYR1 and CACNA1S genes, which are inherited in an autosomal-dominant pattern, a heterozygous genotype is considered to be diagnostic of the trait [18]. The variants in RYR1 and CACNA1S genes under consideration here predispose individuals to a severe and sometimes fatal hypermetabolic reaction with symptoms that include muscle rigidity, high fever, and a fast heart rate, and can include rhabdomyolysis and high blood potassium. For individuals with SNPs in the stated genes, succinylcholine and volatile anesthetics should be avoided due to increased malignant hyperthermia susceptibility. The presence of a single pathogenic variant in RYR1 or CACNA1S found by molecular genetic testing is considered diagnostic for the trait [35].

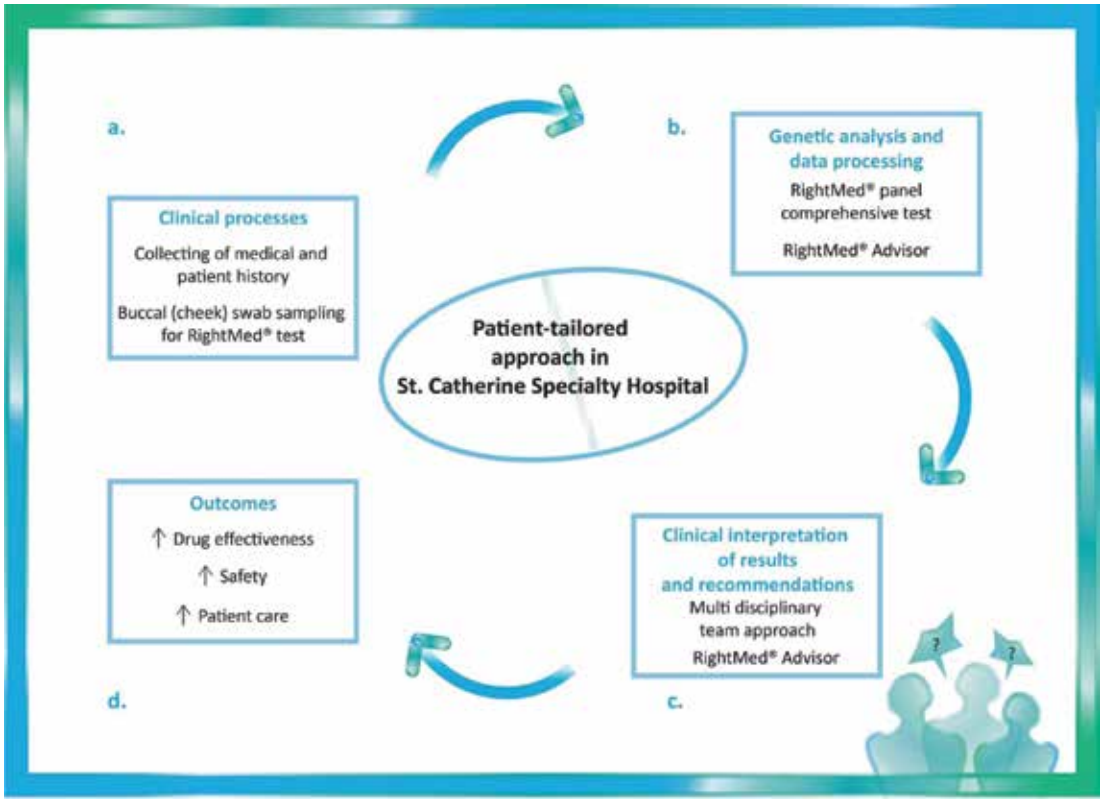

Figure 1. A schematic representation of implementation personalized pharmacogenomic-based treatment and healthcare system. The first step is to collect medical and patient history via a specific form followed by a buccal swab for DNA sampling for RT-PCR. b. RightMed® panel comprehensive test processes the PGx results using an algorithm. RightMed® Advisor is being generated here. c. Results are then interpreted by a multi-disciplinary team. In addition to drug-gene interactions, the RightMed® Advisor platform checks for drug-drug, drug-food (supplement) interactions. d. The results aid in providing better patient care, superior therapy outcome and greater drug effectiveness while at the same time reducing the rate of ADRs.

Our approach

At St. Catherine Specialty Hospital, where the personalized approach to patient care is pioneered, patients referred for pharmacogenomic testing are first interviewed by one of our specialists in the outpatient clinic (Figure 1). A detailed patient history focusing on current and previous drug therapy is taken, after which a buccal swab is performed in order to obtain a sample of the patient's DNA. The obtained DNA is then analyzed using the RightMed panel developed by OneOme in collaboration with Mayo Clinic. The panel determines SNPs using a TaqMan real-time PCR method and CNV analysis. The 25 analyzed genes include genes responsible for the synthesis of enzymes included in the first phase of drug metabolism (cytochrome P450 family), enzymes included in the second phase of drug metabolism (TPMT, UGT1A1), other enzymes included in drug metabolism (DPYD, VKORC1, NUDT15), drug transporters (SLC6A4, SLCO1B1), drug receptors (HTR2A, HTR2C, DRD2, OPRM1, GRIK4, COMT), other proteins important for drug function (IFNL4, HLA-A, HLA-B). The results are then generated as individual test reports that are interpreted by a genetic counseling team in St. Catherine Specialty Hospital. Once the report is made, the patient is scheduled for a follow-up with one of our specialists to determine if any corrections have to be made to their current therapy and to provide suggestions for potential future therapy needs based on the clinical assessment.

Conclusions

Pharmacogenomic testing performed once can provide lifetime benefits. Although more effort is still needed to implement pharmacogenomics in daily clinical practice, evidence suggests that personalized medicine is the treatment approach of the future and pharmacogenomic testing is at the center of it, with the benefits of cost reductions and improved quality of care which every healthcare system should value. In the future, digital tools should be made available for all healthcare professionals that come across comprehensive pharmacogenomic test results to ease their interpretation and reinforce drug prescription on the basis of individualized medicine.

Note:

Pharmacogenomics – the key to personalized medicine is an excerpt from the texts prepared for: Personalized medicine, scientific journal (Bach-Rojecky L, Vađunec D, Žunić K, Kurija J, Šipicki S, Gregg R, Mikula I, Primorac D. Continuing war on pain: a personalized approach to the therapy with nonsteroidal anti-inflammatory drugs and opioids. Per Med. 2019;16(2):171-184. doi: 10.2217/pme-2018-0116.) and Pharmacogenomics, scientific journal (Primorac D, Bach-Rojecky L, Vađunec D, Juginović A, Žunić K, Matišić V, Skelin A, Arsov B, Boban L, Erceg D, Erceg Ivkošić I, Molnar V, Ćatić J, Mikula I, Boban Lj, Primorac L, Esquivel B, Donaldson M. Pharmacogenomics at the center of precision medicine: challenges and perspective in an era of Big Data. Pharmacogenomics. 2020 Jan;21(2):141-156. doi: 10.2217/pgs-2019-0134.) in which the genetic basis of pain and pain therapy and a comprehensive review of implementation of pharmacogenomics to clinical practice were prepared and presented in full.

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