Applied Pharmacogenomics in Neurology and Psychiatry: a case series presentation

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Abstract

Introduction: *Pharmacogenomics (PGx) is the scientific domain that combines Pharmacology and Genomics focusing on an individual's genetic response to a specific medication. The role of PGx-guided personalized medicine is to find the best responding medication and to reduce the occurrence of adverse drug effects, aiming to save time and costs from failed treatment options that at the same time drive the patient to anxiety and frustration.* ***Methodology:*** *We used pharmacogenomics analysis in 5 cases; 3 male and 2 female patients, aging from 19 to 72 years old, diagnosed with epilepsy, bipolar disorder, Parkinson disease and Depression. Genetic material was collected from bucchal cells or saliva and the genomic DNA was used in PGx analysis of 24 Single-Nucleotide Polymorphisms (SNPs), corresponding to 13 genes that participate in drug metabolism.* ***Results:*** *Based on PGx-testing results, patients' medication was altered leading to clinical improvement. In the first two cases epileptic seizures were reduced after medication's change. In cases 3 and 4, antidepressants given according to PGx testing led to improvement of depressive mood and neuropsychological assessment. Finally in case 5, the previous medication caused serious adverse side effects like hyponatremia and aminotransferases' elevation while the PGx-guided therapy proved totally safe. PGx analysis results rely on international guidelines and the current scientific data. However, instructions derived from PGx analysis are not a panacea. Personalized precision medicine provides with valuable molecular information that supports the physician's decision regarding the selection of the most suitable medical treatment for a patient.*

Keywords: Pharmacogenomics, iDNA-Genomics, case series, neurology, psychiatry

JEL classifications: I10, I11, I12, I15

Introduction

The 1950s marked the beginning of our modern conceptualization of pharmacogenetics as a distinct discipline. In 1959, the German human geneticist Friedrich Otto Vogel first introduced the term "pharmacogenetics" (Eschenhagen et al., 2011). Pharmacogenomics (PGx) focuses on the identification of genetic variants that are associated with drug effects in individual patients. It lies on the intersection of genomics and pharmacology, and has achieved a great impact on the clinical practice in Neurology, Psychiatry, Cardiology and Oncology (Kalinin et al., 2018). Pharmacogenomics contributes important information to the field of precision medicine, as a significant diagnostic tool for the selection of the most suitable medication with the fewer adverse effects, based on the genotype of each patient.

PGx can help to predict drug efficacy or toxicity. Response rates of patients to medication varies widely in therapeutic classes, from 80% for analgesics to ~25% for oncology treatment(Spear et al., 2001). According to the 'National Institute for Health and Clinical Excellence' (NICE), selective serotonin reuptake inhibitors adminnistered as antidepressants, should be the first line of treatment for moderate or severe depression. Yet nearly 50% of patients either do not respond or have side-effects rendering them unable to continue the course of treatment (Moncrieff & Kirsch, 2005; Wang et al., 2019). Olfson et al recently noted that in a sample of 829 patients, the 42% discontinued their antidepressant treatment during the first 30 days and 72% had stopped within 90 days (Mitchell, 2006; Olfson et al., 2006).

In addition, adverse drug reactions (ADRs) also range widely and consist a significant clinical concern. Two million ADR events are estimated every year in the US, which result in over 100,000 deaths per year (Bush, 1998; Shastry, 2006). According to a European review of all epidemiological studies between 1 January 2000 and 3 September 2014, the median percentage of hospital admissions due to ADRs was 3.5 % (Bouvy et al., 2015). Moreover, the JADE study, which included 448 patients with 22,733 patient-days in a psychiatric hospital and psychiatric units, identified 955 ADRs and 398 medication errors. Among ADEs, 1.4% were classified as life-threatening, 28% as serious and 71% as significant. Antipsychotics were associated with half of all ADEs (Ayani et al., 2016). In addition, a cross-sectional study at University of Gondar Referral Hospital included 354 adult epileptic patients reports that 16.6% of patients showed adverse drug effects (Ayalew & Muche, 2018). Polypharmacy is another serious issue which is particularly common in geriatric population. Over 50% of older adults in the United States take four or more medications, which may lead to medication errors and adverse drug events (Osborn et al., 2014).

However, until now physicians, caregivers and patients, have all been sceptic in employing pharmacogenomics analysis, despite recommendations by the US FDA. It has been proven that on top of being clinically beneficial, PGx-guided treatment is cost-effective comparing to the alternative strategies. Indeed, out of the 137 PGx associations registered in the FDA table, 10 of them were included in 44 economic evaluations. The 57% of these evaluations drew conclusions in favor of PGx testing; 30% were classified as cost-effective (more effective at an acceptable additional cost) and 27% were characterized as cost-

saving or dominant (more effective at a lower cost), whereas 18% did not reach a definite conclusion. If genetic information was freely available 75% of economic evaluations would support PGx-guided treatment (Verbelen et al., 2017).

The role of individualized and precision medicine is very important to minimize health-related risks and costs and maximize treatment benefits. The genetic profile utterly contributes as a principal factor of drug response. Approximately 7% of medications (FDA approved) are affected by actionable inherited pharmacogenes, whereas approximately 18% of outpatient prescriptions in the US are affected by actionable germline pharmacogenomics. Drug–drug interactions (DDIs) are recognized as a major cause of ADRs. However, in addition to DDIs, CYP genotyping now allows drug–gene interactions (DGIs) and drug–drug–gene interactions (DDGIs) to be identified as a potential source of ADRs as well. According to a study including 501 individuals with 1053 major or substantial interactions, the 34% was attributed to drug-gene or drug-drug-gene interactions (Verbeurgt et al., 2014). Genetic information (DNA sequence, gene expression, genetic polymorphisms) is used to explain inter-individual differences in Pharmacokinetics (drug metabolism, absorption, distribution and excretion) and Pharmacodynamics (target, mechanism of action, drug response, toxicity, efficacy) (Hess et al., 2015). PGx testing is now available for many drugs for a wide range of health conditions or diseases, including diabetes, cardiovascular diseases, autoimmune disorders, mental health disorders, infectious diseases, and its application is anticipated to be recommended or required in the future to precede treatment.
There have been many surveys for the evaluation of the potential benefit of an integrated pharmacogenomic testing. According to a clinical trial conducted by the Mayo Clinic for the treatment of major depressive disorder, patients' satisfaction with their physicians' prescription was increased in the guided group with 40.5% compared with 14.8% in the unguided group. Also, physician satisfaction with care also increased, with the guided group reporting 94.6% satisfaction rate, compared with 61.8% in the unguided group (Hall-Flavin et al., 2013). More recently, a 12-week, double-blind, randomized controlled trial in 316 adult patients with major depressive disorder showed that in the PGx-guided group, the adverse events were significantly lower, and the drug response was statistically higher compared with the unguided group (Pérez et al., 2017). Furthermore, in a study including 1167 patients with major depressive disorder (MDD) without adequate response to their first medication for 8 weeks, PGx testing was used in 681 patients and usual treatment in the other 717 patients. The 33.5% of the patients in PGx-guided group showed improvement in their clinical symptoms, a percentage significantly higher compared with the 21.1% of patients using the usual treatment (Greden et al., 2019).

Apart from MDD, PGx testing has been used with positive results in other neuropsychiatric disorders as well. A recent study evaluated 30 patients of bipolar disorder type I or II, who underwent the PGx testing. The 40% of patients had received a change of therapy consistent to the test, showing a significant statistical improvement in the Clinical Global Impression Item Severity (CGI-S) score at a 3-month follow up, compared to those not having used the PGx test for changing their medication (Ielmini et al., 2018). Furthermore, growing evidence indicates that pharmacogenomics will positively impact treatment for patients with epilepsy in the near future. Until now,

results from most studies have been contradictory, due to several flaws, including small sample sizes, inaccurate phenotyping, and genotyping strategies (Gambardella et al., 2017). Recently, variants in the CYP2C9 and SCN1A (the latter encodes a protein expressed at high levels in the CNS) genes are found statistically more often in patients treated with the highest doses of both phenytoin and carbamazepine in cohorts of 425 and 281 patients, respectively. (Escayg & Goldin, 2010; Tate et al., 2005). Obsessive–compulsive disorder (OCD) is a chronic disorder occurring in approximately 2% of the population. Between 40 and 60% of patients are non-responders to serotonin reuptake inhibitor treatment. Potentially relevant polymorphisms in the serotonergic system (SLC6A4 and HTR2A), BDNF and SLC1A1 have been identified. Also, genes in the cytochrome system (e.g., CYP2D6) may be promising candidates for determining drug tolerability and response; however, further research is required (Brandl et al., 2012). Moreover, L-dopa-induced dyskinesias (LIDs) affect >50% of patients with Parkinson's disease (PD) after five years of L-dopa treatment. Some patients exhibit severe dyskinesias soon after starting low doses of l-dopa, whereas other patients remain free of this disabling complication despite treatment with l-dopa. This could be due to genetic polymorphisms among patients; therefore, pharmacogenetic studies may provide an explanation of neuronal plasticity among Parkinson patients (Linazasoro, 2005).

In addition, patients with dementia (PwD) may take >6-10 drugs/day with a consequent risk for adverse drug interactions (>80%), which accelerates cognitive decline. Geno-phenotypes CYP2C9, CYP2D6, CYP2C19, CYP3A4/5 are involved in the metabolism of over 90% of currently prescriptive drugs in patients with dementia (PwD), and only 20% of this population is an extensive metabolizer of this tetragenic cluster. The incorporation of pharmacogenomics strategies for a personalized treatment in dementia is an effective option to optimize limited therapeutic resources and to reduce unwanted side-effects (Cacabelos, 2020).

However, PGx-guidance application requires the physicians' comprehension and interpretation of the PGx-testing results. Physicians should be informed about the benefits of PGx-guided therapy, the sampling procedure and how to read a PGx-Panel Report. Continuing the education of established providers as well as clinical trainees is an important step in this process, which will continuously evolve as technology and clinical evidence informing testing and application are advanced. According to a questionnaire about the evaluation of iDNA Genomics PGx-testing in Greece answered by 67 clinical doctors (54 psychiatrists and 13 neurologists), 81% reported that the results of PGx testing are completely comprehensible and compose a useful tool to their clinical practice. Moreover, 52% of doctors recommend iDNA PGx-CNS to every patient, whereas 81% recommend it in patients without response following their first medication (communication with IDNA Genomics).

Polymorphisms and Pharmacogenetics

Patients drug response may differ when administrated with the same drug in a standard dose. Both genetic and non-genetic factors (gender, lifestyle, age, comorbidities, polypharmacy) can modulate the medication's efficacy. However, another factor responsible for the

individual variability in drug response is the presence of single nucleotide polymorphisms (SNPs) in the sequence of the genes encoding proteins that are involved in the absorption, distribution, metabolism and excretion of many therapeutic agents. Based on this level of enzyme activity, patients can be divided into four phenotypes: (i) Poor metabolizer (PM) - no activity; (ii) Intermediate metabolizer (IM) - reduced activity; (iii) Extensive metabolizer (EM) - normal activity; and (iv) Ultra-extensive or Ultrarapid metabolizer (UM) – increased activity (Umamaheswaran et al., 2014). The prevalence of SNPs may vary among different ethnic populations but remains in high frequency in global level. For example, the CYP3A4*1B allele (drug-metabolizing enzyme) occurs in more than 54% of Africans but only in 5% of Caucasians (Chowbay et al., 2005). Therefore, the knowledge of genetic variations is essential to estimate prognosis, therapeutic response and toxicity in patients.

iDNA Genomics private company (Greece, 2020) analyzes 24 SNPs on 13 genes (**Table 1**) that influence antidepressant, antipsychotic, antiepileptic and some other drug metabolism, mechanism of action or response (**Table 2**). These include (i) the cytochrome P450 2D6 gene (*CYP2D6*); (ii) the cytochrome P450 2C19 gene (*CYP2C19*); (iii) the cytochrome P450 2C9 gene (*CYP2C9*); (iv) the dopamine receptor genes (*DRD2, DRD3*); (v) TaqIA (SNP, rs1800497) located in *ANKK1* gene, is associated with reduced striatal D2/3 receptor binding in healthy individuals (ANKK1/DRD2); (vi) the microsomal epoxide hydrolase 1 (EPHX1); (vii) the FK506-binding protein 51 gene (FKBP5); (viii) the Melanocortical 4 receptor gene (MC4R); (ix) the Glutamate Ionotropic Receptor Kainate Type Subunit 1 (GRIK1); (x) the Sodium Voltage-Gated Channel Alpha Subunit 1 gene (*SCN1A*); (xi) the 5-Hydroxytryptamine Receptor 2C gene (HTR2C); (xii) The UDP Glucuronosyltransferase Family 2 Member B7 gene (UGT2B7).

CYP enzymes are responsible for phase I metabolism (involves chemical reactions such as oxidation, reduction and hydrolysis) over 90% of drugs and naturally occurring xenobiotics and endogenous substrates. Polymorphisms or genetic variations account for up to 30% of inter-individual differences seen in a variety of drug responses. Firstly, CYP2C19 is responsible for the metabolism of more than 25 drug groups including a lot of psychotropics, proton pump inhibitors and anticonvulsants. Also, it contributes to the clearance of S-mephenytoin, diazepam, omeprazole, proguanil and R-warfarin. The most common allelic variants are CYP2C19*2 and CYP2C19*3, which reduce enzyme function. Another variant, CYP2C19*17, is associated with increased enzyme function (Alessandrini et al., 2013; Scordo et al., 2004). The iDNA Genomics private company PGx-CNS panel includes the allelic variants CYP2C19*2, *3, *4, *17. Secondly, CYP2C9, which is greatly polymorphic and the most abundant isoform of *CYP2C*, metabolizes a variety of drug groups including anticoagulants, anticonvulsants, and non-steroidal anti-inflammatory agents. More than thirty *CYP2C9* variants and sub-variants have been identified. *CYP2C9**2 and *CYP2C9**3, the most common allelic variants, induce a decreased enzyme activity, both of them being included in the iDNA Genomics Panel Report (Alessandrini et al., 2013; Bothos et al., 2021). Thirdly, *CYP2D6* is responsible for hydroxylation or demethylation of approximately 25% of clinically important drugs such as antiarrhythmic, psychiatric, antihistaminic and antidepressant. Over one hundred variant alleles of

CYP2D6 have been documented. While some alleles cause normal or increased activity in enzyme function (*1, *2 and *35), some other lead to a decreased activity (*9, *10, *17, *29, and *41) or to a loss of enzyme function (*3, *4, *5, and *6) (Arici & Özhan, 2017). In iDNA Genomics Panel Report, the *CYP2D6* (*3, *4, *6, *9, *10, *41) variants are included.

FK506 binding protein 51 (FKBP51, FKBP5) belongs to immunophilins and functions as a co-chaperone for androgen, glucocorticoid, mineralocorticoid and progesterone receptors. The FKBP51 can act as an important determinant of the responses to steroids, especially to glucocorticoids in stress and mood disorders and androgens in prostate cancer, raising medical and pharmacological interests in the protein and its gene (Jääskeläinen et al., 2011). The Melanocortical 4 receptor gene (*MC4R*) influence fat mass, weight and obesity risk, according to a meta-analysis of SNPs location in *MC4R* and patterns of phenotypic associations (Loos et al., 2009). HTR2C denotes the human gene encoding the 5-HT2C receptor. Some variants of this gene, like the rs1414334 C allele, have been associated with an increased risk of metabolic syndrome. This risk is particularly strong in carriers of the C allele using risperidone or clozapine (Mulder et al., 2009). Another meta-analysis for the T allele of *HTR2C* gene (rs3813929) showed that carriers of T allele are less likely to have antipsychotic-induced weight gain (Chen et al., 2020). Another example of a common polymorphism that influences drug response is one in *SCN1A*, the gene encoding the target of certain antiepileptic drugs. The SCN1A IVS5N+5 G→A polymorphism (rs3812718, formerly *SCN1A* IVS4-91G→A) was shown to be significantly associated with maximum dose of both phenytoin and carbamazepine in a cohort of patients with various forms of epilepsy (Heinzen et al., 2007). In addition, the polymorphism (rs2832407, C-allele) in *GRIK1*, the gene encoding the GluK1 kainate subunit, has been associated with higher levels of self-efficacy in treatment with topiramate and lower levels of nighttime drinking (Kranzler et al., 2016). Moreover, the human mEH, encoded by the *EPHX1* gene, is expressed polymorphically. Many studies have proven that variants in *EPHX1* affect carbamazepine metabolism, either resulting in no effect on Concentration/dose ratio (CDR) or reduced concentrations of CBZ and its related metabolites on plasma (Daci et al., 2015; Nakajima et al., 2005). Finally, there have been many studies for SNPs in *ANKK1/DRD2*. The TaqIA polymorphism, located in the ankyrin repeat and protein kinase domain-containing protein (*ANKK1*) gene is closely linked to the dopamine D2 receptor (*DRD2*) gene affecting its availability. Experimental studies support that TaqIA polymorphism is associated with food preferences, plasma triglyceride concentrations in diabetic patients and the related metabolic phenotype (Ramos-lopez et al., 2019). Also, another functional polymorphism (rs2734849) in the *ANKK1* gene is associated with antipsychotic-induced hyperprolactinemia in patients with schizophrenia (Fedorenko et al., 2020).

Table 1

GENE	POLYMORPHISM	ALLELIC
ANKK1/DRD2	rs1800497	GG
CYP2C19	rs12248560	TT
	rs28399504	AA
	rs4244285	GG
	rs4986893	GG
CYP2C9	rs1057910	AA
	rs1799853	CC
CYP2D6	rs1065852	AG
	rs28371725	CC
	rs35742686	TT
	rs3892097	CT
	rs5030655	AA
	rs5030656	TCTTCT
DRD2	rs1799978	TT
DRD3	rs963468	GG
EPHX1	rs1051740	TT
	rs2234922	AA
FKBP5	rs4713916	GG
GRIK1	rs2832407	CC
HTR2C	rs1414334	GG
MC4R	rs17782313	TT
	rs489693	CC
SCN1A	rs3812718	CT
UGT2B7	rs7668258	CC
iDNA Genomics I.K.E		

Table 2

Antidepressants	Antipsychotics	Antiepileptics	Other drugs acting in CNS
Amitriptyline	Amisulpride	Phenytoin	Acetylsalicylic acid
Escitalopram	Aripiprazole	Topiramate	Clobazam
Citalopram	Clozapine	Valproic acid	Diazepam
Fluoxetine	Haloperidol	Carbamazepine	Donepezil
Sertraline	Olanzapine	Lamotrigine	Galantamine
Duloxetine	Paliperidone		
Fluvoxamine	Quetiapine		
Mirtazapine	Risperidone		
Clomipramine	Ziprasidone		
paroxetine			
Venlafaxine			
vortioxetine			
iDNA Genomics I.K.E			

Methodology

In Greek Association of Alzheimer's Disease and Related Disorders (Alzheimer Hellas), five patients with diagnosed neuropsychiatric diseases used the PGx-CNS testing (iDNA Genomics private company, Athens, Greece) in order to improve their medication's outcome. In all these cases the previous therapeutic choice was unsatisfying or was accompanied by mild or severe adverse drug effects. It is important to mention that apart from patients with memory impairment, Alzheimer Hellas addresses to PwD relatives with mental health disorders, as well.

The sampling of genetic material was performed by a non-invasive procedure as it was collected from the patient's saliva (using a bucchal swab). After sample's collection, the genomic DNA was extracted and analyzed by phasmatophotometry measuring the concentration and purity of the acquired genomic DNA sample. Subsequently, each sample was used for genotyping analysis using the SNP TaqMan assay and the QuantStudio 12K flex qPCR instrument, according to the manufacturer's instructions. Bioinformatic analysis of the genotyping results was performed by the iDNA Genomics platform, developed by HybridSTAT private company, producing an interpretative classification report, based on the level of molecular, biochemical, pharmaceutical, and clinical evidence, in line with the PharmGKB PGx information (Whirl-Carrillo et al., 2012).

Results

Case A

A female, 66-year-old patient with a diagnosis of early onset Alzheimer Disease and Normal Pressure Hydrocephalous. The patient has ten-year memory impairment, gait imbalance and falls. She also suffered from epileptic seizures, whose frequency has increased dramatically in the last 3 years. In 2018 patient started levetiracetam (2000mg, 1*2); in 2019 the neurologist added also lacosamide (50 mg, 1*2) because patient's response to levetiracetam was inefficient. On November, 2020 the prescription was changed from lacosamide to valproic acid (200mg, 1*3), due to no good response to lacosamide. After two months, patient's situation was stable. Epileptic seizures were not reduced leading her to disappointment. So, after doctor's suggestion, patient used PCx-testing aiming to guide a proper medical treatment for her genetic profile. The results of PGx-CNS report of antiepileptic drugs are presented in **Table 3**. There is a moderate gene-drug interaction for all the antiepileptic drugs. In some cases, the interaction refers to the drug's metabolism, so we have to consider starting with a reducing or increasing dose, whereas in some other cases the interaction refers to an increased risk of specific side effects. Doctor suggested a drug combination of topiramate (25mg, 1*2) and levetiracetam (10ml/6h). After two weeks with the new treatment, epileptic seizures were reduced but not stopped. This situation remained stable for the next two months. So, topiramate was substituted by lamotrigine, as a safe option

according to PGx testing. Patient's situation after the medication change couldn't be evaluated because he was admitted at the local Hospital for a check-tup and there the neurologist reduced the doses of antiepileptic drugs.

Case B

A 19-year-old male patient with secondary generalized seizures after recovering from meningitis (ICD-10-CM Code F84.9) 3 years ago was prescribed with levetiracetam (1000mg 2/day) and oxcarbazepine (600mg +900mg/day) without adequate response. Patient's situation was unstable, and the epileptic seizures were periodic on a weekly basis which was confirmed by his mother. In addition, the patient suffered from panic attacks, aggression and suicidal ideation. Followed the doctor's advice, patient used PGx testing. The results are presented in **Table 4**. All antiepileptic drugs seem to be safe for patient's genetic profile, as they show minimal or moderate interaction with his genes. Neurologist added lamotrigine (25mg 2/day) to his previous medication which belongs to the category of Moderate Gene-Drug Interaction. According to PGx results there is not an increased risk for side effects using Lamotrigine, but the neurologist has to consider the drug's dose. After one month, panic attacks, aggression and suicidal ideation are absent, but epileptic seizures, even reduced, are still unstable. Neurologist thought that maybe levetiracetam or oxcarbazepine should be replaced by an alternative antiepileptic.
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Table 3

Case 1 Antiepileptic drugs- PGx Panel Report		
Minimal Gene-Drug Interaction	Moderate Gene-Drug Interaction	Strong Gene-Drug Interaction
	Lamotrigine 2 Topiramate 1,2 Valproic acid 1,2 Carbamazepine 5 Phenytoin 1,3,5	
Clinical advices		
1. Start treatment with the initial dose recommended in the Package Leaflet and adjust. **2. Consider reducing the dose and cogitate the side effects.** **3. Consider reducing the maintenance dose by 25%.** 4. Consider reducing the dose by 50% or choose an alternative therapy. 5. **Consider increasing the dose and cogitating the side effects or choose an alternative treatment.** 6. Increased risk of adverse drug effects, or decreased drug efficacy. 7. Increased risk of weight gain. 8. Consult interpretive analysis and adjust the dose. 9. Avoid using this category of drugs. Consider an alternative medication.		
iDNA Genomics I.K.E, PGx-CNS Panel Report		

Table 4

Case 2	Antiepileptic drugs- PGx Panel Report	
Minimal Gene-Drug Interaction	Moderate Gene-Drug Interaction	Strong Gene-Drug Interaction
Topiramate Valproic acid phenytoin	Lamotrigine 1, 5, 8 Carbamazepine 5	
Clinical advices		
1. Start treatment with the initial dose recommended in the Package Leaflet and adjust. 2. Consider reducing the dose and cogitate the side effects. 3. Consider reducing the maintenance dose by 25%. 4. Consider reducing the dose by 50% or choose an alternative therapy. **5. Consider increasing the dose and cogitating the side effects or choose an alternative treatment.** 6. Increased risk of adverse drug effects, or decreased drug efficacy. 7. Increased risk of weight gain. **8. Consult interpretive analysis and adjust the dose.** 9. Avoid using this category of drugs. Consider an alternative medication.		
iDNA Genomics I.K.E, PGx-CNS Panel Report		

Case C

A male 46-year-old patient who suffered from Hashimoto's thyroiditis the last 15 years and from depression, anxiety disorder, accompanied by panic attacks the last 10 years. He visited the Greek Association of Alzheimer's Disease and Related Disorders (Alzheimer Hellas) in November of 2020. Until then, he had visited many doctors and hospitals being unsatisfied by his medication. His neuropsychological assessment included Mini Mental State Examination=28, Short Anxiety Screening Test=35 and Hamilton Depression Rating Scale=25. His previous antidepressant medication was escitalopram 10mg/day. He reported insomnia, depressive mood, severe sweating. The psychiatric neurologist changed escitalopram to citalopram (40mg/day). Apart from antidepressant treatment, patient takes bromazepam, hydroxyzine and L-thyroxine. Two weeks after medication's change, patient's situation was stable, without adequate response. So, after doctor's suggestion, patient chose to use PCx-testing in order to find the proper medical treatment for his genetic profile. The results of PGx-Panel report of antidepressant drugs are presented in **Table 5**. With PGx guidance, doctor decided to change citalopram to mirtazapine (15mg/day).

Mirtazapine showed minimal interaction with CYP2D6 gene, which means normal drug clearance and moderate interaction with FKBP5 gene, which refers to a possibility of low response. One month after starting the new treatment, patient reported he had no more sweating, no depressive mood and he could finally sleep well.

Table 5

Case 3	Antidepressant drugs- PGx Panel Report	
Minimal Gene-Drug Interaction	Moderate Gene-Drug Interaction	Strong Gene-Drug Interaction
Clomipramine Duloxetine Fluvoxamine Mirtazapine Paroxetine Sertraline Venlafaxine vortioxetine	Citalopram 1, 5 Escitalopram 1, 5 Fluoxetine 1, 2	Amitriptyline 5, 9
Clinical advices		
1. **Start treatment with the initial dose recommended in the Package Leaflet and adjust.** 2. **Consider reducing the dose and cogitate the side effects.** 3. Consider reducing the maintenance dose by 25%. 4. Consider reducing the dose by 50% or choose an alternative therapy. 5. **Consider increasing the dose and cogitating the side effects or choose an alternative treatment.** 6. Increased risk of adverse drug effects, or decreased drug efficacy. 7. Increased risk of weight gain. 8. Consult interpretive analysis and adjust the dose. 9. **Avoid using this category of drugs. Consider an alternative medication.**		
iDNA Genomics I.K.E, PGx-CNS Panel Report		

Case D

A 72-year-old male patient suffers from Parkinson Disease, dementia, depression, coronary heart disease and benign prostatic hyperplasia. The last two months, his caregiver mentioned that he presented auditory and visual hallucinations. His medication included rivastigmine (9,5mg/day), memantine (10mg 2/day), low doses of L-Dopa, hydroxyzine (25mg 6/day) and escitalopram (20mg 2/day). Antidepressant treatment considered insufficient as he had depressive mood, sadness and sleep disorder. His neuropsychological assessment included Mini Mental State Examination=22, Neuropsychiatric Inventory-Diary Rating Scale (NPI)=48 and Hamilton Depression Rating Scale (HAM)=28. Patient's comorbidities and polypharmacy consisted an additional factor to use PGx-testing in order to find the suitable medication for his genetic profile. Results of pharmacogenomics analysis are presented in **Table 6**. Apart from amitriptyline and clomipramine which showed significant interaction with patient's gene CYP2C19, the other drugs seem safe to use. Psychiatric neurologist decided to reduce escitalopram in half dose and add vortioxetine (10mg/day) aiming at escitalopram's discontinuation. According to PGx panel, vortioxetine seems to have normal clearance and there is no evidence supporting possibility of adverse side effects. With the new medication, patient's neuropsychological assessment was impressively improved. After 2 weeks NPI was reduced in 34 and HAM in

20, whereas after 6 weeks NPI was 12 and HAM was 13! The patient mentioned being satisfied and grateful for the new treatment.

Table 6

Case 4 Antidepressant drugs- PGx Panel Report

Minimal Gene-Drug Interaction	Moderate Gene-Drug Interaction	Strong Gene-Drug Interaction
Clomipramine	Citalopram 1, 5	Amitriptyline 5, 9
Fluvoxamine	Duloxetine 6	
Mirtazapine	Escitalopram 1, 5	
Paroxetine	Fluoxetine 1, 2	
Sertraline		
Venlafaxine		
Vortioxetine		

Clinical advices

1. **Start treatment with the initial dose recommended in the Package Leaflet and adjust.**
2. **Consider reducing the dose and cogitate the side effects.**
3. Consider reducing the maintenance dose by 25%.
4. Consider reducing the dose by 50% or choose an alternative therapy.
5. **Consider increasing the dose and cogitating the side effects or choose an alternative treatment.**
6. **Increased risk of adverse drug effects, or decreased drug efficacy.**
7. Increased risk of weight gain.
8. Consult interpretive analysis and adjust the dose.
9. **Avoid using this category of drugs. Consider an alternative medication.**

iDNA Genomics I.K.E, PGx-CNS Panel Report

Case E

A 65-year-old female with diagnosed bipolar disorder the last months developed epileptic seizures. Her medication consisted of valproic acid (500mg/day), lamotrigine (200mg/day), venlafaxine (75mg/day) and hydroxyzine (25mg/day). Antiepileptics were considered responsible for liver aminotransferases' elevation in blood. Also, venlafaxine caused sodium level disturbance (hyponatremia). Doctor suggested a brain imaging examination (Magnetic Resonance Imaging, MRI) and PGx testing for choosing the best medication according to her genetic profile. MRI revealed a brain tumor which considered culpable for her epileptic seizures. The patient underwent surgical tumor excision and stopped her medication. PGx-CNS Panel Report for antipsychotics and antidepressants are presented in **Table 7** and **Table 8**, respectively. From antipsychotics, risperidone was chosen as a safe option, as there was minimal interaction with DRD2, CYP2D6, HTR2C genes (which means normal clearance, good drug response, increased possibility of clinical improvement, reduced possibility of metabolic syndrome) and moderate interaction with ANKK1/DRD2 and MC4R genes (which refers to a possibility of tardive dyskinesia). From antidepressants, citalopram was chosen as a safe option as well, which presented moderate interaction with CYP2C19 and FKBP5 genes. This interaction refers to an

increased drug metabolism and clearance, so the doctor has to consider starting with an increased dose. As directed, venlafaxine seems to be safe according to patient's genetic profile. Perhaps hyponatremia was not a venlafaxine's side effect but was caused by the brain tumor. However, psychiatric neurologist decided to give another drug for safety. Patient was given the new medication of risperidone 1mg and citalopram 30mg/day 14 days before hospitalized for the surgical removal. Hospital doctors reported that she continued taking the same medication for the entire month being hospitalized as it was sufficient, without causing any adverse effects.

Table 7

Case 5 Antipsychotics drugs- PGx Panel Report

Minimal Gene-Drug Interaction	Moderate Gene-Drug Interaction	Strong Gene-Drug Interaction
Amisupride Aripiprazole Haloperidol Paliperidone Quetiapine Risperidone Ziprasidone		Clozapine 6,9 Olanzapine 9

Clinical advice

1. Start treatment with the initial dose recommended in the Package Leaflet and adjust.
2. Consider reducing the dose and cogitate the side effects.
3. Consider reducing the maintenance dose by 25%.
4. Consider reducing the dose by 50% or choose an alternative therapy.
5. Consider increasing the dose and cogitating the side effects or choose an alternative treatment.
6. **Increased risk of adverse drug effects, or decreased drug efficacy.**
7. Increased risk of weight gain.
8. Consult interpretive analysis and adjust the dose.
9. **Avoid using this category of drugs. Consider an alternative medication.**

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Table 8

Case 5 Antidepressant drugs- PGx Panel Report

Minimal Gene-Drug Interaction	Moderate Gene-Drug Interaction	Strong Gene-Drug Interaction
Clomipramine Duloxetine Fluvoxamine Mirtazapine Paroxetine Venlafaxine Vortioxetine	Citalopram 1,5 Escitalopram 1,2,5 Fluoxetine 1 Sertraline 1	Amitriptyline 5, 9

Clinical advice
1. Start treatment with the initial dose recommended in the Package Leaflet and adjust. **2. Consider reducing the dose and cogitate the side effects.** 3. Consider reducing the maintenance dose by 25%. 4. Consider reducing the dose by 50% or choose an alternative therapy. 5. **Consider increasing the dose and cogitating the side effects or choose an alternative treatment.** 6. Increased risk of adverse drug effects, or decreased drug efficacy. 7. Increased risk of weight gain. 8. Consult interpretive analysis and adjust the dose. 9. **Avoid using this category of drugs. Consider an alternative medication.**
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Conclusions

From our experience PGx-guided therapy improved patients' symptoms and limited the side-effects compared with their previous medication. Although further investigation remains necessary to assess the genetic influence on treatment response in other disorders as well.

The adoption of PGx-guided therapy faces commercial, economical, educational and ethical barriers to integration into clinical practice and acceptance by practitioners, patients and payers. Despite the controversies regarding when pharmacogenomic testing should be used, either before starting any medication or after an insufficient drug response, the improvements in technology supporting these tests, improved accessibility of testing options, and the growing number of resources that help clinicians understand how to use this information when it is available are making this aspect of personalized or precision medicine a reality. Thus, it is important for physicians to become more aware of the scientific and clinical relevance of pharmacogenomic tests.

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Notes

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