REemptive Pharmacogenomic testing for Preventing Adverse drug REactions (PREPARE) is the first prospective, pre-emptive pharmacogenomic study conducted in Europe, within the frame of the Horizon 2020 program. It aims to determine whether implementing pre-emptive pharmacogenomics (PGx) testing of clinically relevant biomarkers, so as the dose and drug selection to be guided, will result in an overall reduction of both the occurrence and the severity of drug-genotype-associated adverse drug reactions (ADRs). To achieve that, two groups of patients will be recruited; one that will receive treatment according to standard clinical practice and one other that will receive pharmacogenomic-guided treatment. The Laboratory of Pharmacogenomics and Individualized Treatment of the University of Patras, which coordinates and represents Greece in this study, in collaboration with the Department of Psychiatry of the General University Hospital of Patras, the Department of Psychiatry of the Hospital “Attikon”, and the Department of Psychiatry of the Psychiatric Hospital of Athens “Dafni” is going to recruit 1500 psychiatric patients that are going to receive antidepressant or antipsychotic treatment. Our scientific hypothesis is that patients who receive pharmacogenomic guided drug and dose selection will experience 30% less ADRs than patients following standard care. Eligible drugs for inclusion in the PREPARE study, are those for which the clinical decision regarding drug and dose choice can be guided according to the Dutch Pharmacogenomics Working Group Guidelines (DPWG). Overall, 7 antidepressants (citalopram, escitalopram, sertraline, paroxetine, venlafaxine, clomipramine, amitriptyline) and 3 antipsychotics (haloperidol, zuclopenthixol, aripiprazole) related to 17 genetic variations in 2 genes (CYP2D6, CYP2C19) will be examined. Occurrence, severity and causality of adverse drug events (ADEs) will be assessed during monitoring, at month 1 and 3 after starting the index-drug,
Introduction

“Pharmacogenomics” (PGx) is the science studying the relationship between genetic polymorphisms and drugs; specifically, the response of patients to a given drug and the emergence of adverse effects which may occur after the use of certain medications, depending on the genetic background of a patient. This approach, whereas the choice of a pharmaceutical treatment is guided by the patients’ genome/genotype, is a form of personalized medicine.1–3

In recent years, pharmacogenomics has contributed to the personalization of treatment, increasing efficacy and reducing the expected rate of adverse drug events (ADEs). The challenging promise of implementing pre-emptive PGx testing in clinical practice—before treatment— in contrast to reactive PGx testing—after treatment failures— is the reduction of disease burden, in terms of increased efficacy and tolerance, in a cost-effective manner.4 This would be particularly relevant for psychiatry, in the context of the rising and probably underestimated global burden of mental illness.5

Since 2011, studies of implementing pharmacogenomics into clinical care are conducted in the USA. Studies such as the “Cleveland Clinic’s Personalized Medicine Program” in Ohio,6 the pharmacogenomics study “CLIPMERGE,”7 the “Electronic Medical Records and Genomics Network-Pharmacogenomics-eMERGE-PGx),8 the “Implementing Genomics in Practice-IGNITE”,9 the INdiana GENomics Implementation: an opportunity for the Under Served- INGENIOUS), 10 the “Pharmacogenomics Research Network Translational Pharmacogenetics Program” (PGRN),11 the “Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment Project-PREDICT”,12 the “Right drug, right dose, right time- RIGHT),13 the “1200 Patients Project”,14 and others, aim at demonstrating the usefulness and importance of implementation of PGx into clinical care, as well as overcoming the obstacles in the way.

The U-PGx study

The first European study of PGx implementation into clinical care is being conducted since 2016, with patients’ enrollment taking place since January 2017. The study is funded by the Horizon 2020 programme, which is to last until the end of 2020, and participating countries are Holland, the UK, Austria, Italy, Spain, Slovenia and Greece. The program “Ubiquitous Pharmacogenomics” (U-PGx) is firstly designed to overcome the obstacles that render application of pharmacogenomics difficult in clinical routine. Such obstacles include, among others, lack of clinicians’ confidence and familiarity with genetics and genomics, logistics and infrastructure of incorporating PGx testing into the clinical routine, public attitudes, cost and ethical issues.15 Secondly, it aims to provide evidence that PGx testing can aid the choice of the right drug at the right dose based on the patients genetic background.16,17

For this reason, training of the physicians and the health professionals participating in the program has been undertaken, as well as the registering of the pharmacogenes and the guidelines per drug, according to the Dutch Pharmacogenomics Working Group Guidelines- DPWG, www.dpwg.org, the installation of the equipment required for the analyses and the development of the appropriate bioinformatic tools for the translation of the genotype results into actionable and usable information for the clinician. The next step is the patients’ recruitment.

In a pilot study comprising 200 patients, it has been demonstrated that in about 30% of incident prescriptions there had been at least one combination of an actionable genotype, a drug and a gene
Therefore it is expected that the integration of PGx into clinical routine in the present study will result in a detectable, significant reduction of drug adverse events.

The PREPARE study

The most important part of the U-PGx project is the PREPARE (PREemptive Pharmacogenomics for Preventing Adverse Drug Reactions) study. This study aims at the recruitment of 8100 patients who will be administered antidepressant, antipsychotic, stimulant, antiarrhythmic, analgesic, anticancer, anticoagulant, antiepileptic antihypertensive, antibiotic, immunosuppressant or cholesterol lowering drugs, according to clinical recommendation, for drugs that there already exist DPWG guidelines.

More specifically, preemptive PGx analyses of a number of clinically important pharmacogenomic biomarkers will be applied, with the purpose of guiding drug and dose choice for 10 commonly prescribed antidepressant and antipsychotic drugs, and the overall reduction of adverse events rate and severity will be examined, for those which are related with the drug-gene interaction. We hypothesize that applying pharmacogenomic guided treatment, regarding drug and dose choice, will result in the reduction of emergence and/or severity of adverse events related to drug-gene interaction compared to patients who will receive treatment as usual. Also, we hypothesize that with this approach, there will be reduction to the number of dose changes, and the number of discontinuations for the index drug.

For the Greek patients who will be recruited, apart from the Pharmacogenomics and Personalized Treatment Laboratory of the University of Patras, which coordinates the study in Greece, participating departments are the Department of Psychiatry of the University Hospital of Patras, the 2nd Department of Psychiatry of the University Hospital “ATTIKON” and the Departments of Psychiatry of the Psychiatric Hospital of Athens “Dafni”.

Index Drugs

Our group will focus on patients with psychiatric disorders who are prescribed antipsychotic or antidepressant treatment. The drugs that are eligible for recruitment, in the context of the PREPARE study, are those for which the clinical decision regarding drug and dose choice can be guided according to the DPWG guidelines. The genes and the genetic variants that have been found to be relevant to the above drugs have been registered (table 1).

These drugs are commonly prescribed in Greece for the treatment of various psychiatric disorders, and are also selected according to everyday clinical practice in Greece. The drugs imipramine, nortriptyline and doxepine are not currently available in Greece and therefore, although included in the PREPARE study, are not listed in table 1. Overall, 7 antidepressants and 3 antipsychotics related to 2 genes and 17 genetic variations will be examined.

Patients’ recruitment

Patients’ recruitment will be conducted in two arms, the arm with PGx intervention and the arm without (figure 1). For the patients recruited to the intervention arm, the PGx analysis will be performed and the result will be provided to the clinician, so that the treating doctor will be able to modify the dose or the drug choice accordingly. For the patients without PGx intervention, clinical routine will be followed as usual. In the end of the study, PGx analysis will be performed to the patients of the arm with clinical routine as usual, so as to examine whether

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Number of SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>CYP2C19</td>
<td>4</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>CYP2C19</td>
<td>3</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>CYP2D6</td>
<td>4</td>
</tr>
<tr>
<td>Sertraline</td>
<td>CYP2D6</td>
<td>4</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>CYP2D6</td>
<td>6</td>
</tr>
<tr>
<td>Amitryptiline</td>
<td>CYP2D6</td>
<td>6</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>CYP2D6</td>
<td>13</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>CYP2D6</td>
<td>13</td>
</tr>
<tr>
<td>Haloperidole</td>
<td>CYP2D6</td>
<td>8</td>
</tr>
<tr>
<td>Zuclopenthixole</td>
<td>CYP2D6</td>
<td>3</td>
</tr>
</tbody>
</table>
the drug or dose modification could have reduced the adverse drug reactions. Each arm, extending to 18 months, will include 750 Greek patients, consecutively hospitalized or consecutively assessed at the outpatient clinic, suffering from any psychiatric disorder.

Any patient is eligible for the study, provided that the below selection criteria are met: (1) age ≥18, (2) no pregnancy, (3) the patient is willing to participate in the study and provide genetic material, (4) is willing and available to conduct the clinician at one month, three months from the beginning of treatment with the index drug and at the end of the study, (5) the patient provides written informed consent, (6) the patient is started on a medication from table 1, which he has not received for the past 12 months.

Figure 1. Recruiting and follow up procedure of patients in the two arms of the PREPARE study
The above information is provided during the interview with the treating clinician. Specifically, the patient is informed that it is a voluntary research study, which is approved by the local ethical and deontology committee of the hospital, that a written informed consent is needed, that a blood sample of 10 mL is required, as well as future conduct of the patient with the treating clinician for the recording of adverse events, clinical and demographic data, health behavior and quality of life. The patient is also informed that he/she is eligible for the study because he/she will receive one of the drugs of the study, which he/she is going to receive either participating or not, and for which there are documented scientific data that it can be given in a personalized mode. Before the patient decides to consent to participate to the study, more information is provided for the aims of the study, either orally or by reading the informed consent leaflet, and is encouraged to discuss any issues with the treating clinician, the family and others. The patient can retract his consent at any time, without any consequence.

**The “Safety Code” card**

In case of participating in the study, the patient is informed that a card (safety code card) will be provided, which will include information for other drugs as well, such as antiarrythmics, analgesics, anticancer, anticoagulants, antiepileptics, antihypertensives, antibiotics, immunosuppressants, psychostimulants and drugs lowering cholesterol, some of which the patient might need to receive in the future (figure 2). It is therefore important to explain to the patient that this information remains stable throughout the lifespan, and it can be used for the personalized tailoring of future treatments. The patient is encouraged to show the card to any physician that will be visited in the future for any disease.

After patients’ written consent, a 10 mL blood sampling takes place, in 4 test tubes containing EDTA anticoagulant. The samples are kept in 2–8 °C, until they

![The Safety Code Card](image-url)
are sent to the Laboratory of Pharmacogenomics and Individualized Therapy (LaPIT) of the Department of Pharmacy of the University of Patras (Head: Prof G. Patrinos), for the genetic analysis. For the analysis the SNPline platform of the LGC company is going to be used, for the fast and simultaneous analysis of many genetic variations.

**Patients' Data Recording**

The patient record file is compiled during the recruitment, containing demographic data, health behaviors, index drug, quality of life measures, knowledge and awareness of PGx, comorbidities and co-administered medications. At time intervals of one month and three months and at the end of each arm the clinician or the research nurse is conducting the patient and data regarding emerging side effects and relevant information is recorded, for example duration of adverse events and costs, as well as the patients’ quality of life. All the above information is registered on line in the Electronic Case Report Form -e CRF of the study.

**Results of Pharmacogenomics Testing**

The patients of the arm without pharmacogenomic intervention, will receive the indicated drug chosen by the treating clinician without pharmacogenomic guidance of drug and dose choice. The patients in the arm with PGx intervention can be started on medication during the waiting time for the results of the testing. The time lag between blood sampling and the receipt of the PGx results has been set at a maximum of 7 days. In time course, the clinician can adapt the dose regimen or choose an alternative medication, based on the results of the PGx testing if recommended by the CPIC guidelines and if the clinician agrees with this option.

The genes, drugs and rate of metabolism are presented in table 2. The pharmacogenetic testing can also operate preemptively, that is, can be used for treatment adaptations in the future, for any relevant drug that the patient would need.

More specifically, poor metabolizers (PM) have two deficient alleles resulting in absence of metabolic activity. This would practically mean that lower dosage than usually recommended is needed, because, as the elimination rate of the drug is slower, higher levels are achieved and for longer time, resulting in increased rate and severity of dose-related side effects. Intermediate metabolizers (IM) have one deficient allele or two partially functional, resulting in intermediate enzymatic activity, whereas extensive metabolizers (EM) have two functional alleles and prompt enzymatic activity. Finally, ultra-rapid metabolizers (UM) exhibit increased enzymatic activity and elimination rates of the drug, and therefore higher doses would be needed for efficacy. In any of cases, the aim is to achieve the best combination of efficacy and safety with the most appropriate adaptation of drug and dose choices.

**Table 2. Metabolism profiles of index drugs.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>CYP2C19</td>
<td>PM, IM, EM</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>CYP2C19</td>
<td>PM, IM, EM</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>CYP2D6</td>
<td>PM, IM, EM, UM</td>
</tr>
<tr>
<td>Sertraline</td>
<td>CYP2C19</td>
<td>PM, IM, EM</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>CYP2D6</td>
<td>PM, IM, EM, UM</td>
</tr>
<tr>
<td>Amitriptiline</td>
<td>CYP2D6</td>
<td>PM, IM, EM, UM</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>CYP2D6</td>
<td>PM, IM, EM, UM</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>CYP2D6</td>
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<tr>
<td>Haloperidol</td>
<td>CYP2D6</td>
<td>PM, IM, EM, UM</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>CYP2D6</td>
<td>PM, IM, EM, UM</td>
</tr>
</tbody>
</table>


**Adverse drug events**

Data relevant to ADEs will be collected during monitoring, at month 1 and 3 after starting the index-drug, and at the end of each arm.

ADEs will be categorized according to severity, following the «Common Terminology Criteria for Adverse Events (CTCAE)»20 (table 3) and causality, by using the Liverpool Causality Assessment Tool (LCAT)21 algorithm (figure 3).

**Statistical analysis**

Following patients’ recruitment, there will be data analysis of those patients only who presented a clinically important relationship between genotype and
index drug. There will be two stages. At first stage, there will be a comparison between patients with and patients without pharmacogenomic intervention, who underwent at least one clinically relevant adverse event, within 3 months from the initiation of the index drug, causally related to the drug. In case there is a statistically significant result from this analysis, a second analysis will be conducted, the same as the first one, including all the patients of the study. The aim of the first analysis is to define the effect of

Table 3. Grades of severity of ADRs according to Common Terminology Criteria for Adverse Events (CTCAE) and DPWG guidelines.

<table>
<thead>
<tr>
<th>DPWG</th>
<th>CTCAE</th>
<th>CTCAE Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>C</td>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*</td>
</tr>
<tr>
<td>D</td>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**</td>
</tr>
<tr>
<td>E</td>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>F</td>
<td>Grade 5</td>
<td>Death related to ADR</td>
</tr>
</tbody>
</table>

*Instrumental Activities of Daily Living: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care Activities of Daily Living: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Figure 3. The Liverpool Adverse Drug Reaction Causality Assessment Tool (LCAT)²¹ for the determination of causal relationship between drug and adverse drug reaction.
PGx guided treatment on the rate of adverse events, and the aim of the second is to show the positive effect of the implementation of PGx guided treatment on a broad population.

Importantly, it should be stressed that the PREPARE study focuses on the reduction of ADEs, and it is not anticipated that the pharmacogenomic guidance of the treatment is going to significantly influence efficacy. However, as secondary results, certain variables relevant to efficacy will be collected, specifically the comparative rates of discontinuation of the index drug due to inefficacy between patients with and without PGx intervention. Moreover, the levels of the index drug in the plasma of patients where the dose was modified according to guidelines versus those who did not undergo modification will be compared. We suppose that the exposure of patients of both arms is similar, and therefore drug efficacy would be expected to be the same.

Furthermore, data regarding costs relating to ADEs will be recorded, and a cost-effectiveness analysis will be conducted in each one of the participating countries. The implementation of CPIC guidelines by the treating clinician, for the index drugs and any subsequent drug included in the guidelines, and the other clinicians involved in the PREPARE study, will also be evaluated. Lastly, data regarding attitudes and knowledge of PGs by the patients are going to be collected, in the beginning and in the end of the study.

Discussion

The global burden of mental illness is on the rise, and most probably underestimated. With at least 10% of the population affected by one of a wide range of mental disorders, the personal, societal and economic costs are enormous; cost estimates amount to an extraordinary US$6.0 trillion by 2030, representing treatment expenditures and loss of productivity. In 2015, 547 million prescriptions of antidepressant and antipsychotic drugs took place, costing 21.2 billion US dollars. Treatment of psychiatric disorders is harassed by suboptimal efficacy and adverse drug reactions, which increase morbidity and mortality and have detrimental effects on treatment adherence and patients' quality of life. Recommended dosages of medications have been determined by the doses administered to samples of the general population during clinical trials. However, these doses are not optimal for the whole population; PGx attempts to optimize efficacy and minimize adverse effects by utilizing genetic information relevant to drug pharmacokinetics and pharmacodynamics of the patient, in the sense of individualizing treatment. The delivering of more efficacious and better tolerated treatment is called for. For now, the implementation of PGx in everyday clinical routine faces various obstacles, such as awareness of the population and clinicians, bioinformatics issues, and very importantly, costs. On the other hand, PGx carries the promise of benefits for the patients, in terms of efficacy and safety, whereas cost-effectiveness remains to be demonstrated. The present study aims to better define these obstacles, to find ways of remediation, and determine cost parameters. It is expected that the implementation of PGx guided treatment, by helping to optimize clinical treatment decisions, will eventually result in reducing adverse events and improving patients’ adherence to treatment and quality of life, cost-effectively.

Turning to limitations of the study, it should be commented that the inclusion of only three antipsychotics, which represent only part of the routine prescribers’ practice, could interfere with the results. Since the study is based on existing DPWG guidelines, however, other frequently prescribed drugs, for example clozapine, olanzapine, risperidone, quetiapine and others, cannot currently be examined. Secondly, the choice of LCAT as an assessment tool for causality could raise some arguments, since it has been shown in one study, that the researchers could not achieve as high an interrater agreement as that reported by the developers of the LCAT tool. On the other hand, LCAT presents important strengths, such as simplicity and practicability, and therefore was decided to be suitable for a multicenter study with heterogeneous patient sample such as the one presented here.

Acknowledgements: Funding: European Commission, Horizon 2020 (H2020-668353; Ubiquitous Pharmacogenomics). The authors wish to cordially thank the patients for participating in this study. GPP is full member and national representative at the European Medicines Agency, CHMP-Pharmacogenomics Working Party, Amsterdam, the Netherlands.
Κλινική εφαρμογή της προληπτικής φαρμακογονιδιωματικής στην ψυχιατρική: Η μελέτη “PREPARE”

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για την ομάδα U-PGx στην Ελλάδα

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Η μελέτη «Προληπτική φαρμακογονιδιωματική ανάλυση για την πρόληψη ανεπιθύμητων ενεργειών φαρμάκων» (PREemptive Pharmacogenomic testing for Preventing Adverse drug REACTIONS - PREPARE) είναι η πρώτη προοπτική μελέτη προληπτικής εφαρμογής της φαρμακογονιδιωματικής στην κλινική πράξη στην Ευρώπη και πραγματοποιείται στα πλαίσια του προγράμματος Horizon 2020. Σκοπός της μελέτης είναι να προσδιορισθεί το κατά πόσο η προληπτική εφαρμογή της φαρμακογονιδιωματικής (PGx) εξέτασης κλινικά κατάλληλων βιοδεικτών, με σκοπό την καθοδήγηση της επιλογής της δόσης και του φαρμάκου, θα οδηγήσει στη μείωση της εμφάνισης και της σοβαρότητας ανεπιθύμητων ενεργειών που σχετίζονται με τον γονότυπο. Για την επίτευξη του στόχου της μελέτης θα υπάρξουν δύο ομάδες ασθενών, μια ομάδα που θα λάβει θεραπεία κατά τη συνήθη κλινική πράξη και μια άλλη που θα ακολουθήσει φαρμακογονιδιωματικά καθοδηγούμενη επιλογή φαρμάκου και δόσης. Το Εργαστήριο Φαρμακογονιδιωματικής και Εξατομικευμένης Θεραπείας του Τμήματος Φαρμακευτικής του Πανεπιστημίου της Πάτρας, που συντονίζει τη μελέτη στην Ελλάδα, σε συνεργασία με την Ψυχιατρική κλινική του Γενικού Πανεπιστημιακού Νοσοκομείου της Πάτρας, την Ψυχιατρική Κλινική του Νοσοκομείου «Αττικόν» και τις Ψυχιατρικές Κλινικές του Ψυχιατρικού Νοσοκομείου Αττικής «Δαφνί», θα επικεντρωθεί στην ένταξη 1500 ασθενών με ψυχικά νόσημα οι οποίοι θα λάβουν αντικαταθλιπτική ή αντιψυχωτική θεραπεία. Η επιστημονική μας υπόθεση είναι ότι η εφαρμογή της PGx-καθοδηγούμενης επιλογής φαρμάκου και δόσης θα οδηγήσει σε 30% μείωση των κλινικά σημαντικών ADRs. Στη μελέτη θα συμπεριληφθούν φάρμακα για τα οποία υπάρχουν διαθέσιμες κατευθυντήριες γραμμές για την καθοδήγηση της κλινικής επιλογής φαρμάκου και δόσης από την Ολλανδική Ομάδα Εργασίας για τη Φαρμακογονιδιωματική (Dutch Pharmacogenomics Working Group Guidelines, DPWG). Θα εξετασθούν συνολικά 7 αντικαταθλιπτικά (σιταλοπράμη, εσιταλοπράμη, σερτραλίνη, παροξετίνη, βενλαφαξίνη, κλομιπραμίνη, αμιτριπτυλίνη) και 3 αντιψυχωτικά φάρμακα (αλοπεριδόλη, ζουκλοπενθιξόλη, αριπιπραζόλη), σχετιζόμενα με 17 πολυμορφισμούς 2 γονιδίων (CYP2D6, CYP2C19). Η εκτίμηση της εμφάνισης, της βαρύτητας των ανεπιθύμητων ενέργειων και του βαθμού αιτιότητας του φαρμάκου για τις ανεπιθύμητες ενέργειες (Adverse Drug Reactions, ADRs) θα γίνει κατά την παρακολούθηση στον 1 και στους 3 μήνες από την έναρξη του φαρμάκου, και στο τέλος του κάθε βραχίονα, και με τη χρήση της Κλίμακας των Κοινών Κριτηρίων Τοξικότητας για τις Ανεπιθύμητες Ενέργειες (Common Toxicity Criteria for Adverse Events Scale, CTCAE) και του αλγορίθμου του Εργαλείου Εκτίμησης Αιτιότητας του Λίβερπουλ (Liverpool Causality Assessment Tool, LCAT). Τα αποτελέσματα της μελέτης μας αναμένεται να συμβάλλουν σημαντικά στη βελτίωση της ποιότητας
ζωής των ασθενών με ψυχικά νοσήματα, παρέχοντας το κατάλληλο φάρμακο, στην κατάλληλη δόση, με γνώμονα την αποτελεσματικότητα, την ασφάλεια και το κόστος.

Λέξεις ευρετηρίου: Προληπτική φαρμακογονιδιωματική, εξατομικευμένη ιατρική, αντιψυχωτικά φάρμακα, αντικαθαθλιπτικά φάρμακα, CYP2D6, CYP2C19.

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