DOMETI FARMAKOGENOMIKE U PRECIZNOJ MEDICINI

Nada Božina

Odjel za farmakogenomiku i individualizaciju terapije,

KZLD, Klinički bolnički centar Zagreb

Zavod za farmakologiju, Medicinski fakultet Sveučilište u Zagrebu

PRIMIJENJENA GENOMIKA – PRECIZNA MEDICINA
23. listopada 2018. HAZU

Smjernice

PharmGKB
The Pharmacogenomics Knowledgebase

CPIC™
Clinical Pharmacogenetics Implementation Consortium

DPWG: Dutch Pharmacogenetics Working Group

KNMP

Pharmacogenetics: From Bench to Byte—An Update of Guidelines

JJ Swen[1], M Nijenhuis[2], A de Boer[3], L Grandia[2], AH Maitland-van der Zee[3], H Mulder[3,4], GAPJM Rongen[5,6,7], RHN van Schaik[8], T Schalekamp[3], DJ Touw[9], J van der Weide[10], B Wilffert[11], VHM Deneer[12] and H-J Guchelaar[1]

Farmakogenomske smjernice za doziranje lijekova (70 lijekova)

LIJEK	GEN	LIJEK	GEN
abakavir	*HLA-B*	klozapin	*CYP2D6*
acenokumarol	*CYP2C9, VKORC1*	kodein	*CYP2D6*
alopurinol	*HLA-B*	lansoprazol	*CYP2C19*
amitriptilin	*CYP2C19, CYP2D6*	merkaptopurin	*TPMT*
aripiprazol	*CYP2D6*	metoprolol	*CYP2D6*
atazanavir	*UGT1A1*	mirtazapin	*CYP2D6*
atomoksetin	*CYP2D6*	moklobemid	*CYP2C19*
azatioprin	*TPMT*	nortriptilin	*CYP2D6*
cisplatina	*TPMT*	oksikodon	*CYP2D6*
citalopram	*CYP2C19*	olanzapin	*CYP2D6*
daunorubicin	*RARG, SLC28A3, UGT1A6*	omeprazol	*CYP2C19*
dezipramin	*CYP2D6*	ondansetron	*CYP2D6*
doksepin	*CYP2C19, CYP2D6*	pantoprazol	*CYP2C19*
doksorubicin	*RARG, SLC28A3, UGT1A6*	paroksetin	*CYP2D6*
duloksetin	*CYP2D6*	peginterferon alfa-2a	*IFNL3 (IL28B)*
escitalopram	*CYP2C19*	peginterferon alfa-2b	

Farmakogenomske smjernice za doziranje lijekova...

LIJEK	GEN	LIJEK	GEN
esomeprazol	*CYP2C19*	propafenon	*CYP2D6*
faktor V, horm. pripravci	*Faktor V Leiden (FVL)*	rabeprazol	*CYP2C19*
fenitoin	*CYP2C9, HLA-B*	razburikaza	*G6PD*
fenprokumon	*CYP2C9 VKORC1*	ribavirin	*IFNL3*
flekainid	*CYP2D6*	risperidon	*CYP2D6*
fluorouracil	*DPYD*	sertralin	*CYP2C19*
fluvoksamin	*CYP2D6*	simvastatin	*SLCO1B1*
glibenklamid	*CYP2C9*	takrolimus	*CYP3A5*
gliklazid	*CYP2C9*	tamoksifen	*CYP2D6*
glimepirid	*CYP2C9*	tegafur	*DPYD*
haloperidol	*CYP2D6*	tiogvanin	*TPMT*
imipramin	*CYP2C19, CYP2D6*	tolbutamid	*CYP2C9*
irinotekan	*UGT1A1*	tramadol	*CYP2D6*
ivakaftor	*CFTR*	trimipramin	*CYP2C19, CYP2D6*
kapecitabin	*DPYD*	tropisetron	*CYP2D6*
karvedilol	*CYP2D6*	varfarin	*CYP2C9, VKORC1, CYP4F2*
karbamazepin	*HLA-A, HLA-B*	venlafaksin	*CYP2D6*
klomipramin	*CYP2C19, CYP2D6*	vorikonazol	*CYP2C19*
klopidogrel	*CYP2C19*	zuklopentiksol	*CYP2D6*

Farmakogenomska informacija u SmPC (cca 270 lijekova)

	Drug	FDA	EMA
1	abacavir	Testing required	Testing required
2	abemaciclib	Testing required	
3	abiraterone	Informative PGx	
4	afatinib	Testing required	Testing required
5	afutuzumab	Informative PGx	
6	alectinib	Testing required	
7	alirocumab	Informative PGx	
8	aliskiren		Informative PGx
9	amitriptyline	Actionable PGx	
10	anastrozole	Testing required	
11	arformoterol	Informative PGx	
12	aripiprazole	Actionable PGx (has dosing info)	Actionable PGx
13	aripiprazole lauroxil	Actionable PGx (has dosing info)	

	Drug	FDA	EMA
14	arsenic trioxide	Testing required	Testing required
15	atazanavir		Testing recommended
16	atezolizumab	Informative PGx	
17	atomoxetine	Actionable PGx (has dosing info)	
18	atorvastatin	Informative PGx	
19	avatrombopag	Actionable PGx	
20	avelumab	Informative PGx	
21	axitinib		Informative PGx
22	azathioprine	Testing recommended	
23	belimumab	Informative PGx	Informative PGx
24	belinostat	Actionable PGx (has dosing info)	
25	binimetinib	Testing required, Informative PGx	
26	blinatumomab	Testing required	
27	boceprevir	Informative PGx	Informative PGx
28	bosutinib	Testing required	Testing required
29	brentuximab vedotin	Informative PGx	Testing required

Za 67 lijekova - "Testing required" FDA
Za 34 lijeka - "Testing required" EMA

Za 107 lijekova - "Actionable PGx" FDA
Za 17 lijekova je - "Actionable PGx" EMA

Za 79 lijekova je "Informative PGx" FDA
Za 35 lijekova je "Informative PGx" EMA

PGx Level

Testing required The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients. PharmGKB considers labels that state the variant is an indication for the drug, as implying a test requirement. If the label states a test "should be" performed, this is also interpreted as a requirement.

Testing recommended The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended before using this drug. This recommendation may only be for a particular subset of patients. PharmGKB considers labels that say testing "should be considered" to be recommending testing.

Actionable PGx The label does not discuss genetic or other testing for gene/protein/chromosomal variants, but does contain information about changes in efficacy, dosage or toxicity due to such variants. The label may mention contraindication of the drug in a particular subset of patients but does not require or recommend gene, protein or chromosomal testing.

Informative PGx The label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response.

Istraživački projekti za implementaciju PGx

Table 1 An overview of current clinical implementation studies and programs across the United States and Europe

Implementation initiative	Objectives	Clinical sites (country)	Strategy	No. PGx genes tested	Platform	Drug-gene pairs implemented in clinical care (clinical guidelines)	Population, no.
Cleveland Clinic's Personalized Medication Program[30,47]	-Implementing a CDSS to guide pharmacogenetics test ordering and provide gene-based dosing recommendations at the point-of-care. In parallel, a PGx consultation service is available.	-Cleveland Clinic (USA)	-Implementing alerts that recommend ordering a PGx test at the point-of-care -Implementing drug-gene pairs one at a time	N/A	N/A	*HLA-B*57:01*/abacavir *TPMT*/thiopurines (as per the CPIC guidelines)	Patients treated in a tertiary care adult hospital, children's hospital, regional hospital, or ambulatory locations across Ohio
CLIPMERGE PGx[48,49]	-Provide insight into the mechanisms, tools, and processes that will best support the use of PGx in clinical care -Contribute to the emerging body of data needed for forthcoming larger studies that will assess the utility of PGx in medication safety and efficacy	-Icahn School of Medicine at Mount Sinai (USA)	Implementing preemptive genotyping and real-time CDSS deployed through the EHR into routine care using a bio-bank derived cohort	36[20]	Sequenom iPLEX ADME PGx[20]	*CYP2C19*/clopidogrel *CYP2C9*/warfarin *VKORC1*/warfarin *SLCO1B1*/simvastatin *CYP2D6*/TCAs *CYP2C19*/TCAs *CYP2D6*/SSRIs (as per CPIC guidelines)	Pilot study: primary care patients who consented to Bio*ME* biobank (N = 1,500). Eventual aim is to recruit all Bio*ME* participants
eMERGE-PGx[50–52]	-Install an NGS sequencing platform assessing sequence variation in patients likely to be prescribed a drug of interest in a 1–3-year timeframe -Integrate clinically validated genotypes into the EHR and CDSS and to assess the impact on clinical outcomes and process of implementation -Develop a repository of variants of unknown significance linked to clinical phenotype data to expand PGx understanding	-Boston Children's Hospital -Children's Hospital of Philadelphia -Cincinnati Children's Hospital -Geisinger Health System -Group Health/University of Washington -Marshfield Clinic -Mayo Clinic (RIGHT) -Icahn School of Medicine at Mount Sinai (CLIPMERGE) -Northwestern University -Vanderbilt University Medical Center (PREDICT) (all above in USA)	Multicenter project evaluating pre-emptive sequencing and pre-emptive genotyping	84	PGRNseq	Varies across clinical sites (as per CPIC guidelines)	Individuals likely to be prescribed drugs of interest within a 1–3-year timeframe, specific therapeutic focus among all sites (N = 9,000)
IGNITE (PGx initiatives)[53]	-To develop methods for, and evaluate the feasibility of, incorporating an individual patient's genomic information into their clinical care	-University of Florida (USA) -Vanderbilt University (USA) -Indiana University (USA)	A network of healthcare systems who each implement PGx in their site	N/A	N/A	N/A	N/A

Table 1 Continued on next page

Table 1 Continued

Implementation initiative	Objectives	Clinical sites (country)	Strategy	No. PGx genes tested	Platform	Drug-gene pairs implemented in clinical care (clinical guidelines)	Population, no.
RIGHT[61,62]	-Develop best practices for the implementation of genetic sequence data into clinical systems	Mayo Clinic (USA)	Implementing pre-emptive sequencing and genotyping in routine care	84	PGRNseq and Luminex CYP2D6 ASPE kit	*SLOCO1B1*/simvastatin *CYP2C19*/clopidogrel *IFNL2*/interferon *CYP2D6*/tramadol *CYP2D6*/tamoxifen *CYP2D6*/codeine *HLA-B*1502*/carbamazepine *HLA-B*1501*/abacavir *TPMT*/thiopurines (as per CPIC guidelines)	Patients likely to receive statin therapy within 3 years, recruited from the Mayo Clinic Biobank (N = 1,013)[20]
The 1,200 Patients Project[63–65]	-To determine the feasibility and utility of incorporating pre-emptive pharmacogenomics testing in clinical care. -Future aims include examining the impact of providing PGx results on prescribing decisions and patient outcomes.	University of Chicago (USA)	Observational study implementing pre-emptive genotyping	N/A	Sequenom ADME and Sequenom custom panel	N/A	Adults receiving outpatient medical care and using 1–6 prescription medications (N = 1,200)
U-PGx and the PREPARE Study	-Implementation of pre-emptive PGx testing, of a panel of clinically relevant markers -Assessing the impact on incidence of adverse event incidence and healthcare costs -Performing exploratory analyses to expand understanding of PGx	-Leiden University Medical Center (NLD) -Royal Liverpool University Hospital (UK) -University of Patras (GRC) -University of Ljubljana (SVN) -Medical University of Vienna (AUT) -National Cancer Institute Aviano (ITA) -University Hospital Granada (ESP)	Block-randomized clinical study to implement pre-emptive genotyping of a panel of clinically relevant markers. Additional NGS sequencing among those presenting extreme phenotypes	13	LGC Group SNPline	Clinically relevant pharmacogenes associated with the response of 43 drugs (see **Table 2** for actionable drug-gene combinations) (as per DPWG guidelines)	Individuals who receive a first prescription of a drug of interest. First line, oncology, renal, and liver transplant, cardiology, and psychiatric patients (N = 8,100)

ADME, absorption, distribution, metabolism, elimination; AUT, Austria; CDSS, clinical decision support system; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenomics Working Group; EHR, electronic health record; ESP, Spain; GRC, Greece; HLA, human leucocyte antigen; IGNITE, Implementing Genomics in Practice; INGENIOUS, INdiana GENomics Implementation: an Opportunity for the UnderServed; ITA, Italy; N/A, not applicable; NGS, next-generation sequencing; NLD, The Netherlands; PGRN, Pharmacogenomics Research Network; PGRNseq, Pharmacogenomics Research Network sequencing; PGx, pharmacogenetic; PREDICT, Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment; RIGHTS, Right Drug, Right Dose, Right Time study; SSRI, serotonin reuptake inhibitor; SVN, Slovenia; TCA, tricyclic antidepressant; TPMT, thiopurine S-methyltransferase; UK, United Kingdom; U-PGx, Ubiquitous Pharmacogenomics Consortium; USA, United States of America.

Table 1 Continued

Implementation initiative	Objectives	Clinical sites (country)	Strategy	No. PGx genes tested	Platform	Drug-gene pairs implemented in clinical care (clinical guidelines)	Population, no.
INGENIOUS[54,55]	-To assess whether PGx testing for a panel of clinically relevant markers impacts annual healthcare costs and adverse event incidence	-Indiana Institute of Personalized Medicine at Indiana School of Medicine (USA)	Operational implementation of pre-emptive genotyping of a panel of clinically relevant markers in routine care, in a safety-net hospital	14	Open array	Clinically relevant pharmacogenes associated with the response of 28 drugs (as per CPIC guidelines)	Adult patients receiving care at the Eskenazi Health System (N = 6,000)
Personalized Medicine Program[56,57]	-Developing a pre-emptive, chip-based genotyping approach that is cost-effective, initially for implementation of a single drug-gene pair but eventually expanding to many others	-University of Florida and Shands Hospital (USA)	Implementing pre-emptive genotyping in routine care	120[20]	Life Technologies Quant Studio Open Array[20]	*CYP2C19*/clopidogrel (as per CPIC guidelines)	Patients receiving antiplatelet therapy and undergoing percutaneous coronary intervention (N = 800)
PG4KDS[58,59]	-Ultimately migrate all CPIC drug-pairs into the EHR and CDSS	-St. Jude Children's Research Hospital (USA)	Research protocol implementing pre-emptive genotyping	230	Affymetrix DMET Plus Array	*TPMT*, *CYP2D6*, *SLOC1B1*, and *CYP2C19* coupled to 12 high-risk drugs (as per CPIC guidelines)	St. Jude (pediatric) patients with a primary medical record at St. Jude Hospital (N = 1,559)
PGRN[52]	-To assess the implementation of routine evidence-based pharmacogenetic testing in six diverse healthcare systems	-University of Maryland (USA) -University of Florida (USA) -St. Jude Children's Research Hospital (USA) -Vanderbilt University (USA) -Mayo Clinic (USA) -Ohio State University (USA)	Each site has implemented pharmacogenomics testing of one or more drug-gene pairs, both through point-of-care and pre-emptive models	N/A	N/A	Several drug-gene pairs as per the CPIC guidelines	N/A
PREDICT[21,60]	-To establish a framework and infrastructure for pre-emptive incorporation of genomic information into the EHR	-Vanderbilt University Medical Center (USA)	Operational implementation of pre-emptive genotyping in routine care	34	VeraCode ADME Core Panel	*CYP2C19*/clopidogrel *CYP2C9*/warfarin *VKORC1*/warfarin (as per CPIC guidelines)	Patients receiving antiplatelet therapy following placement of cardiovascular stent (N = 10,000)

Table 1 Continued on next page

OUR FOCUS

We want to improve the safety and efficacy of pharmacotherapy for every European patient by enabling clinical pharmacogenomics

SHARED EUROPEAN GUIDELINES

Maintenance and dissemination of pharmacogenomics guidelines in the European Union

IMPLEMENTATION AND EVALUATION

Clinical implementation and outcome evaluation of pre-emptive pharmacogenomics in a multitude of European countries

ENABLING TECHNOLOGIES

Development of powerful and barrier-free clinical decision support systems and novel pharmacogenomics methodologies

COMMUNICATION AND EDUCATION

Development of a program to reach out to patients, health care professionals, regulatory agencies, politics and health insurance organisations

The Ubiquitous Pharmacogenomics, U-PGx, Consortium: the European Commission's Horizon - 2020 program.
In a prospective, block-randomized, controlled clinical study (PREemptive Pharmacogenomic testing for prevention of Adverse drug REactions [PREPARE]), **pre-emptive genotyping of a panel of clinically relevant PGx-markers, for which guidelines are available, will be implemented across healthcare institutions in seven European countries.**
The impact on patient outcomes and cost-effectiveness will be investigated.
The program is unique in its **multicenter, multigene, multidrug, multi-ethnic, and multihealthcare system approach**.


ESPT
European Society of Pharmacogenomics and Personalised Therapy
A Scientific Society for Individualised Medicine
HOME
LEADING EUROPEAN
ORGANIZATION IN THE FIELD
OF PHARMACOGENOMICS

Osim PGx testova koji se koriste u medicinskim centrima na tržištu postoje brojni komercijalno dostupni testovi - paneli

List of Analyses

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Gene Analysis

What is Being Tested?

List of Analyses

How it works

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We are proud to be working with the world's leading pharmacogenetics laboratories and to provide the highest quality genetic analysis.

Usually only a few SNPs, in other words base pair mutations, are tested. PharmGenetix uses a specially developed PGx panel to analyse more than 160 SNPs that play an important role in drug compatibility and tolerance. The series of SNPs tested (the PGx panel) is continually adapted and extended according to the latest scientific findings.

The analysis takes an average of 30 working days to complete, starting from the time of arrival of the blood sample in the laboratory. Since in some cases the results are needed urgently, we also offer express analyses (requires a telephone consultation and an extra charge of approx. €500, depending on the analysis). For further information, please contact us directly.

Analysis	Description	Price €
Pharmacogenetic Analysis	Broad PGx-Panel (>160 SNPs) + CYP2D6 CNV	€ 1.800 incl. VAT

In addition to SNPs that can reduce or increase the function of CYP enzymes, CYP2D6 is also susceptible to gene duplications. It is possible to detect these gene duplications by determining the Copy Number Variation (CNV). As a result, CYP2D6 is an extremely complex gene that can be difficult to analyse.

In addition to our pharmacogenetic analysis, we offer complete sequencing of the CYP2D6 gene. Within Europe, only PharmGenetix offers such a detailed, in-depth analysis of CYP2D6. If you are interested in this opportunity, please contact us directly.

1. Order Blood Collection Kit

Please complete the form on the right and click on “order genetic analysis”. Your analysis box (blood collection set) will be sent to you by mail.

You can also visit one of our partner physicians, they have our boxes too.

2. Blood Sample

Please visit your doctor with your analysis kit and send the blood sample together with the completed forms (declaration of consent and order) in the enclosed envelope to our laboratory. The doctor must confirm your identity. Please note that the order is binding on receipt of the blood sample in our laboratory.

3. Report sent to your doctor

After up to 15 working days your report will be sent to your doctor. Your doctor now has the opportunity to discuss your results with you and to optimize your therapy.

In emergency cases we also offer express analyses – just contact us!

If you have ordered a PharmGenetix customer card, your doctor will hand it out to you. It gives you secure online access to your interactive *Medication Check*.

Analysis Costs

PharmGenetix offers many different analyses in the range of € 300- € 1800 incl. VAT. Our staff will gladly advise you to find the best product for you.


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SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET

Which drugs have genetic variation?

Show 100 entries

Previous 1 2 Next Search:

Active ingredient	Tradenames
abacavir	Kivexa,Triumeq,Trizivir,Ziagen
allopurinol	Allonol,Apurin Sandoz,Zyloric
amitriptyline	Klotriptyl,Klotriptyl Mite,Limbitrol,Pertriptyl,Triptyl
aripiprazole	Abilify,Abilify Maintena,Aripiprazole Accord,Aripiprazole Avansor,Aripiprazole Ratiopharm,Aripiprazole Sandoz,Aripiprazol Krka,Aripiprazol Stada,Le

Showing 1 to 100 of 119 entries

Typical pharmacogenetic test includes genes like:
ALDH2, BCHE, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A5, DPYD, F2, F5, G6PD, IFNL3, SLCO1B1, TPMT, UGT1A1 and VKORC1

Abomics – supporting the use of genomics in medical care

Abomics' goal is to be the essential link in translating genomics research into clinical practice. Especially in the practical use of pharmacogenomics the need is widely recognized. Up-to-date genomic information needs to be readily available and easy to understand in order for personalized medicine to become a reality. Abomics Ltd does not compete with research laboratories or producers of genetic tests, but rather serves as their reliable partner. Abomics develops solutions with which the results of genetic tests done at laboratories can be more easily put to practical use in everyday patient care. The aim is to create the best possible conditions for personalized health.

Drug safety and efficacy (CYP2C19)

CYP2C19 is a liver enzyme that is responsible for the metabolism of many pharmaceuticals. These include several psychiatric and cardiovascular medications, for example. The activity of CYP2C19 can be exceptionally rapid or slow, depending on the genetic makeup of the individual. This either increases or lowers the efficacy of specific drugs. The CYP2C19 genetic test helps to determine the right medication with the right dose tailored to your personal genome.

UM Ultrarapid Metabolizer

*1/*17

30.11.2016 LABORATORY NAME

Analyzed 10 of 10 single nucleotide polymorphisms (SNP).

Drug safety and efficacy (CYP2C9)

CYP2C9 is a liver enzyme that is responsible for the metabolism of many pharmaceuticals. The activity of CYP2C9 can be exceptionally rapid or slow, depending on the genetic makeup of the individual. This either increases or lowers the efficacy of specific drugs. The CYP2C9 genetic test helps to determine the right medication with the right dose tailored to your personal genome.

NM Normal Metabolizer

*1/*1

30.11.2016 LABORATORY NAME

Analyzed 6 of 6 single nucleotide polymorphisms (SNP).

RECOMMENDATIONS

amitriptyline

Klotriptyl, Klotriptyl Mite, Limbitrol, Pertriptyl, Triptyl

D Efficacy of amitriptyline is potentially lower than normal with this genotype and therefore its use should be avoided. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider alternative drug not metabolized by CYP2D6. If a tricyclic is warranted, consider increasing the starting dose. Utilize therapeutic drug monitoring to guide dose adjustments.

CYP2D6: UM Ultrarapid Metabolizer

B With this genotype the exposure to amitriptyline is potentially decreased. Recommendation by an international board of experts, Clinical Pharmacogenetics Implementation Consortium (CPIC): Consider alternative drug not metabolized by CYP2C19. If a tricyclic is warranted, utilize therapeutic drug monitoring to guide dose adjustments.

CYP2C19: UM Ultrarapid Metabolizer

atomoxetine

Strattera

B With this genotype the exposure to atomoxetine is potentially reduced. Recommendation by a Dutch board of experts (Dutch Pharmacogenetics Working Group): Insufficient data to allow calculation of dose adjustment. Be alert to reduced efficacy or select alternative drug (e.g., methylphenidate, clonidine).

CYP2D6: UM Ultrarapid Metabolizer

aripiprazole

Abilify, Abilify Maintena, Aripiprazole Accord, Aripiprazole Avansor, Aripiprazole Ratiopharm, Aripiprazole Sandoz, Aripiprazol Krka, Aripiprazol Stada, Lemilvo

B Label-recommended dosing and administration.

CYP2D6: UM Ultrarapid Metabolizer

atorvastatin

Atorbir, Atorvastatin Krka, Atorvastatin Orion, Atorvastatin Pfizer, Atorvastatin Ratiopharm, Lipistad, Lipitor, Orbeos, Triveram

A Label-recommended dosing and administration.

CYP3A4: Normal metabolism

STARTUPS, DIAGNOSTICS

Mayo Clinic startup OneOme pitches user-friendly pharmacogenomics

With one foot in diagnostics and another in digital health, Mayo Clinic startup OneOme wants to make pharmacogenomic testing accessible and relevant.

By JULIET PRESTON

Post a comment / Feb 28, 2017 at 6:20 PM

The OneOme pharmacogenomic test kit

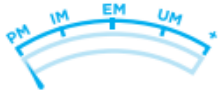
MAYO CLINIC

ONEOME

KBC ZAGREB

SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET

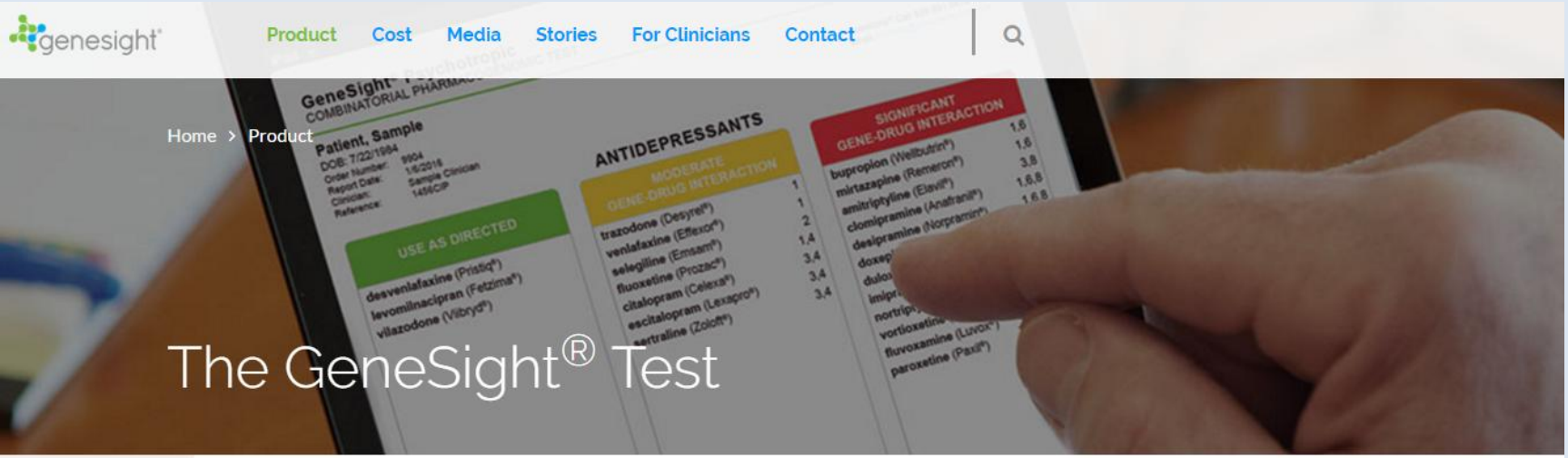
Genotype Results

Gene	Genotype	Phenotype Summary / Metabolic Status	
CYP1A2	**Multiple Variations**		**Extensive to Ultrarapid#** Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolites may lack efficacy.
CYP2C9	***1/*1**		**Extensive** Normal level of activity. Drugs metabolized at a normal rate.
CYP2C19	***3/*17**		**Intermediate to Extensive** Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolites may cause side effects or toxicity.
CYP2D6	***2Ax2/*4**		**Extensive to Ultrarapid** Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolites may lack efficacy.
CYP3A4	***1/*22**		**Intermediate to Extensive** Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolites may cause side effects or toxicity.
CYP3A5	***3/*3**		**Poor** Normal dosing may be required because original dosing guidelines for drugs have been established on patients with poor metabolizer phenotype.
Warfarin Sensitivity (CYP2C9; VKORC1)	***1/*1; c.-1639 GG**		**Low Sensitivity†** Normal sensitivity to warfarin. Refer to warfarindosing.org and FDA package insert for dosing guidelines.
SLCO1B1	***1/*5**		**Increased Risk** Increased risk of Simvastatin-Induced Myopathy. Reduced function of SLCO1B1, simvastatin use may result in myopathy.
HLA-B*58:01	**Negative**		**Decreased Risk** Decreased risk of severe cutaneous reactions induced by allopurinol.

Genotyping performed by the Department of Laboratory Medicine and Pathology, Mayo Clinic. A brief gene description is available in the *Reference Information* section.

\# Increased metabolism possible if exposed to CYP1A2 inducers.

† For Mayo Clinic patients, use the Pharmacogenomics Warfarin Initiation Dosing Recommendation Alert and refer to Ask Mayo Expert for more information.



Precision medicine. Personal wellness.

Stop wondering which medication is right for you and start on your road to recovery. Treating mental health disorders can often be a long, frustrating process as you and your doctor spend months trying multiple medications for depression and other conditions at different doses to find the medication that works for you. During this time you could end up missing work, paying for multiple doctor visits, or losing hope that you'll ever find a medication that can help you. There's a better way.

The GeneSight® test analyzes your DNA and helps your doctor get a better understanding of what medication might work best based on your genetic makeup. Using the GeneSight test report, your doctor can personalize your treatment plan, finding the right medication faster and avoiding medicines that may cause side effects.

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- Pain Medication DNA Insight®
- Cardiac DNA Insight®
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Using genetics to understand and optimize the use of commonly prescribed medications.

Mental Health DNA Insight®

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Stanje u Hrvatskoj

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Zavodi/odjeli

Katalog pretraga

Naručivanje pacijenata

Upute za pacijente

Slanje uzoraka

Odjel za citogenetiku

Odjel za elektroforetsku i imunokemijsku dijagnostiku

Odjel za farmakogenomiku i individualizaciju terapije

Voditeljica: prof. dr. sc. Nada Božina, dr. med.

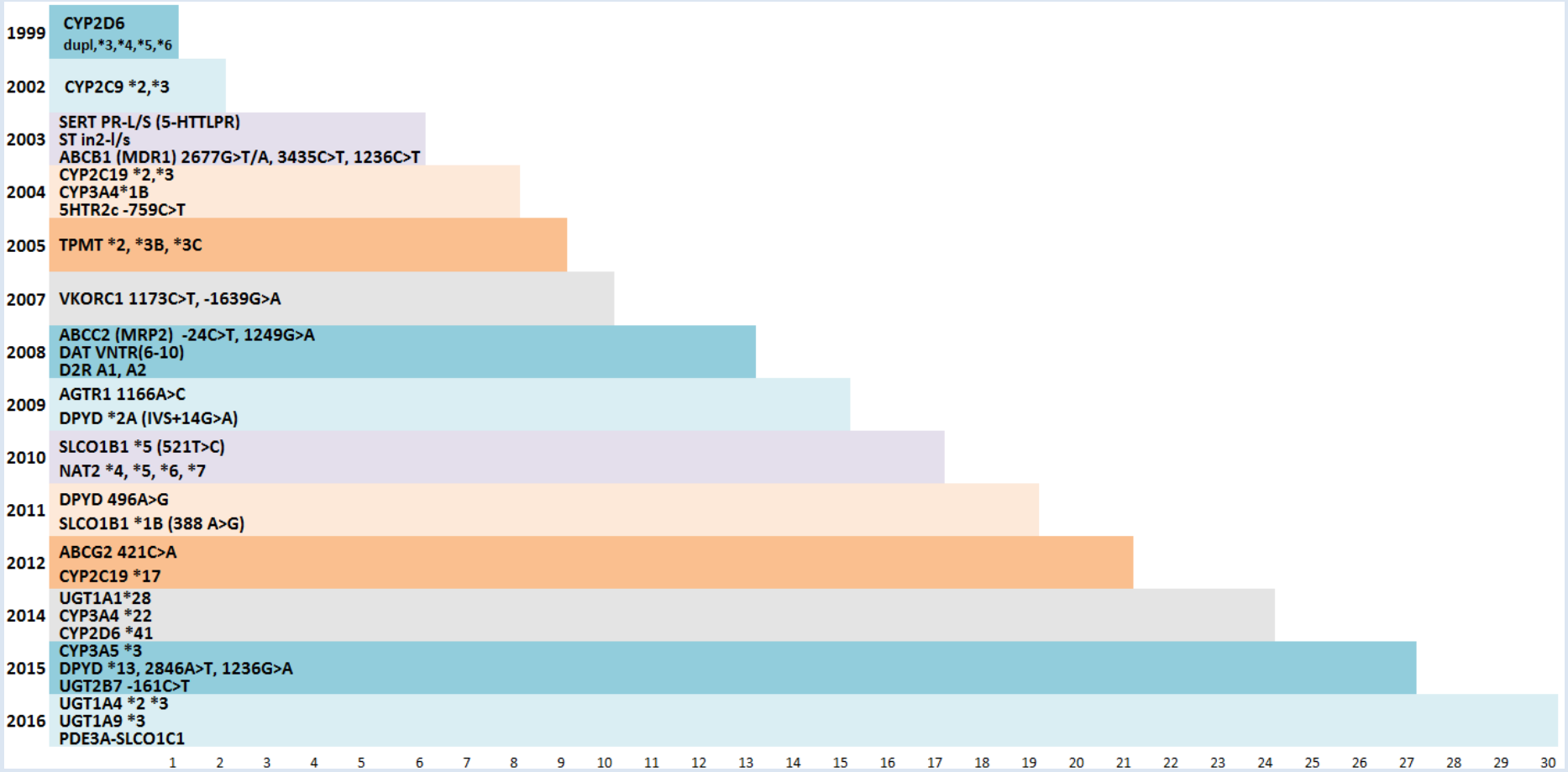
Lana Ganoci, specijalist analitičke toksikologije
Livija Šimičević, specijalist medicinske biokemijei laboratorijske medicine

Odjel za farmakogenomiku i individualizaciju terapije provodi testiranje na farmakogenetičke varijacije koje mogu utjecati na učinkovitost i nuspojave lijekova.
To se ponajprije odnosi na otkrivanje polimorfizama:

- metaboličkih enzima faze I: CYP2C9, CYP2C19, CYP3A4/5, CYP2D6, DPYD
- metaboličkih enzima faze II: TPMT, NAT2, UGT1, UGT2
- transportnih proteina: ABCB1, ABCC2, ABCG2, SLCO1B1, SERT, DAT
- ciljnih mjesta djelovanja lijeka: VKORC1, 5-HTR, DRD2, AGTR1

Farmakogenetički nalaz sadrži i tumačenje te preporuke prema međunarodno usvojenim smjernicama.

Implementacija farmakogenetičkih testova u KBC Zagreb



Pregled testova

Metabolički enzimi:
CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DPYD, NAT2, TPMT, UGT1A1, UGT2B7, VKORC1

Transporteri:
ABCB1 (MDR1), ABCC2 (MRP2), ABCG2 (BCRP2), DAT2, SERT, SLCO1B1, SLCO1C1

Receptori:
D2DR, 5-HT2cR, AGTR1

U 2017. godini napravljeno je više od **5.000** analiza

Vanjska kontrola kvalitete

- Sudjelovanje od 2007 u shemi RfB:
  - CYP2C9
  - CYP2C19
  - CYP2D6
  - CYP3A4
  - CYP3A5
  - DPYD
  - MDR1/ABCB1
  - VKORC1
  - TPMT

ISO 15189
Medicinski laboratoriji - Zahtjevi za kvalitetu i osposobljenost

Analize – paneli u KBC Zagreb

1. Za liječenje **kardiovaskularnih bolesti**

CYP2C9 i VKORC1	za primjenu **kumarinskih antikoagulanata**
CYP3A4 i ABCB1	za primjenu novijih oralnih antikoagulanata (**NOAK**)
CYP2C19, CYP3A4, ABCB1, UGT2B7, P2Y12R	za primjenu **antiagregacijskih lijekova** (klopidogrel, prasugrel, tikagrelor)
SLCO1B1, ABCG2, ABCB1, CYP2C9, CYP2C19, CYP3A4	za primjenu **statina** (simvastatin atorvastatin, rosuvastatin)
CYP2D6, CYP2C9, CYP2C19, UGT1A1, UGT2B7, AGTR1	za primjenu različitih **antihipertenziva, antiaritmika, beta blokatora**

2. Za primjenu **psihotropnih lijekova**:

CYP2D6, CYP2C19, CYP3A4, ABCB1, UGT2B7, UGT1A1, SERT, 5-HT2C, 5-HT2A, DAT, DRD2, BDNF, MAO, COMT

3. Za primjenu **antiepileptika**:

CYP2C9, CYP2C19, CYP4A4/5, UGT2B7, ABCB1, ABCC2, ABCG2

4. Panel za individualizaciju terapije **5-fluorouracilom** (5-FU):

   DPYD

   U slučaju primjene 5-FU zajedno s **irinotekanom** panel uključuje i *UGT1A1 i SLCO1B1*

5. Panel za individualizaciju terapije **tamoksifenom**

   CYP2D6, CYP2C19, CYP3A4, UGT1A1, ABCB1, ABCC2

6. Panel za individualizaciju terapije **tiopurinskim lijekovima** (azatioprin, 6-merkaptopurin, 6-tiogvanin)

   TPMT, ITPA, XO, NUDT15

7. Panel za primjenu drugih antitumorskih lijekova (uključujući **paklitaksel, oksaliplatinu, cisplatinu**)

   CYP2C19, ABCG2, ABCC2, SLCO1B1

8. Panel za individualizaciju terapije **tirozin-kinaznim inhibitorima** (**imatinib, nilotinib, dasatinib, sunitinib, erlotinib, gefitinib**)

   CYP2D6, CYP2C19, CYP2C9, CYP3A4,
   ABC i SLC te *EGFR*

9. Panel za individualizaciju terapije **metotreksatom**

   ABCB1, ABCG2, ABCC2 i SLC (SLCO1B1, SLCO1B3)

Drug Metab Pers Ther. 2017 Mar 1;32(1):11-21. doi: 10.1515/dmpt-2016-0024.

Genetic polymorphisms of cytochrome P450 enzymes: CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 in the Croatian population.

Ganoci L, Božina T, Mirošević Skvrce N, Lovrić M, Mas P, Božina N.

Gen	Genotip	Učestalost (%)	Prediktivni fenotip	Prediktivni fenotip NOVA KL.
CYP2C9	**1/*1*	60	EM	**NM**
	**1/*2, *1/*3*	36	IM	IM
	**2/*2, *2/*3, *3/*3*	4	PM	PM
CYP2C19	**1/*1*	36	EM	**NM**
	**1/*2, *2/*17*	25	IM	IM
	**2/*2*	2	PM	PM
	**1/*17*	31	UM	**RM**
	**17/*17*	6	UM	**URM**
CYP2D6	**1/*1*	56	EM	**NM**
	**1/*3, *1/*4, *1/*5, *1/*6*	34	IM	**IM/NM**
	**3/*4, *4/*4, *3/*6, *4/*6, *6/*6, *4/*4 xN*	6	PM	PM
	**1 xN*	3	URM	URM
	**1/*4 xN*	1	nedefinirano	nedefinirano
CYP3A4	**1/*1*	97	EM	**NM**
	**1/*1B, *1B/*1B*	3	UM	**URM**
	**1/*1*	94,6	EM	**NM**
	**1/*22*	5	IM	IM
	**22/*22*	0,4	PM	PM
CYP3A5	**1/*1*	1	EM	**NM**
	**1/*3*	8	IM	IM
	**3/*3*	91	PM	PM

nature publishing group TRANSLATION

Received 15 June 2011; accepted 8 July 2011; advance online publication 7 September 2011. doi:10.1038/clpt.2011.185

CLINICAL PHARMACOLOGY & THERAPEUTICS

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* Genotypes and Warfarin Dosing

Table 1 Recommended daily warfarin doses (mg/day) to achieve a therapeutic INR based on *CYP2C9* and *VKORC1* genotype using the warfarin product insert approved by the US Food and Drug Administration

VKORC1:	*CYP2C9*1/*1*	*CYP2C9*1/*2*	*CYP2C9*1/*3*	*CYP2C9*2/*2*	*CYP2C9*2/*3*	*CYP2C9*3/*3*
CC	5–7	5–7	3–4	3–4	3–4	0.5–2
CT	5–7	3–4	3–4	3–4	0.5–2	0.5–2
TT	3–4	3–4	0.5–2	0.5–2	0.5–2	0.5–2

Reproduced from updated warfarin (Coumadin) product label.

KLINIČKI BOLNIČKI CENTAR ZAGREB
KLINIČKI ZAVOD ZA LABORATORIJSKU DIJAGNOSTIKU MEDICINSKOG FAKULTETA SVEUČILIŠTA U ZAGREBU
Referentni centar Ministarstva zdravlja za kliničku biokemiju i molekularnu dijagnostiku
Kišpatićeva 12, 10000 Zagreb; www.kbc-zagreb.hr
Predstojnik: doc.dr.sc. Dunja Rogić, tel: +385 (0)1 2367 289

KLINIČKA JEDINICA ZA FARMAKOGENOMIKU I INDIVIDUALIZACIJU TERAPIJE
Pročelnik: doc.dr.sc. Nada Božina, dr.med. e-mail: nbozina@kbc-zagreb.hr tel: +385(0)1/2367- 266, 2367-249

FARMAKOGENETIČKI NALAZ

Klinika/odjel:	DZ-PI	Barkod:	
Liječnik:		Broj protokola:	2013
Datum i vrijeme uzorkovanja:	2.1.2013	Matični broj:	
Datum primitka uzorka:	2.1.2013	Datum rođenja:	
Datum izdavanja nalaza:	4.1.2013	Spol:	m

PREZIME I IME: Click here to enter text.

Gen - alel	Genotip	Fenotip	Metoda
CYP2C9 *2, *3	*1/*1	brzi metabolizam - EM	PCR u stvarnom vremenu TaqMan® DME Genotyping
VKORC1 1173C>T	C/C	visoka aktivnost enzima	PCR u stvarnom vremenu TaqMan® DME Genotyping

PREDIKTIVNI FENOTIP
Prema nalazu genotipizacije ispitanik je brzi metabolizator lijekova - supstrata CYP2C9 (varfarin, fenitoin, sartani, tolbutamid, glipizid, nateglinid, fluvastatin, NSAR, sulfametoksazol, metronidazol i dr.), i ima visoku aktivnost vitamin K-epoksid reduktaze (VKORC1).

PREPORUKE DOZIRANJA
U ispitanika bi mogle biti indicirane prosječne do više doze antikoagulantnih lijekova kumarinskog tipa i drugih lijekova - supstrata CYP2C9. Doziranje varfarina prema FDA za ovu kombinaciju genotipova je 5-7 mg/dan. Doziranje ovisi i o istovremenoj primjeni drugih lijekova supstrata.

Literatura:
Johnson JA et al., Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing., *Clin Pharmacol Ther. 2011; 90(4):625-9.*
Swen JJ et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther. 2011; 89(5):662-73.*

Izradila/o:
Maja Mezak Herceg, bacc.med.lab.diagn.
Zrinka Mirković, kem.teh.

Odgovorna osoba:
doc.dr.sc. Nada Božina, dr.med.

Vanjsku kontrolu kvalitete provodi DGKL (Deutsche Vereinte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin e.V.)

OZ-5.8-000-6/1

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2018) **84** 2106–2119 2106

ORIGINAL ARTICLE

Interaction between *ABCG2 421C>A* polymorphism and valproate in their effects on steady-state disposition of lamotrigine in adults with epilepsy

Correspondence Professor Nada Božina, MD, PhD, Department of Laboratory Diagnostics, Division of Pharmacogenomics and Therapy Individualization, University Hospital Centre Zagreb, Kišpatićeva 12, 10000 Zagreb. Tel.: +385 1 2367249; E-mail: nbozina@kbc-zagreb.hr

Received 17 November 2017; **Revised** 8 May 2018; **Accepted** 10 May 2018

Iva Klarica Domjanović[1], Mila Lovrić[2], Vladimir Trkulja[3], Željka Petelin-Gadže[4,5], Lana Ganoci[6], Ivana Čajić[4] and Nada Božina[3,6,*]

[1]Croatian Agency for Medicinal Products and Medical Devices, Zagreb, Croatia, [2]University Hospital Centre Zagreb, Analytical Toxicology and Pharmacology Division, Department of Laboratory Diagnostics, Zagreb, Croatia, [3]University of Zagreb, School of Medicine, Department of Pharmacology, Zagreb, Croatia, [4]University Hospital Centre Zagreb, Department of Neurology, Referral Centre for Epilepsy, Zagreb, Croatia, [5]University of Zagreb, School of Medicine, Zagreb, Croatia, and [6]University Hospital Centre Zagreb, Division of Pharmacogenomics and Therapy Individualization, Department of Laboratory Diagnostics, Zagreb, Croatia

*Principal investigator.

Keywords Clinical Pharmacology, Drug Interactions, Drug Transporter, Genetics And Pharmacogenetic, Pharmacogenomics, Pharmacokinetics

WHAT THIS STUDY ADDS

Variant allele at *ABCG2 421C>A* and valproate interact in their effects on lamotrigine disposition.

Lamotrigine mono-treated variant allele carriers (vs. wild type homozygotes) have **25% lower troughs**, but when valproate co-treated, they have **70% higher lamotrigine troughs.**

Valproate increases lamotrigine troughs by **2.3-fold in wild type homozygotes** and by **5.2-fold in variant allele carriers**.

BCPT Basic & Clinical Pharmacology & Toxicology

Basic & Clinical Pharmacology & Toxicology, 2018, **123**, 509–518 Doi: 10.1111/bcpt.13035

Case Report

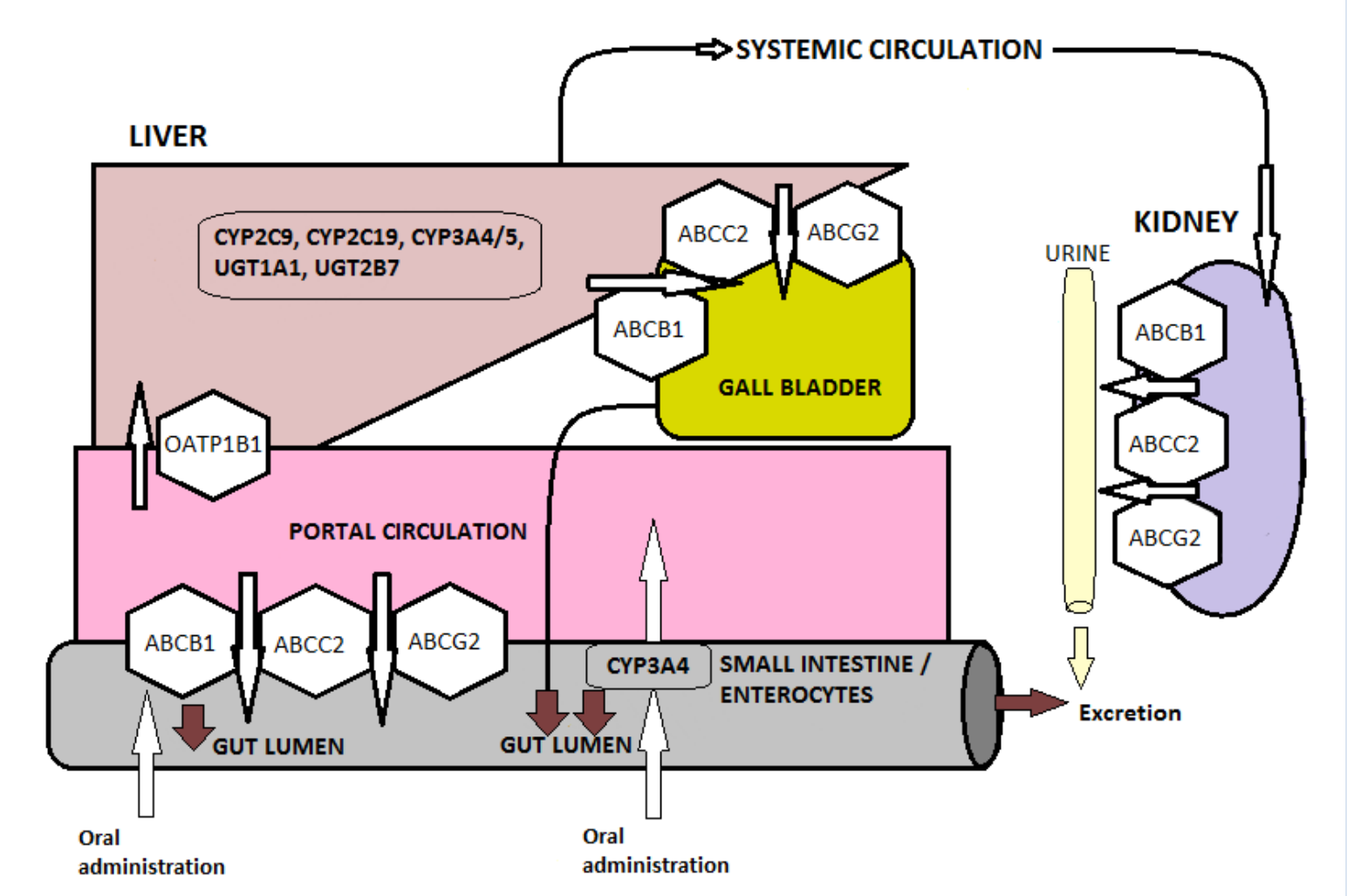
Rosuvastatin-Induced Rhabdomyolysis – Possible Role of Ticagrelor and Patients' Pharmacogenetic Profile

Majda Vrkić Kirhmajer[1], Viola Macolić Šarinić[2], Livija Šimičević[3], Iva Ladić[4], Krešimir Putarek[5], Ljiljana Banfić[1] and Nada Božina[6]

[1]Department of Cardiovascular Diseases, University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia, [2]Safety and Vigilance, WHO, Geneva, Switzerland, [3]Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia, [4]Department of Internal Medicine, Bjelovar General Hospital, Bjelovar, Croatia, [5]Department of Cardiovascular Diseases, University Hospital Centre Zagreb, Zagreb, Croatia and [6]Department of Pharmacology, University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

(Received 5 March 2018; Accepted 23 April 2018)

Abstract: Up to the beginning of 2018, a total of eight cases describing rare but clinically important drug interactions between rosuvastatin and ticagrelor which resulted in rhabdomyolysis have been noted in the Global World Health Organization (WHO) adverse drug reaction (ADR) database (VigiBase) as well as in available literature. There are several possible factors which could contribute to the onset of rhabdomyolysis: old age, initially excessive rosuvastatin dose, drug–drug interactions (DDI) on metabolic enzymes (CYPs and UGTs) and drug transporter levels (ABCB1, ABCG2, OATP1B1) and pharmacogenetic predisposition. We reviewed all available cases plus the case of an 87-year-old female Croatian/Caucasian patient who developed rhabdomyolysis following concomitant treatment with rosuvastatin and ticagrelor. The results of the pharmacogenetic analysis indicated that the patient was a carrier of inactivating alleles *CYP2C9*1/*3, CYP3A4*1/*22, CYP3A5*3/*3,* CYP2D6**1/*4, UGT1A1*28/*28, UGT2B7* -161C/T, *ABCB1 3435C/T and ABCB1 1237C/T* which could have added to the interactions not only between ticagrelor and rosuvastatin but also other concomitantly prescribed medicines, such as amiodarone and proton pump inhibitors. In this case report, the possible multifactorial causes for rhabdomyolysis following concomitant use of rosuvastatin and ticagrelor such as old age, polypharmacy, renal impairment, along with pharmacogenetics will be discussed.



Distribution of drug metabolism enzymes and transporters involved in possible mechanisms of presented adverse drug reactions

Basic Clin Pharmacol Toxicol 2018;123(4):509-518.

European Journal of Clinical Pharmacology (2018) 74:1191–1192
https://doi.org/10.1007/s00228-018-2485-6

LETTER TO THE EDITOR

Acute kidney injury, agranulocytosis, drug-induced liver injury, and posterior reversible encephalopathy syndrome caused by high-dose methotrexate—possible role of low activity ABC and SLC drug transporters

L. Bielen[1,2] · I. Kralj[3] · Ela Ćurčić[2] · M. Vodanović[2] · A. Boban[2] · N. Božina[1,2]

Received: 20 March 2018 / Accepted: 14 May 2018 / Published online: 22 May 2018

Eur J Clin Pharmacol. 2017 Sep;73(9):1129-1140. doi: 10.1007/s00228-017-2285-4. Epub 2017 Jun 18.

Steady-state pharmacokinetics of mycophenolic acid in renal transplant patients: exploratory analysis of the effects of cyclosporine, recipients' and donors' ABCC2 gene variants, and their interactions.

Božina N[1,2], Lalić Z[3], Nađ-Škegro S[4], Borić-Bilušić A[5], Božina T[6], Kaštelan Ž[7], Trkulja V[8].

⊕ Author information

Abstract

PURPOSE: The study aims to evaluate the impact of recipients' and donors' polymorphisms in multidrug resistance-associated protein 2 (MRP2) gene ABCC2 -24C>T and 1249G>A on disposition of mycophenolic acid (MPA) and their interaction with cyclosporine (CsA) (compared to tacrolimus, TAC) in stable de novo adult renal transplant patients of Croatian origin.

METHODS: A total of 68 recipient-donor pairs were genotyped. Steady-state pharmacokinetics of MPA was assessed by the model-independent method.

RESULTS: Adjusted for MPA formulation, renal function, type of calcineurin inhibitor and recipients' and donors' genotypes at the two loci, donors' A-allele at 1249G>A was associated with a reduced peak (29%) and early (AUC_{0-2}, 33%) exposure and increased MPA clearance (26%). Donors' A-allele combined with CsA was associated with 78% higher MPA clearance, 49% lower early and 48% lower total exposure as compared to wild type homozygosity + TAC. Recipients' SNPs per se did not reflect on MPA disposition. However, A-allele at 1249G>A + CsA (compared to wild type + TAC) was associated with a numerically greater increase in MPA clearance (59 vs. 41%), reduction in total exposure (36 vs. 27%) and increase in absorption rate (C_{max}/AUC) (56 vs. 37%) than observed for the main effect of CsA. Less pronounced effects were observed for the combination of variant allele at -24C>T and CsA.

CONCLUSION: Considering MPA disposition, data indicate: donors' ABCC2 1249G>A polymorphism increases clearance and reduces exposure; CsA increases clearance and reduces exposure by inhibiting MRP2 in the gut, the liver, and the kidney; donors' ABCC2 1249G>A polymorphism enhances the renal CsA effect, while recipients' polymorphism seems to enhance the liver and the gut CsA effects.

The pharmacogenomics of hypolipemics: ABCG2 as a apotential predictor of hepatotoxicity

Nada Božina[1,2], Livija Šimičević[1], Ivan Pećin[2,3], Tamara Božina[2], Željko Reiner[2,3]

[1]Department of Laboratory Diagnostics, University Hospital Center Zagreb, Zagreb, Croatia
[2]School of Medicine, University of Zagreb, Zagreb, Croatia
[3]Department of Internal Medicine, University Hospital Center Zagreb, Zagreb, Croatia

Biochemia Medica 2018;28(Suppl 1):S1–S223

Clin Ther. 2016 Oct 6;38(10S):e24-e25. doi: 10.1016/j.clinthera.2016.07.145.

The Role of Pharmacogenetic Testing in the Evaluation of Drug-Induced Liver Injury.

Stanić Benić M[1], Mirošević Skvrce N[2], Božina N[3].

Author information

1 Clinical Hospital Centre Rijeka, Rijeka, Croatia.
2 Agency for Medicinal Products and Medical Devices, Zagreb, Croatia.
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Ther Drug Monit. 2018 Jun;40(3):362-368. doi: 10.1097/FTD.0000000000000501.

Warfarin Dosing According to the Genotype-guided Algorithm is Most Beneficial in Patients With Atrial Fibrillation: A Randomized Parallel Group Trial.

Makar-Aušperger K[1], Krželj K[2], Lovrić Benčić M[3], Radačić Aumiler M[1], Erdeljić Turk V[1], Božina N[4,5].

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Pharmacogenomics. 2016 Aug;17(13):1385-9. doi: 10.2217/pgs-2016-0069. Epub 2016 Jul 29.

CYP2D6 *6/*6 genotype and drug interactions as cause of haloperidol-induced extrapyramidal symptoms.

Šimić I[1,2], Potočnjak I[3], Kraljičković I[2], Stanić Benić M[4], Čegec I[2], Juričić Nahal D[2], Ganoci L[1,5], Božina N[1,5].

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3 Clinical Unit of Clinical Pharmacology & Toxicology, Department of Medicine, University Hospital Centre Sisters of Charity, Zagreb, Croatia.
4 Unit for Clinical Pharmacology, University Hospital Centre Rijeka, Rijeka, Croatia.
5 Department of Laboratory Diagnostics, University Hospital Centre Zagreb, University of Zagreb School of Medicine, Zagreb, Croatia.

Abstract

A 66-year-old male Caucasian, received 1 mg of haloperidol orally and rapidly developed severe iatrogenic extrapyramidal symptoms. Treatment was immediately discontinued, and the side effects resolved. Haloperidol is mainly metabolized by Phase I CYP2D6 and to the lesser extent by CYP3A4 and by Phase II UGT2B7 enzymes. Genotyping was performed revealing CYP2D6*6/*6, CYP3A4*1/*1, and UGT2B7 -161 C/T genotypes, implicating poor, extensive and intermediate metabolism, respectively. Of the CYPs, haloperidol is metabolized by CYP2D6 and CYP3A4 primarily. It was the introduction of ciprofloxacin which was a trigger for the development of adverse drug reaction due to inhibition of CYP3A4, which was in presented patient main metabolic pathway for haloperidol since he was CYP2D6 poor metabolizer. Presented case report highlights the importance of genotyping. Pharmacogenetics testing should be considered when drug toxicity is suspected, polymorphic metabolic pathways used and drugs concomitantly applied.

Pharmacogenomics. 2015 Jul;16(8):803-15. doi: 10.2217/pgs.15.47. Epub 2015 Jun 18.

ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case-control study.

Mirošević Skvrce N[1], Macolić Šarinić V[1], Šimić I[2], Ganoci L[3], Muačević Katanec D[2], Božina N[3].

Author information

Abstract

AIM: To explore the association between dose-related adverse drug reactions (ADRs) of atorvastatin and polymorphisms of ABCG2, taking into account the influence of CYP3A4 and SLCO1B1 genes.

MATERIALS & METHODS: Sixty patients who experienced atorvastatin dose-related ADRs and 90 matched patients without ADRs were enrolled in the study. Genotyping for ABCG2 421C > A, CYP3A4*22, SLCO1B1 388A > G, SLCO1B1 521T > C variants was performed by real-time PCR.

RESULTS: Patients with ABCG2 421CA or AA genotypes had 2.9 times greater odds of developing atorvastatin dose-dependent ADRs (OR: 2.91; 95% CI: 1.22-6.95; p = 0.016) than those with ABCG2 421CC genotype. After adjustments for clinical and genetic risk factors, ABCG2 remained a statistically significant predictor of adverse drug reactions (OR: 2.75; 95% CI: 1.1-6.87; p = 0.03;). Also, carriers of SLCO1B1 521 TC or CC genotypes had 2.3 greater odds (OR: 1.03-4.98; 95% CI: 1.03-4.98; p = 0.043) of experiencing ADRs caused by atorvastatin in comparison with carriers of SLCO1B1 521 TT genotype.

CONCLUSION: Our study demonstrated an association between atorvastatin-induced ADRs and genetic variants in the ABCG2 gene.

KEYWORDS: ABCG2; CYP3A4; SLCO1B1; adverse drug reactions; atorvastatin; gene polymorphism

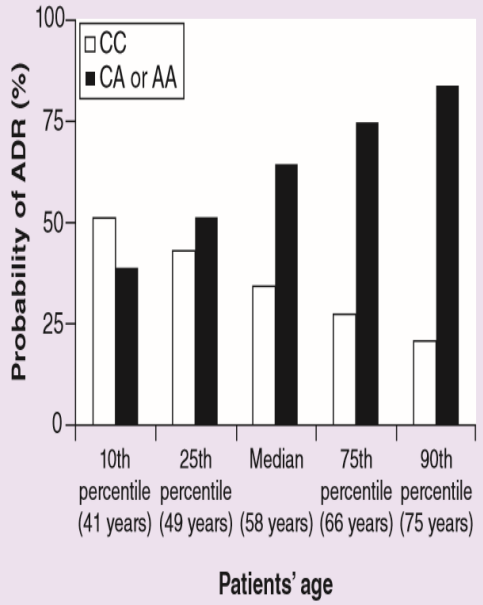

Figure 1. Probability of adverse drug reaction by different *ABCG2* 421 C > A genotypes and patients' age, after adjustment for diabetes mellitus, interactions with other drugs, *SLCO1B1* 388A > G and *SLCO1B1* 521T > C genotypes (n = 150).
ADR: Adverse drug reaction.

Cancer Chemother Pharmacol. 2015 Dec;76(6):1317-9. doi: 10.1007/s00280-015-2885-6. Epub 2015 Oct 20.

Erlotinib-related rhabdomyolysis: the role of pharmacogenetics and drug-drug interaction.

Koršić M[1], Muršić D[2], Badovinac S[3], Božina N[4], Roglić M[5], Jakopović M[6], Čučević B[7].

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1 Clinic for Lung Diseases Jordanovac, University Hospital Centre Zagreb, Jordanovac 104, 10000, Zagreb, Croatia. mkorsic70@gmail.com.

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Pharmacogenomics. 2013 Sep;14(12):1419-31. doi: 10.2217/pgs.13.135.

CYP2C9 and ABCG2 polymorphisms as risk factors for developing adverse drug reactions in renal transplant patients taking fluvastatin: a case-control study.

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Abstract

AIM: To investigate whether an association exists between fluvastatin-induced adverse drug reactions (ADRs) and polymorphisms in genes encoding the metabolizing enzyme CYP2C9 and the drug transporter ABCG2 in renal transplant recipients (RTRs).

MATERIALS & METHODS: Fifty-two RTRs that experienced fluvastatin ADRs and 52 controls matched for age, gender, dose of fluvastatin and immunosuppressive use were enrolled in the study. Genotyping for CYP2C9*2, *3 and ABCG2 421C>A variants was performed by real-time PCR.

RESULTS: CYP2C9 homozygous and heterozygous mutant allele (*2 or *3) carriers had 2.5-times greater odds of developing adverse effects ($\chi^2 = 4.370$; degrees of freedom = 1; $p = 0.037$; $\varphi = 0.21$, odds ratio [OR]: 2.44; 95% CI: 1.05-5.71). Patients who were the carriers of at least one mutant CYP2C9 allele (*2 or *3) and who were receiving CYP2C9 inhibitors, had more than six-times greater odds of having adverse effects than those without the inhibitor included in their therapy ($p = 0.027$; OR: 6.59; 95% CI: 1.24-35.08). Patients with ABCG2 421CA or AA (taken together) had almost four-times greater odds of developing adverse effects than those with ABCG2 421CC genotype ($\chi^2 = 6.190$; degrees of freedom = 1; $p = 0.013$; $\varphi = 0.24$, OR: 3.81; 95% CI: 1.27-11.45). Patients with A allele had 2.75-times (95% CI: 1.02-7.40) greater odds of developing adverse effects than those with C allele.

CONCLUSION: Our preliminary data demonstrate an association between fluvastatin-induced ADRs in RTRs and genetic variants in the CYP2C9 and ABCG2 genes.

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The association study of polymorphisms in DAT, DRD2, and COMT genes and acute extrapyramidal adverse effects in male schizophrenic patients treated with haloperidol.

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Abstract

Extrapyramidal symptoms (EPSs) are common adverse effects of antipsychotics. The development of acute EPSs could depend on the activity of dopaminergic system and its gene variants. The aim of this study was to determine the association between dopaminergic type 2 receptor (DRD2) dopamine transporter (SLC6A3) and catechol-O-methyltransferase (COMT) gene polymorphisms and acute EPSs in 240 male schizophrenic patients treated with haloperidol (15-mg/d) over a period of 2 weeks. Acute EPSs were assessed with Simpson-Angus Scale. Three dopaminergic gene polymorphisms, the DRD2 Taq1A, the SLC6A3 VNTR, and the COMT Val158Met, were determined. Extrapyramidal symptoms occurred in 116 (48.3%) of patients. Statistically significant associations were found for SLC6A3 VNTR and COMT Val158Met polymorphisms and EPS susceptibility. Patients with SLC6A3 9/10 genotype had almost twice the odds to develop EPSs compared with those with all other SLC6A3 genotypes (odds ratio, 1.9; 95% confidence interval, 1.13-3.30), and patients with COMT Val/Met genotype had 1.7 times greater odds to develop EPSs than those with all other COMT genotypes (odds ratio, 1.7; 95% confidence interval, 1.01-2.88). There was no statistically significant association between genotype and allele frequencies of DRD2, SLC6A3, or COMT polymorphisms and the development of particular EPSs.In conclusion, the results of the present study showed for the first time the association between acute haloperidol-induced EPSs and SLC6A3 VNTR and COMT Val158Met polymorphisms. Although the precise biological mechanisms underlying these findings are not yet understood, the results suggest that the dopaminergic gene variations could predict the vulnerability to the development of the acute EPSs in haloperidol-treated schizophrenic patients.

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Atorvastatin-related rhabdomyolysis and acute renal failure in a genetically predisposed patient with potential drug-drug interaction.

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Author information

Abstract

CASE DESCRIPTION: A 75-year-old man developed rhabdomyolysis and acute renal failure during atorvastatin therapy. All medications were discontinued and the patient was treated with intermittent hemodialysis throughout the course of hospitalization. After four weeks, patient's kidney function tests and serum myoglobin levels decreased to normal values and muscle weakness gradually disappeared. Genotyping results showed that the patient had a single-nucleotide polymorphism within genes encoding the organic anion-transporting polypeptide 1B1 and ATP binding cassette sub-family B member 1, which predisposed him for statin-induced myopathy. He was also a poor metabolizer of cytochrome P450 2C19. Concomitant therapy with pantoprazole could have resulted in the inhibition of cytochrome P450 3A4-mediated metabolism of atorvastatin and contributed to the development of rhabdomyolysis.

CONCLUSION: The case illustrates the clinical relevance and relationship between pharmacogenetic and pharmacokinetic factors in the development of statin-induced myopathy.

Pharmacogenomics J. 2011 Feb;11(1):35-44. doi: 10.1038/tpj.2010.7. Epub 2010 Mar 2.

Association study of MDR1 and 5-HT2C genetic polymorphisms and antipsychotic-induced metabolic disturbances in female patients with schizophrenia.

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Abstract

The objective of this study was to determine the association of 5-HT2C (serotonin 2C receptor) and MDR1 (multidrug resistant protein) genetic polymorphisms and antipsychotic-induced metabolic abnormalities among female patients with DSM IV schizophrenia spectrum disorders. We have previously reported the associations of -759CT 5-HT2C and G2677T and C3435T MDR1 genetic polymorphisms and olanzapine/risperidone-induced weight gain in a similar sample of patients. Here, we included a total of 101 previously non-medicated female patients treated with olanzapine/risperidone over a 3-month period. The variables analyzed included fasting glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein and triglyceride levels in blood, blood pressure and waist circumferences. We observed significant association of -759T 5-HT2C genetic variant and greater increase in waist circumference (P=0.03), fasting glucose level (P=0.046) and triglyceride level (P=0.045) in blood after a 3-month period. The 2677T and 3435T MDR1 genetic variants were significantly associated with the greater increase in fasting glucose level in blood when patients were using olanzapine (P<0.001 and P=0.028, respectively). Our data indicate a possible influence of -759CT 5-HT2C and MDR1 G2677T and C3435T MDR1 genetic polymorphisms on the development of metabolic abnormalities among female patients treated with olanzapine/risperidone.

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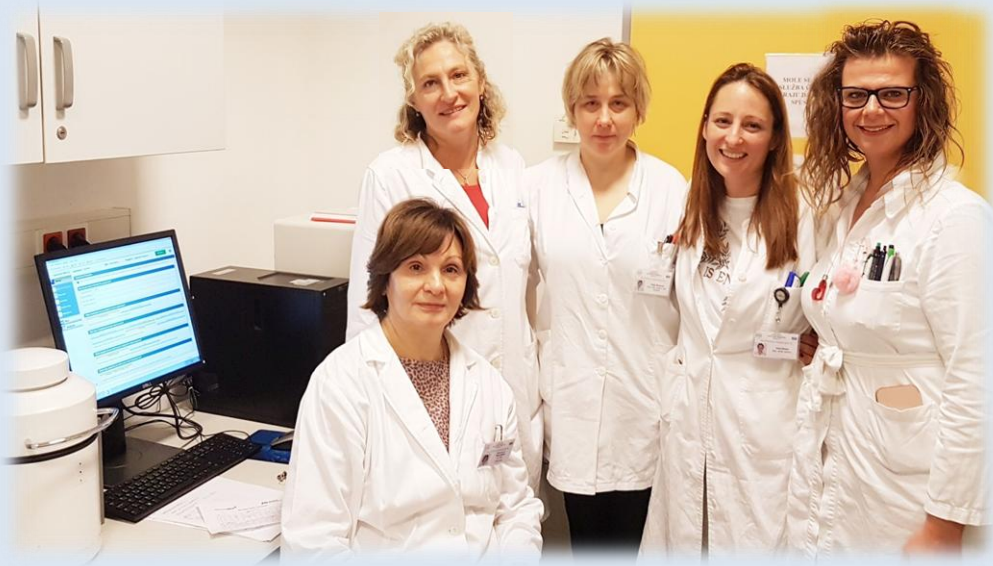

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