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Implementation of pharmacogenomic biomarkers in precision treatment

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Doctoral (Ph.D.) thesis booklet

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I. INTRODUCTION

Pharmacogenomics is a precision medicine tool to maximize treatment effectiveness while limit the drug toxicity by differentiating responders from non-responders to medications, based on an individual's genetic constitution. Despite the scientific results, regulators often encounter challenges by translating data from pharmacogenomic studies into clinically important and useful product information. As a result, although the scientific background of pharmacogenomic biomarkers broadens gradually, the clinical application pursues far behind.

In my thesis, first I assessed the applicability of the major pharmacogenomics biomarker information resource of practicing clinicians: the drug labels of the European Medicines Agency, the National Institute of Pharmacy and Nutrition in Hungary and the United States (US) Food and Drug Administration (FDA). During my work I investigated the potential role of pharmacogenomics in clinical decision-making. The conclusion of my first analysis was that the most dominant clinical field of pharmacogenomics biomarker implementation is oncology.

This led me to study more extensively cancer, specifically prostate cancer, the second most common malignancy in men and one among the leading causes of death among Western males. Evaluation of pharmacogenomic biomarkers in standard docetaxel chemotherapy of metastatic castration resistant prostate cancer was my second step to estimate the translational potential of pharmacogenomics biomarkers in practice. As new therapies for metastatic castration resistant prostate cancer are around the corner, I investigated potential candidate pharmacogenomic biomarkers of poly ADP-ribose polymerase inhibitor (PARPi) treatment of prostate cancer as third step.

Finally, I highlighted the innovative technique of “liquid biopsy” for medical practitioners in my local language, in Hungarian, to pinpoint a future method for biomarker detection and precision medicine in cancer management.

II. AIMS OF THE THESIS

This thesis aimed to examine how pharmacogenomic biomarkers are applied in clinical practice in context of drug labels and what are the current and future perspectives of pharmacogenomics in the specific field of prostate cancer. The following **research questions** have been formulated:

1. **What are the pharmacogenomic biomarker information differences between drug labels in the United States and Hungary?**

    1.a What is the current status of pharmacogenomic biomarker information present in Hungarian and US drug labels in 2019?

    1.b Can we observe any dynamic change in perspective of pharmacogenomic biomarkers in Hungarian and US drug labels?

    1.c Can we highlight any differences in the level of action of pharmacogenomic biomarkers between Hungary and US according to drug labels?

    1.d What are the obstacles of implementation pharmacogenomics into medical practice based on the information present in Hungarian drug labels?

    1.e What recommendations can be made to enhance the uptake of pharmacogenomic implementation by medical practitioners?

2. **Do pharmacogenomic biomarkers modulate docetaxel treatment of prostate cancer?**

    2.a Which germline genomic biomarkers play a potential role in docetaxel monotherapy and docetaxel combination treatment of prostate cancer based on research studies?

    2.b What types of genomic biomarkers are incorporated in docetaxel clinical trials for prostate cancer?

    2.c Are pharmacogenomic biomarkers included in treatment guidelines of prostate cancer?

    2.d What are the challenges and possible solutions of moving pharmacogenomic biomarkers into clinical setting of prostate cancer treatment?

3. **Which candidate genetic biomarkers are identified in PARPi clinical trials of prostate cancer?**

    3.a Are pharmacogenomic biomarkers applicable for future patient selection for targeted PARPi therapy in prostate cancer?

    3.b Do genomic biomarkers predict endpoints in prostate cancer clinical trials?

    3.c According to preliminary results of prostate cancer clinical trials which gene mutations affect these endpoints?

    3.d What are our future recommendations to improve pharmacogenomic biomarker transition into medical practice?

4. **What are the future perspectives of detection and analysis of circulating cell-free DNA in cancer patients' blood?**

III. OUTLINE OF THE THESIS

Paper 1 compared the US and the Hungarian pharmacogenomic biomarker information available in the drug labelling of the same active substance in 2019. Level of action of these pharmacogenomic information was evaluated in the two countries. Equal data collection performed in spring 2017 enabled to provide an overview about the dynamic change of the implementation of pharmacogenomic information in Hungarian drug labels. This research study highlights *available Hungarian resources for pharmacogenomic biomarker implementation in medical practice*, and pinpoints potential needs to enhance it. This paper answered the research question 1.

Paper 2 investigated research studies for germline genomic biomarkers affecting individual differences in docetaxel monotherapy and combination treatment of prostate cancer published between 2006 and 2018. In addition, clinical trials for docetaxel treatment in prostate cancer incorporating a range of genomic signatures have been identified both from ClinicalTrials.gov and from European Union's Clinical Trials Register database. The prostate cancer treatment guidelines of the European Association of Urology and the European Society for Medical Oncology were reviewed for recommendations on pharmacogenetic testing in connection with docetaxel treatment of prostate cancer. *Synthesis of knowledge about clinical translational potential of identified germline genomic biomarkers in docetaxel treatment of prostate cancer* has been done. This paper answered the research questions 2.

Paper 3 presented the results of a study where the publicly available database www.clinicaltrials.gov was mined for the registered clinical trials to *identify candidate genetic biomarkers in PARP inhibitor clinical trials for possible application in precision treatment selection of prostate cancer patients*. This paper answered research questions 3.

In **Paper 4,** we discussed the *potential role and future perspective of "liquid biopsy" in cancer patient management and treatme*nt in comparison to classic tissue biopsy. The paper was published *in Hungarian* in order to enhance medical practitioner knowledge on their local language. This paper answered research question 4.

The **Novel findings** section of the academic dissertation lists the results of the PhD candidate.

The **Summary of new observations and future perspective** section gives a recapitulative overview of the thesis, recommendations for clinical practice, research and regulatory agencies.

IV. NOVEL FINDINGS

Novel findings of Paper 1.:

Pharmacogenomic biomarker information differences between drug labels in the United States and Hungary: implementation from medical practitioner view

Varnai R, Szabo I, Tarlos G, Szentpeteri LJ, Sik A, Balogh S, Sipeky C.

Pharmacogenomics J. 2019 Dec 2.

- 264 drugs were identified in the US FDA Table of Pharmacogenomic Biomarkers in Drug Labeling. Out of these 264 active ingredients we were able to identify 195 (74%) through the website of the National Institute of Pharmacy and Nutrition in Hungary being available in Hungary.
- Among the 195 drugs 145 (75%) have pharmacogenomic information included in Hungarian drug labels. Pharmacogenomic information was partially present in drug label of 20 (10%), completely missing from drug label of 30 (15%) available active ingredients in Hungary compared to US FDA. These drugs without pharmacogenomic biomarker information in their label belong to diverse therapeutic areas like 23% to oncology, 23% to anesthesiology, 20% to infectious diseases, 7% to cardiology, 7% to inborn error, 7% to rheumatology, 3% to dermatology, 3% to hematology, 3% to psychiatry, 3% to pulmonology.
- The identified 195 drugs with pharmacogenomic data dispose 222 biomarkers in the Hungarian drug labels. In the Hungarian drug labels we identified information either on metabolizing enzymes (n=102, 46%), pharmacological targets (n=90, 41%) or other features (n=30, 13%).
- The most common biomarkers in Hungarian drug labels are the *CYP2D6* (n=40, 18%), the *CYP2C19* (n=18, 8%), the estrogen and progesterone hormone receptors (*ESR*, *PGR*, n=15, 6%), the *ERBB2* (n=12, 5%) and the *G6PD* (n=10, 4%).

- We also observed that none of the drug labels containing pharmacogenomic biomarker data have any pharmacogenomic evidence specifically for Hungarian population neither on clinical endpoints nor on pharmacokinetics.
- According to the Hungarian product summary, the aim of pharmacogenomic biomarker use can be the following: effects efficacy (n=84), indicates toxicity (n=67), belongs to the inclusion criteria (n=67), belongs to the exclusion criteria (n=24) because of elevated toxicity risk or effects dosage (n=18). Moreover, 53 biomarkers (24% of all) are involved in drug-drug interaction management as dose modification or elevated toxicity risk was connected to the presence of enzyme inhibitor/inductor irrespective of the pharmacogenomic background. Highly importantly, 8 biomarkers (4 %) are factual in point of dosing and formulate exact algorithm to manage gene-drug interaction.
- Out of the biomarkers available in US drug labels, 62 (22%) are missing from the Hungarian drug labels. Most of the missing pharmacogenomic biomarkers belong to the therapeutic area of oncology (42%), followed by anesthesiology (18%), infectious diseases (13%), hematology (8%); cardiology, dermatology, gastroenterology, inborn errors of metabolism, psychiatry, pulmonology, rheumatology represent minor proportions (less than 4% each).
- The level of action of pharmacogenomic biomarkers between Hungary and US was compared. Testing is required at 72 biomarkers (25 %) in Hungary, from which 66 (92%) belong to field of oncology. In US, in case of 79 (28%) biomarkers testing is obligatory before treatment. 4 (1%) biomarkers in Hungarian drug labels are ranked into testing recommended category, 6 (2%) biomarkers in US. Pharmacogenomic information is actionable at 95 (34%) biomarkers in Hungary, compared to 108 (38%) in US. Out of the actionable biomarkers in US, 14 (5%) biomarkers dispose exact dosing adjustment in PharmGKB recommendation, but only 8 (3%) of them are ranked into the same category in Hungary. The 6 (3%) remaining biomarkers predispose only actionable pharmacogenomic data without dosing info in Hungarian drug inserts. 51 (18%) biomarkers have informative pharmacogenomic data in Hungarian drug label, however in the US 77 (27%) biomarkers are counted into this category (p=0.009). Even from US FDA biomarkers 14 (5%) are missing from PharmGKB, which shows generally a rather delayed implementation of pharmacogenomic information. This was the case for 62 (22%) biomarkers for Hungarian drug labels.

- Talking about the pharmacogenomic level of action, out of the 62 missing biomarkers from Hungarian drug labels 7 (11%) belong to testing required category, 27 (44%) belong to actionable pharmacogenomic category and 21 (29%) belong to informative pharmacogenomic category according to PharmGKB.
- The partially missing biomarkers in Hungarian drug labels belong to 20 drugs, completely missing biomarkers to 30 drugs. Notably, after checking the level of action, in case of 7 from these 50 drugs biomarker testing is required before treatment according to PharmGKB. It is of utmost importance, that 6 from these 7 drugs belong to oncology medication and therefore define cancer treatment. On the other hand, in case of 9 oncology drugs the Hungarian drug labels are even stricter than the FDA recommendation and genetic testing is required before treatment.

Dynamic update:

- The number of drugs with pharmacogenomic information in the drug label has elevated in US with 57% vs in Hungary with 46% in last 26 months (May 2017 - July 2019).
- The percentage of missing pharmacogenomic data in Hungarian drug labels has doubled compared to US in last 26 months as a result of accelerated pharmacogenomic biomarker implementation in US FDA drug labeling.

Recommendation:

- None of the Hungarian product summaries did ever refer on an exact laboratory for biomarker testing. The information on lab test availability is based on clinics internal regulation and doctor's daily routine either on commercial test or on academic setting. More information for clinicians is needed about lab availability and test methodology.
- More factual, clear, clinically relevant pharmacogenomic information in Hungarian drug labels would reinforce implementation of pharmacogenetics.

Novel findings of Paper 2.:

Pharmacogenomic Biomarkers in Docetaxel Treatment of Prostate Cancer: From Discovery to Implementation

Varnai R, Koskinen LM, Mäntylä LE, Szabo I, FitzGerald LM, Sipeky C.

Genes (Basel). 2019 Aug 8;10(8). pii: E599.

Identified germline genomic biomarkers affecting individual treatment differences in docetaxel mono- and combination therapy of PC published between 2006 and 2018 are the following:

- *AAG, ABCB1, ABCB4, ABCB11, ABCC2, ABCC5, ABCC6, ABCG2, ATP7A, ATP8A2, CHST3, CYP1B1, CYP2D6, CYP3A4, CYP3A5, CYP4B1, CYP19A1, ESR1, GSTP1, MDR1, NAT2, PPAR-δ, SLCO1B3, SLC5A6, SLC10A2, SPG7, SULT1C2, VAC14* and *VEGF-A.*

Clinical translational potential of germline genomic biomarkers in docetaxel treatment of prostate cancer according to publications between 2006 and 2018 are the followings:

- Clinical response was influenced by *CYP1B1* (rs1056836), *ABCG2* (rs2231142), *CHST3* (rs4148950, rs1871450, rs4148945).
- Toxicity risk was increased by *CHST3* (rs4148950, rs1871450, rs4148945), *MDR1/ABCB1* (rs1045642, rs2032582) and *ABCC2* (rs12762549).
- Dosing was reduced by *ABCC2* (rs12762549).
- Overall survival was improved by *CYP1B1* (rs1056836), *ABCG2* (rs2231142) and *MDR1/ABCB1* (rs1045642, rs2032582).
- Progression free survival was enhanced by *CYP1B1* (rs1056836).

Results of main relevant clinical trials of docetaxel treatment in prostate cancer incorporating genomic signatures are the following:

- The aim of NCT00503984 was to determine whether azacitidine could reverse docetaxel resistance in metastatic castration resistant prostate cancer patients by decreasing methylation of the proapoptotic *GADD45A* gene. With regards to the second *terminated trial* (NCT01253642), only the frequency of *MAOA* (monoamine oxidase A) overexpression in tumors that have progressed during docetaxel treatment was reported. *MAOA* overexpression was observed in all investigated progressing tumors.
- The focus of several *ongoing clinical trials* was treatment response to docetaxel treatment in combination with emerging new medications in tumors harboring inactivating mutations in homologous recombination genes, including *BRCA1*, *BRCA2* and *ATM*.

Implementation of biomarkers in treatment guidelines:

- There are no predictive biomarkers to guide treatment decisions in prostate cancer according to European Association of Urology and European Society for Medical Oncology guidelines, even though there are some known prognostic biomarkers. On the other hand, the European Association of Urology guideline discussed multiple diagnostic or prognostic genetic biomarkers and their use in the clinic.
- Guidelines suggest that the first future application of pre-emptive genetic testing commences and involves the homologous recombination deficiency genes, since these patients might benefit from treatment with PARP inhibitors, but no definite recommendation has been made yet.

Novel findings of Paper 3.:

Precision treatment of prostate cancer: will genetic biomarker guided PARP inhibitors introduce a game-change?

Varnai R, Sipeky C.

Pharmacogenomics**.** *Under review*

- Application of DNA damage repair genes as predictive biomarkers in patient selection aids to design biomarker-driven targeted PARPi therapy in prostate cancer.
- Clinical trials with preliminary results showed that *BRCA2, BRCA1, ATM, BRIP1, FANCA* and *CDK12* mutations affect endpoints like prostate specific antigen response rate, radiographic response, prostate specific antigen progression free survival and overall survival in castration resistant prostate cancer.
- Beyond these mutations, ongoing trials explore the role of *ATR, BARD1, CHEK1, CHEK2, ERCC3, FAM175A, FANCD2, FANCL, GEN1, HDAC2, MLH1, MLH3, MRE11, MSH2, MSH6, NBN, PALB2, PMS2, PIK3CA, PPP2R2A, PTEN, RAD51, RAD51B, RAD51C, RAD51D* and *RAD54L* mutations in additional endpoints as disease-free state and dose limiting toxicity of prostate cancer patients.
- Most frequently investigated PARPi in prostate cancer was olaparib followed by rucaparib, niraparib, talazoparib and veliparib.

Novel findings of Paper 4.:

"Liquid Biopsy" in the service of clinical oncology: A dream or an emerging reality?

Várnai R, Sipeky C.

Orvosi Hetilap. 2019, 60. évfolyam, 7. szám, 279.

- Circulating tumor DNA analysis could be used for cancer treatment in *monitoring tumor progression,* in *detection of residual tumor* after surgical intervention and in *early detection of acquired resistance* during chemotherapy.
- Standardized circulating tumor DNA studies have to be evaluated and the results included in therapeutic protocols in order to support clinical decision-making.
- The reduction of DNA analysis costs and improved collaboration with bioinformaticians are crucial during adaption of “liquid biopsy” results for clinical implementation.

V. SUMMARY OF NEW OBSEVATIONS AND FUTURE PERSPECTIVES

Summary of pharmacogenomic biomarker information found in US FDA and Hungarian drug labels:

1. US drug labels displayed significantly more specific pharmacogenomic subtitles than similar Hungarian drug labels. Oncology is the most common therapeutic area with pharmacogenomic information in the drug label both in US and in Hungary. Regarding oncological drugs, Hungarian drug labels are stricter in genetic testing requirement than US labels.
2. Principal objective of pharmacogenomic biomarker use in Hungarian drug labels is the improvement of treatment efficacy. In Hungary, the most frequently tested biomarkers in oncology are pharmacological targets where molecular diagnostics is required for patient selection and genotype-directed precision therapy.
3. US FDA offers more relevant data about dose modifications than Hungarian drug labels.
4. Pharmacogenomic biomarker information is usually based on adult studies both in Hungarian and in US drug labels; pediatric patient groups are rarity.
5. Hungarian drug labels do not clearly categorize the pharmacogenomic biomarker into metabolizing enzymes, pharmacological targets and others. However, classification of biomarkers has to be included in Hungarian drug labels, in order to provide clear pharmacogenomic information and enable consequent implementation of genetic biomarkers in clinical setting.
6. Europe-wide database for pharmacogenomic laboratory test availability would enhance clinical implementation. In Hungary pharmacogenomic biomarker tests are provided by three university laboratories (Pécs, Budapest, Debrecen) and by industrial participant in limited sets. Laboratories are selected upon personal practice of the specific doctors now in Hungary. Ready-to-apply implementation platforms could enhance clinical output.
7. Forthcoming perspective is to encourage regulatory stakeholders to improve inclusion of pharmacogenomic biomarkers into Hungarian drug labels and consequently strengthen precision medicine in Hungary.

Summary of pharmacogenomic biomarkers in docetaxel treatment of prostate cancer:

1. More and more research studies propose to determine the association between genetic makeup of prostate cancer patients and docetaxel drug response, resistance and toxicity. Nevertheless, only a few considerable pharmacogenomic candidates moved forward to clinical validation.
2. To push biomarkers in direction of clinical implementation, prospective study designs, larger discovery cohorts and consecutive clinical validation in good quality randomized trials are needed.
3. Following genes seem to have translational potential in clinical response, toxicity, dosing, overall survival, progression free survival during docetaxel treatment of prostate cancer according to our results:
    a) *CYP1B1* gene encodes a member of the cytochrome P450 superfamily of enzymes that catalyze many reactions involved in drug metabolism. The *CYP1B1* rs1056836 gene variant seems to influence clinical response, overall survival, progression free survival during docetaxel treatment of prostate cancer.
    b) *ABCB1*, also known as multi-drug resistance protein 1 (*MDRP1*), is one of members in the superfamily of human adenosine triphosphate (ATP)-binding cassette (ABC) transporters that encode transporter and channel proteins that function as drug efflux pumps for xenobiotics compounds with broad substrate specificity and are involved in multidrug resistance. It is liable for decreased drug accumulation in multidrug-resistant cells and generally mediates the expansion of resistance to anticancer drugs. *MDR1/ABCB1* (rs1045642 and rs2032582) influences overall survival in docetaxel treatment of prostate cancer.
    c) *ABCG2* encodes an ATP-binding cassette (ABC) transporter. *ABCG2* rs2231142 gene variant affects clinical response and overall survival during docetaxel treatment of prostate cancer according to findings.
    d) *ABCC2* encodes another member of the superfamily of ABC transporters. These proteins are member of the MRP subfamily, and are involved in multi-drug resistance. Our result synthesis show, that *ABCC2* rs12762549 gene variant is associated with dose reduction and increased toxicity risk.

e) *CHST3* gene encodes an enzyme which catalyzes the sulfation of chondroitin, a proteoglycan found in the extracellular matrix and most cells which is involved in cell migration and differentiation [48,49]. *CHST3* (rs4148950, rs1871450 and rs4148945) influences clinical response and toxicity risk according the results.

Summary of genomic biomarkers guiding PARPi treatment in prostate cancer:

1. Next to *BRCA1/2,* deleterious mutations of other DNA damage repair genes could be associated with PARPi response according to preliminary results of clinical trials in prostate cancer. Especially *ATM* gene alterations may appear as second line predictive biomarkers of PARPi sensitivity.
2. Based on these results, *BRCA2, BRCA1, ATM, BRIP1, FANCA* and *CDK12* mutations are candidate genomic biomarkers for PARPi sensitivity in castration resistant prostate cancer.
3. Constructing a homologous recombination deficiency score is an eventual opportunity.
4. PARPis offer potential for a subgroup of DNA damage repair gene mutated metastatic castration resistant prostate cancer patients. More trials have to be directed to amplify available therapies with the number of actionable genes and genomic alterations available. Long-term follow up is essential according to the cytotoxic adverse effects of PARPis influencing normal healthy cells.
5. Validation of existing biomarkers have to be done for all prostate cancer subtypes, e.g. primary prostate cancer, locally advanced prostate cancer, aggressive type prostate cancer, castration resistant prostate cancer, metastatic castration resistant prostate cancer.

Summary of liquid biopsy perspectives:

1. Liquid biopsy is predicted to become a precision treatment tool in cancer patient management in the near future. Liquid biopsy based tests would be most feasible to detect DNA repair defects in circulating tumor DNA from whole blood in clinical setting.
2. Expanded multigene pharmacogenomic panels defined by drug efficacy, drug toxicity, clinical response or survival would improve the predictive capacity of pharmacogenomic biomarkers.
3. Continued pharmacogenomic education is needed for clinical oncologists about the benefits of using genetic polymorphisms as predictive biomarkers in clinical routine and research.
4. Practicing medical doctors have to be informed about pharmacogenomic biomarkers included in treatment guidelines, about available laboratory tests and about implementation tools to carry out pharmacogenomic in clinical setting.

VI. PUBLICATION LIST

Scientometrics (as of February 2020)

Number of publications: 24

Indexed in PubMed: 9 (2 review, 7 research articles)

Cumulative impact factor: 20,457

Impact factor related to the thesis: 7,398

Impact factor of a submitted paper under review related to the thesis: 2,265

Total citations: 38

H-index: 3

i10-index: 1

First author: 15 articles

Co-author: 9 articles

Q1 article: The Pharmacogenomics Journal

ORCID: https://orcid.org/0000-0001-8440-3955

Google Scholar: https://scholar.google.com/citations?view_op=list_works&hl=en&user=fYcDXLwAAAAJ

Articles related to the thesis

1. **Varnai R**, Szabo I, Tarlos G, Szentpeteri LJ, Sik A, Balogh S, Sipeky C. Pharmacogenomic biomarker information differences between drug labels in the United States and Hungary: implementation from medical practitioner view. **Pharmacogenomics J**. 2019 Dec 2. **IF:3.503**
2. **Varnai R**, Koskinen LM, Mäntylä LE, Szabo I, FitzGerald LM, Sipeky C. Pharmacogenomic Biomarkers in Docetaxel Treatment of Prostate Cancer: From Discovery to Implementation. **Genes (Basel)**. 2019 Aug 8;10(8). pii: E599. **IF: 3.331**
3. **Varnai R**, Sipeky C. Precision treatment of prostate cancer: will genetic biomarker guided PARP inhibitors introduce a game-change? **Pharmacogenomics.** *Under review* **IF: 2.265**
4. **Várnai R**, Sipeky C. „Folyékony biopszia" a klinikai onkológia szolgálatában: álom vagy küszöbönálló valóság? **Orvosi Hetilap**. 2019, 60. évfolyam, 7. szám, 279. **IF: 0.564**

Conference proceedings related to the thesis

(oral presentation, unless otherwise indicated)

1. **Várnai R,** Szentpéteri JL, Szabó I, Balogh S, Sipeky Cs. Precíziós orvoslás lehetősége farmakogenetiaki biomarkerek alkalmazásával Magyarországon. Családorvos Kutatók Országos Szervezetének XIX. Kongresszusa, Győr, 2020. február 27-29.
2. **Varnai R**, Koskinen LM, Mäntylä LE, Szabo I, FitzGerald LM, Sipeky C. Germline biomarkers guiding docetaxel treatment of prostate cancer. European Society of Pharmacogenomics and Personalised Therapy, (ESPT) Biennial meeting, Sevilla, 16-18. Oct 2019. Poster presentation
3. **Várnai R**. Farmakogenetikai vizsgálatok az alapellátásban. Baranya Megyei Háziorvosok XXX. Fóruma, Pécs, 2019. október 11-13.
4. **Várnai R,** Szentpéteri JL, Szabó I, Balogh S, Sipeky Cs. Elérhető farmakogenetikai vizsgálatok az alapellátásban Magyarországon. Családorvos Kutatók Országos Szervezetének XVIII. Kongresszusa, Debrecen, 2019. február 28 - március 2.
5. **Varnai R**, Szabo I, Szenpeteri LJ, Sík A, Balogh S, Sipeky C. Pharmacogenomic biomarker information in drug labels in Hungary compared to United States: do they support clinical practice? European Society of Personalized Therapy (ESPT) 4th Summer School, Genf, 24-28. September 2018. Poster presentation
6. **Varnai R**. Pre-emptive pharmacogenomic testing. Case study of a workflow from sample to result. European Society of Personalized Therapy (ESPT) 4th Summer School, Genf, 24-28. September 2018. Invited speaker of working group
7. **Várnai Réka**, Szentpéteri József, Szabó István, Sík Attila, Balogh Sándor, Sipeky Csilla. Farmakogenetikai információk szerepe (?) a háziorvoslás során hozott terápiás döntésekben. Családorvos Kutatók Országos Szervezetének XVI. Kongresszusa, Harkány, 2018. február 22-24.
8. **Varnai R,** LJ Szentpeteri LJ, Szabo I, Balogh S, Sik A, Sipeky C. Pharmacogenomic biomarker information in drug labels in Hungary: ready for personalized medicine? European Society of Pharmacogenomics and Personalised Therapy (ESPT) Biennial meeting, Catania, 4-7 Oct 2017. Poster presentation.

Award

- **Best article in topic of general medicine 2020.** Családorvos Kutatók Országos Szervezete: **Varnai R**, Szabo I, Tarlos G, Szentpeteri LJ, Sik A, Balogh S, Sipeky C. Pharmacogenomic biomarker information differences between drug labels in the United States and Hungary: implementation from medical practitioner view. Pharmacogenomics J. 2019 Dec 2.

Additional articles

1. Simonyi Gábor, Paksy András, **Várnai Réka**, Medvegy Mihály. Orális antikoagulánssal kezelt betegek terápiahűsége a mindennapokban. Orvosi Hetilap. *Accepted* **IF: 0.564**
2. Virtanen V, Paunu K, Ahlskog JK, **Varnai R**, Sipeky C, Sundvall M. PARP Inhibitors in Prostate Cancer—The Preclinical Rationale and Current Clinical Development. Genes (Basel). 2019 Jul 26;10(8). **IF: 3.331**
3. Csecsei P, **Varnai R**, Nagy L, Keki S, Molnar T, Illes Zs, Farkas N, Szapary L. L-arginine pathway metabolites can discriminate paroxysmal from permanent atrial fibrillation in acute ischemic stroke. Ideggyógyászati Szemle/Clinical Neuroscience. 2019, 72: 3-4 pp. 79-88. , 10 p. **IF:0.113**
4. **Varnai R**, Sipeky C, Nagy L, Balogh S, Melegh B. CYP2C9 and VKORC1 in therapeutic dosing and safety of acenocoumarol treatment: implication for clinical practice in Hungary. Environ Toxicol Pharmacol. 2017 Oct 8; 56:282-289. **IF: 2.776**
5. **Várnai Réka**, Sipeky Csilla, Balogh Sándor. Orális antikoaguláns terápia a családorvoslás mindennapjaiban. Granum: Orvosi Szakmai Folyóirat. 2016. XIX: 4 pp. 15-17., 3 p.
6. Sipeky C, Weber A, Melegh BI, Matyas P, Janicsek I, Szalai R, Szabo I, **Varnai R**, Tarlos G, Ganczer A, Melegh B. Interethnic variability of CYP4F2 (V433M) in admixed population of Roma and Hungarians. Environ Toxicol Pharmacol. 2015 Jul; 40(1):280-3. **IF: 1.77**
7. **Várnai R**, Nagy L. A terápiahűség növelésének lehetőségei kumarin kezelés során. Háziorvosi Továbbképző Szemle. 2015. 20. évf. 2. sz. 121-125.
8. Sipeky C, Matyas P, Melegh M, Janicsek I, Szalai R, Szabo I, **Varnai R**, Tarlos G, Ganczer A, Melegh B. Lower carrier rate of GJB2 W24X ancestral indian mutation in roma samples from hungary: implication for public health intervention Mol Biol Rep. 2014 Sep,41(9):6105-10. **IF: 2.024**
9. Rideg O, Haber A, Botz L, Szucs F, **Varnai R**, Miseta A, Kovacs LG. Pilot study for the characterization of pharmacogenetically relevant CYP2D6, CYP2C19 and ABCB1 gene polymorphisms in the Hungarian population. Cell Biochemistry and Function. 2011 29: 7 pp. 562-568., 7 p. **IF: 1.771**
10. Rideg O, Háber Á, **Várnai R**, Botz L, Kovács LG. Monitoring of CYP2D6 and CYP2C19 allele frequencies in the Hungarian population with Amplichip CYP450 Test. Laboratóriumi Medicina. 2010. 35: 3 pp. 163-163. 1 p.
11. Nagy L, **Várnai R**: Gyógyszer okozta szervi károsodások a mindennapok gyakorlatában. Háziorvosi Továbbképző Szemle 2009/14, 605-609.
12. Nagy L, **Várnai R**, Radnai B.: Nem kardiovaszkuláris gyógyszerek cardiovascularis mellékhatásai. Granum, 2008, XI. évf. 4.
13. **Várnai R**, Végh M, Pótó L, Nagy L. A per os antikoagulált betegek tudásszintje. Orvosi Hetilap, 2008/149: 43 pp. 2047-2051., 5 p.
14. **Várnai R**, Sipeky Cs, Melegh B, Végh M, Nagy L. Gyógyszermellékhatások szerepe a heveny felső gasztrointestinális vérzések kialakulásában. Magyar Belorvosi Archivum 2007, 60 : Suppl. 1 pp. 49-50. , 2 p.
15. **Varnai R**, Sipeky C, Nagy L, Melegh B. Hemorrhagic events; safety and genetic factors among orally anticoagulated patients – preliminary results. Zeitschrift für Gastroenterologie. 2009, 47 pp. 586-587. , 2 p. **IF: 0.31**

16. **Várnai R**, Végh M, Nagy L: Level of knowledge among patients treated with acenocoumarol in respect of adverse effects and interactions. Zeitschrift für Gastroenterologie 2008/5. **IF:0.40**
17. **Várnai R**, Sipeky Cs, Melegh B, Végh M, Nagy L: Gyógyszermellékhatások szerepe a heveny felső gasztrointesztinalis vérzések kialakulásában: előzetes adatok. Magyar Belorvosi Archívum 2007, LX. évf. 1.
18. **Várnai R.**, Végh M.: Az erektilis diszfunkció előfordulási gyakorisága és megítéltetése családorvosok és specialista szakorvosok között. Háziorvosi Továbbképző Szemle XI. évf. 7/2006.
19. **Várnai R.**, Végh M.,: A merevedési zavarral kapcsolatos nyitottság szakorvosok között. Magyar Belorvosi Archívum, LIX. évf. 2/2006.
20. **Várnai R.**, Végh M.: Are diabetologists, general practitioners, cardiologists, psychiatrists and urologists open-minded regarding erectile dysfunction in Hungary? The Aging Male 9.1/2006.
21. **Várnai R.,** Végh M.: Merevedési zavarok – Intimitás. Marosvásárhelyi Orvosi és Gyógyszerészeti Egyetem: Orvosi és Gyógyszerészeti Szemle 2005/51. 1. Különkiadás

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