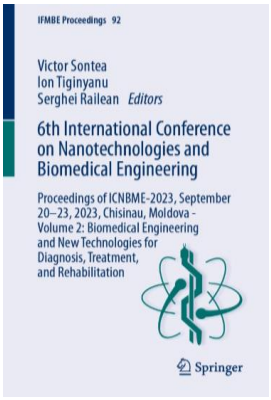


6th International Conference on Nanotechnologies and Biomedical Engineering
Proceedings of ICNBME-2023, September 20–23, 2023, Chisinau, Moldova
Volume 2: Biomedical Engineering and New Technologies for Diagnosis, Treatment, and Rehabilitation

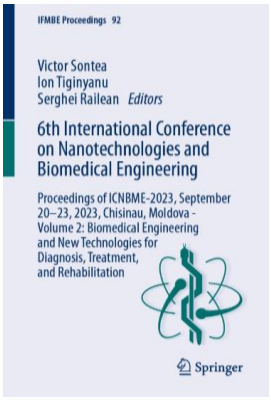
The Implementation of Personalized Medicine in the Republic of Moldova: Challenges and Opportunities in Cardiology

Alexei Levitchi, Daniela Galea-Abdusa, Victor Sontea, Ghenadie Curocichin

https://doi.org/10.1007/978-3-031-42782-4_31

Abstract

Implementing Personalized Medicine in the operational and functional context of a healthcare system is a complex challenge for most countries. Pharmacogenetics represents the application domain of individual genetic profile testing for drug prescription purposes. Health insurance systems are the mechanism by which drug treatment expenses can be covered. Doctors prescribe treatments based on a patient's clinical evaluation, according to the results of clinical studies that demonstrated the efficacy and low risk of adverse reactions of a particular drug tested on a clearly defined group of patients. Historically, most of these studies missed the assessment of individual capacity to metabolize drugs through xenobiotic transformation pathways. Proteins involved in transforming drug's chemical forms have yet to be well known, and studying their activity mechanisms is complex from a methodological point of view. Structural changes in the genes coding these proteins demonstrated an association with drug metabolism capacity, as revealed by GWAS studies for some populations. Inequality in sample collection and access limited the representativeness of many populations, with statistical significance levels being reached only for some of them. Validation of GWAS associations would allow their application in pharmacogenetic testing services in an evidence-based manner. This study represents a survey of the current opportunities to implement recommended genetic testing for the

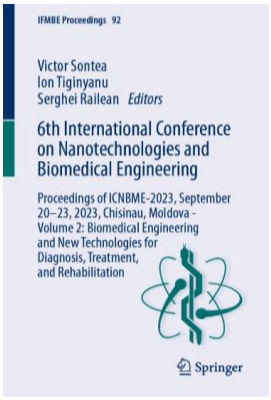


drugs used in CVD treatment compensated for the population by the National Health Insurance Company in the Republic of Moldova.

Keywords: personalized medicine, pharmacogenetics, cardiology, healthcare system

References

1. Strengthening pharmacovigilance to reduce adverse effects of medicines. MEMO/08/782. Brussels,December – November (2008). Accessed 27Apr 2023. http://europa.eu/rapid/pressrelease_MEMO-08-782_en.htm
2. Commission of the European Communities. Commission staff working document Annex 2 of the Report on the impact assessment of strengthening and rationalizing EU Pharmacovigilance. 2008. Brussels, 10.12.2008, SEC (2008) 2671 C6–0514–0515/08
3. Official journal of the European union, council conclusions on personalised medicine for patients, (2015/C 421/03)4
4. Guchelaar, H.-J.: Pharmacogenomics, a novel section in the European journal of human genetics. Eur. J. Hum. Genet. **26**, 1399–1400 (2018). https://doi.org/10.1038/s41431-018-0205-4
5. Schärfe, C.P.I., et al.: Genetic variation in human drug-related genes. Genome Med. **9**, 117 (2017). https://doi.org/10.1186/s13073-017-0502-5
6. Cecchin, E., et al.: Ubiquitous Pharmacogenomics (U-PGx): the time for implementation is now. An Horizon2020 Program to Drive Pharmacogenomics into Clinical Practice. Curr. Pharm. Biotechnol. **18**, 204–209 (2017). https://doi.org/10.2174/1389201018666170103103619
7. Relling, M.V., et al.: The clinical pharmacogenetics implementation consortium: 10 years later. Clin. Pharmacol. Ther. **107**, 171–175 (2020). https://doi.org/10.1002/cpt.1651
8. Swen, J.J., et al.: Pharmacogenetics: from bench to byte–an update of guidelines. Clin. Pharmacol. Ther. **89**, 662–673 (2011). https://doi.org/10.1038/clpt.2011.34
9. Whirl-Carrillo, M., et al.: Pharmacogenomics knowledge for personalized medicine. Clin. Pharmacol. Ther. **92**, 414–417 (2012). https://doi.org/10.1038/clpt.2012.96
10. Bank, P.C.D., Swen, J.J.,Guchelaar,H.-J.: Implementation of Pharmacogenomics in Everyday Clinical Settings. In: Pharmacogenetics, pp. 219–246. Elsevier (2018). https://doi.org/10.1016/bs.apha.2018.04.003



11. Mortalitatea general˘a dup˘a principalele clase ale cauzelor de deces în anul (2020). https://statistica.gov.md/ro/mortalitatea-generala-dupa-principalele-clase-ale-cauzelor-de-deces-in-9460_49930.html

12. Billings, J., et al.: The impact of real-world cardiovascular-related pharmacogenetic testing in an insured population. Int. J. Clin. Pract. **72**, e13088 (2018). https://doi.org/10.1111/ijcp.13088

13. van der Laan, S.W., et al.: From lipid locus to drug target through human genomics. Cardiovasc. Res. **114**, 1258–1270 (2018). https://doi.org/10.1093/cvr/cvy120

14. Gyoerffi, M.: European Union. Personalised Medicine - Current Status. Internal Ref: ENVI 2017–15, PE 614.190. ISBN: 978–92–846–2348–8

15. TheEP PerMed: the strategic, research&innovation agenda (SRIA) for personalised medicine (2023)

16. Kimpton, J.E., et al.: Longitudinal exposure of English primary care patients to pharmacogenomic drugs: an analysis to inform design of pre-emptive pharmacogenomic testing. Br. J. Clin. Pharmacol. **85**, 2734–2746 (2019). https://doi.org/10.1111/bcp.14100

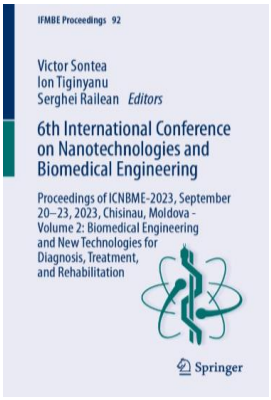
17. Reisberg, S., et al.: Translating genotype data of 44,000 biobank participants into clinical pharmacogenetic recommendations: challenges and solutions. Genet. Med. **21**, 1345–1354 (2019). https://doi.org/10.1038/s41436-018-0337-5

18. VanDriest, S.L., et al.:Clinically actionable genotypes among10,000 patientswith preemptive pharmacogenomic testing. Clin. Pharmacol. Ther. **95**, 423–431 (2014). https://doi.org/10.1038/clpt.2013.229

19. Jithesh, P.V., et al.: A population study of clinically actionable genetic variation affecting drug response from the Middle East. NPJ GenomicMed. **7**, 10 (2022). https://doi.org/10.1038/s41525-022-00281-5

20. Mostafa, S., et al.: An analysis of allele, genotype and phenotype frequencies, actionable pharmacogenomic (PGx) variants and phenoconversion in 5408 Australian patients genotyped for CYP2D6, CYP2C19, CYP2C9 and VKORC1 genes. J. Neural Transm. **126**, 5–18 (2019). https://doi.org/10.1007/s00702-018-1922-0

21. Ji, Y., et al.: Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized



CYP2D6 genotyping cascade. J. Mol. Diagn. JMD. **18**, 438–445 (2016). https://doi.org/10.1016/j.jmoldx.2016.01.003

22. Turner, R.M., et al.: Multimorbidity, polypharmacy, and drug-drug-gene interactions following a non-ST elevation acute coronary syndrome: analysis of a multicentre observational study. BMC Med. **18**, 367 (2020). https://doi.org/10.1186/s12916-020-01827-z

23. Alshabeeb,M.A., et al.: Pharmacogenes that demonstrate high association evidence according to CPIC, DPWG, and PharmGKB. Front. Med. **9**, 1001876 (2022). https://doi.org/10.3389/fmed.2022.1001876

24. Cohn, I., et al.: Genome sequencing as a platform for pharmacogenetic genotyping: a pediatric cohort study. NPJ Genomic Med. **2**, 1–8 (2017). https://doi.org/10.1038/s41525-017-0021-8

25. Asiimwe, I.G., Pirmohamed, M.: Drug–Drug–Gene interactions in cardiovascular medicine. Pharmacogenomics Pers.Med. **15**, 879–911 (2022). https://doi.org/10.2147/PGPM.S338601

26. Patrick, A.R., Avorn, J., Choudhry, N.K.: Cost-Effectiveness of genotype-guided warfarin dosing for patients with atrial fibrillation. Circ. Cardiovasc. Qual. Outcomes. **2**, 429–436 (2009). https://doi.org/10.1161/CIRCOUTCOMES.108.808592

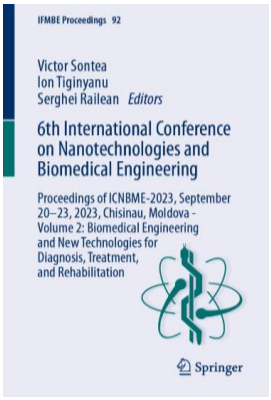
27. Verhoef, T.I., et al.: Cost-effectiveness of pharmacogenetic-guided dosing of warfarin in the United Kingdom and Sweden. Pharmacogenomics J. **16**, 478–484 (2016). https://doi.org/10.1038/tpj.2016.41

28. Brixner, D., et al.: The effect of pharmacogenetic profilingwith a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. J. Med. Econ. **19**, 213–228 (2016). https://doi.org/10.3111/13696998.2015.1110160

29. Cavallari, L.H., et al.: Multi-site investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. JACC Cardiovasc. Interv. **11**, 181–191 (2018). https://doi.org/10.1016/j.jcin.2017.07.022

30. Scott, S.A., et al.: Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450–2C19 (CYP2C19) genotype and clopidogrel therapy. Clin. Pharmacol. Ther. **90**, 328–332 (2011). https://doi.org/10.1038/clpt.2011.132

31. Rettie,A.E.,Tai, G.:The pharmocogenomics ofwarfarin: closing in on personalized medicine. Mol. Interv. **6**, 223–227 (2006). https://doi.org/10.1124/mi.6.4.8



32. Kamali, F.: Genetic influences on the response to warfarin. Curr. Opin. Hematol. **13**, 357–361 (2006). https://doi.org/10.1097/01.moh.0000239708.70792.4f

33. Mitropoulou, C., et al.: Economic evaluation of pharmacogenomic-guided warfarin treatment for elderly Croatian atrial fibrillation patients with ischemic stroke. Pharmacogenomics **16**, 137–148 (2015). https://doi.org/10.2217/pgs.14.167

34. Formanowicz, D., et al.:Control of cholesterolmetabolism using a systems approach.Biology. **11**, 430 (2022). https://doi.org/10.3390/biology11030430

35. Zhou, Y., Lauschke, V.M.: Population pharmacogenomics: an update on ethnogeographicdifferences and opportunities for precision public health.Hum. Genet. **141**, 1113–1136 (2022). https://doi.org/10.1007/s00439-021-02385-x

36. Malsagova, K.A., et al.: Pharmacogenetic testing: a tool for personalized drug therapy optimization. Pharmaceutics. **12**, 1240 (2020). https://doi.org/10.3390/pharmaceutics12121240

37. Barker, C.I.S., et al.: Pharmacogenomic testing in paediatrics: clinical implementation strategies. Br. J. Clin. Pharmacol. **88**, 4297–4310 (2022). https://doi.org/10.1111/bcp.15181

38. Shahandeh, A., et al.: Advantages of array-based technologies for pre-emptive pharmacogenomics testing. Microarrays Basel Switz. **5**, 12 (2016). https://doi.org/10.3390/microarrays5020012

39. van der Wouden, et al.: Implementing pharmacogenomics in Europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. Clin. Pharmacol. Ther. **101**, 341–358 (2017). https://doi.org/10.1002/cpt.602