Pharmacogenomics of Metformin- A Way to Personalised medicine

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ABSTRACT

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. There are atleast 10 different drug classes for the treatment of Type 2 diabetes mellitus (T2DM) but metformin is recommended as the initial medication for treatment of T2DM. Inter-individual variability in response and few clinical or biomarker predictors of response reduces its optimal use. Personalized medicine promises a path for individually optimized treatment, but realizing this promise will require a more comprehensive characterization of disease and drug response. As per American Medical Association, pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, decrease the chance for adverse drug events, and increase the effectiveness of drugs. There are variety of genes controlling metformin transport in the body, for eg- SLC22A1, SLC22A2, SLC22A3, SLC22A4 etc. The purpose of this review article is to explain in brief pharmacogenomics of metformin and its application and practical hurdles in its translation.

Key words: Metformin, Pharmacogenomics, Personalised medicine, Diabetes mellitus, SLC2A4.

Citation: Vakharia MP, Zad VR, Mankar NN, Wadivkar PP, Shah KU. Pharmacogenomics of Metformin- A Way to Personalised medicine. Int J Pharmacol and Clin Sci. 2016;5(2):55-61.

INTRODUCTION

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease.[1,2] The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India.[3] There are atleast 10 different drug classes for the treatment of Type 2 diabetes mellitus (T2DM) but metformin is recommended as the initial medication for treatment of T2DM. The incidence of T2DM and its costs to the health care system continues to rise.[4] Despite its widespread use, there is considerable variation in response to metformin, with about 35% of patients failing to achieve initial glycemic control on metformin monotherapy.[5-7] Inter-individual variability in response and few clinical or biomarker predictors of response reduces its optimal use. Personalized medicine promises a path for individually optimized treatment, but realizing this promise will require a more comprehensive characterization of disease and drug response.[8] Understanding of the genetic determinants of metformin response may lead to the identification and development of effective drug targets for diabetes treatment. Pharmacogenomics as the most widely applied discovery-based approach to date has opened up the opportunity to understand the genetics underlying the inter individual variation in metformin responses so that

Received : 16-04-2016 **Revised :** 20-05-2016;
Accepted : 28-06-2016
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Conflict of interest: Nil ; **Source of support :** Nil

DOI : 10.5530/ijpcs.5.2.4

the clinicians can prescribe treatment to the individuals for better efficacy and safety, metformin for those predicted to respond and alternative therapies for those predicted to be non-responders or who are at increased risk for adverse side effects.[4]

OBJECTIVE

To review the research on metformin pharmacogenomics and its application in improving patient outcomes.

METHODS

Relevant articles were identified in MEDLINE, PUBMED using MeSH terms Metformin, Pharmacogenomics and Personalized medicine.

Why to study pharmacogenomics of metformin?

As per American Medical Association, pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, decrease the chance for adverse drug events, and increase the effectiveness of drugs. Currently, much of the research in the field of pharmacogenomics is focused on genes encoding either metabolic enzymes that can alter a drug's activity or defective structural proteins that result in increased susceptibility to disease. Variability in drug response, with respect to efficacy, tolerability, and safety, is a major issue for most drugs. Diabetes, like other complex diseases, is the product of many genes interacting with environmental factors. These interactions affect many pathways and even whole signaling networks in ways that cause disease. The promise of personalized medicine is that this complexity can be teased apart to refine the definition of disease, identify disease subtypes, and ultimately define biomarkers capable of discriminating between the patients most likely to benefit from a specific treatment and those unlikely to respond or likely to experience adverse events.[9]

Anticipated benefits of pharmacogenomics

More powerful medicines: Pharmaceutical companies will be able to produce therapies more targeted to specific diseases, maximizing therapeutic effects while decreasing damage to nearby healthy cells.

Better, safer drugs the first time: Recovery time will go down and safety will go up as the likelihood of adverse reactions goes down or is eliminated altogether.

More accurate methods of determining appropriate drug dosages: Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics- how well the body processes the medicine and the time it takes to metabolize it.

Economic issues from molecule to marketplace Pharmacogenomics eventually can lead to an overall decrease in the cost of health care because of decreases in:

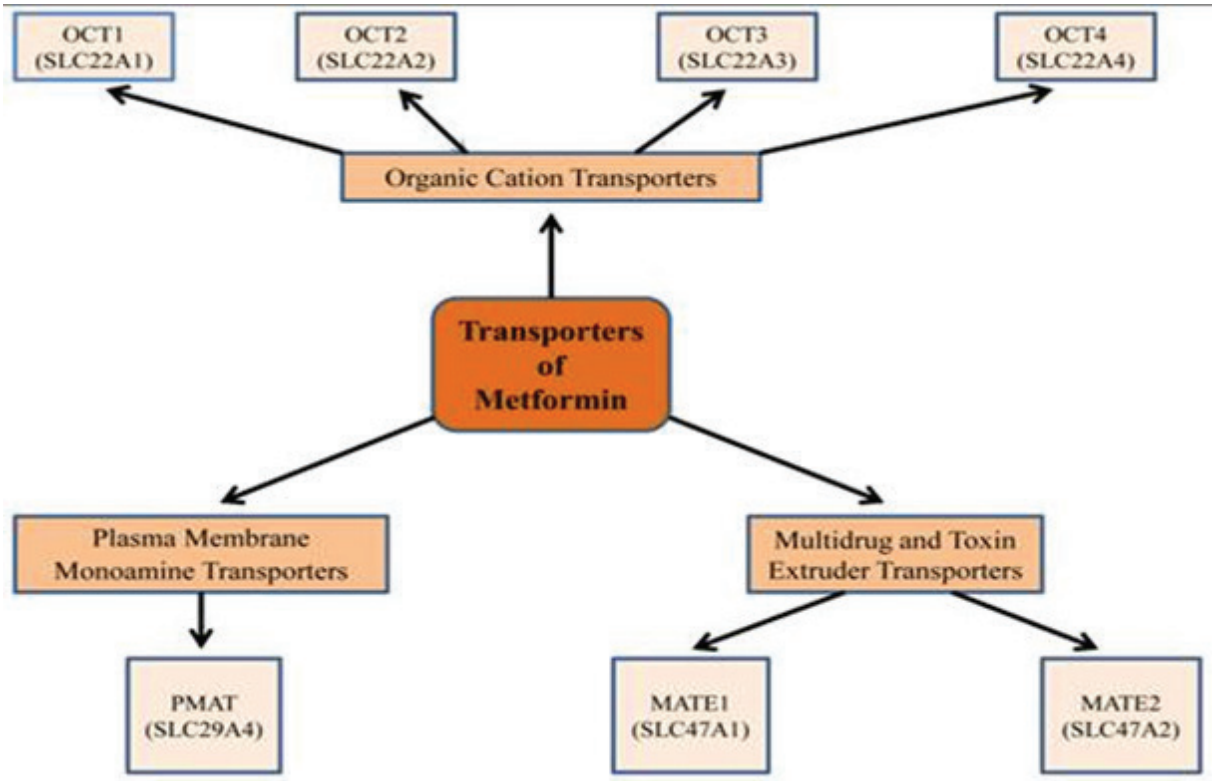
- the number of adverse drug reactions,
- the number of failed drug trials,
- the time it takes to get a drug approved,
- the length of time patients are on medication,
- the number of medications patients must take to find an effective therapy, and
- the effects of a disease on the body (through early detection).

Metformin

Metformin and phenformin were discovered in the 1920s in a search for guanidine containing compounds with antidiabetic activities. Phenformin was withdrawn in the 1970s due to its potential to induce lactic acidosis. Metformin was approved for use in the United States in 1995.[6] A major action of metformin is suppression of hepatic glucose production. In addition to its efficacy in lowering glucose levels, metformin has the clinical advantages of inducing mild weight reduction and only a minimal risk of hypoglycemia, but it has some gastrointestinal side effects and, very rarely, causes lactic acidosis.

Metformin Pharmacokinetics

Metformin is not metabolized in the liver or kidney but rather excreted intact in the urine. Briefly, metformin appears to be taken up from the intestine by plasma monoamine transporter (PMAT; SLC29A4) and organic cation transporter 3 (OCT3; SLC22A3), transported into the bloodstream by OCT1 (SLC22A1), and taken up into target tissues by other members of the OCT family. (Figure 1). Metformin appears to be actively removed from target tissues by multi-antimicrobial extrusion protein 1 (MATE1; SLC47A1) and then passed from proximal tubule cells into the urine via MATE1 and MATE2 (SLC47A2). About 50% of an orally administered dose is absorbed into the systemic circulation. The half-life of the drug measured in plasma is between 4 and 8 h in individuals without renal dysfunction, and the clearance exceeds glomerular filtration rate, consistent with tubular secretion (Figure 2).



Transporters of Metformin.

Figure 1: Various transporters with corresponding genes involved in metformin absorption, hepatic uptake and excretion.

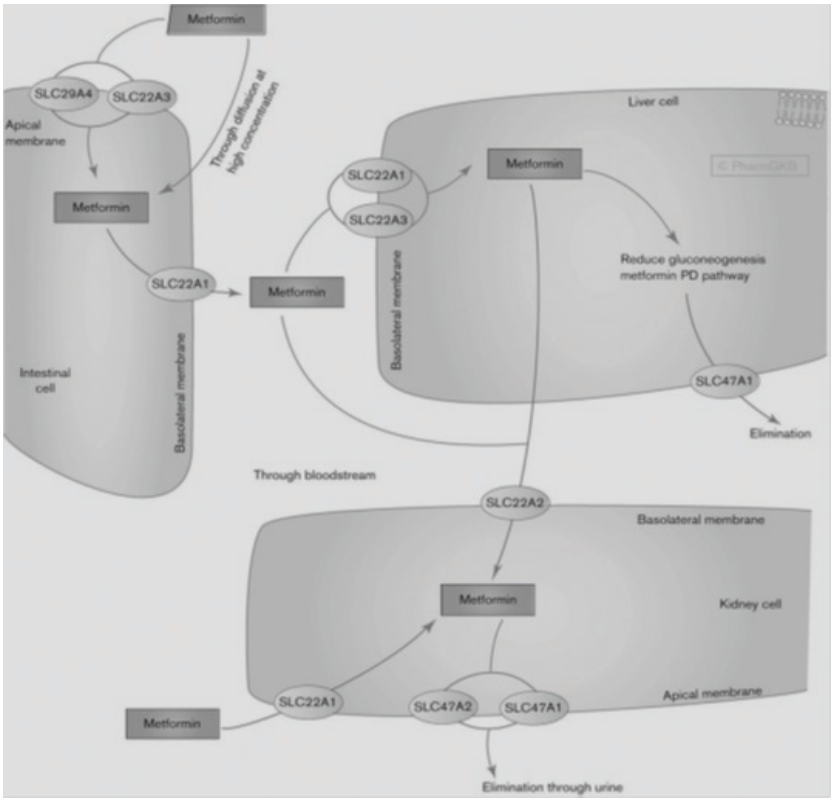


Figure 2: Illustration showing transport of metformin from the gastrointestinal tract into the bloodstream, disposition into the liver, and secretion intact by the kidneys.[4]

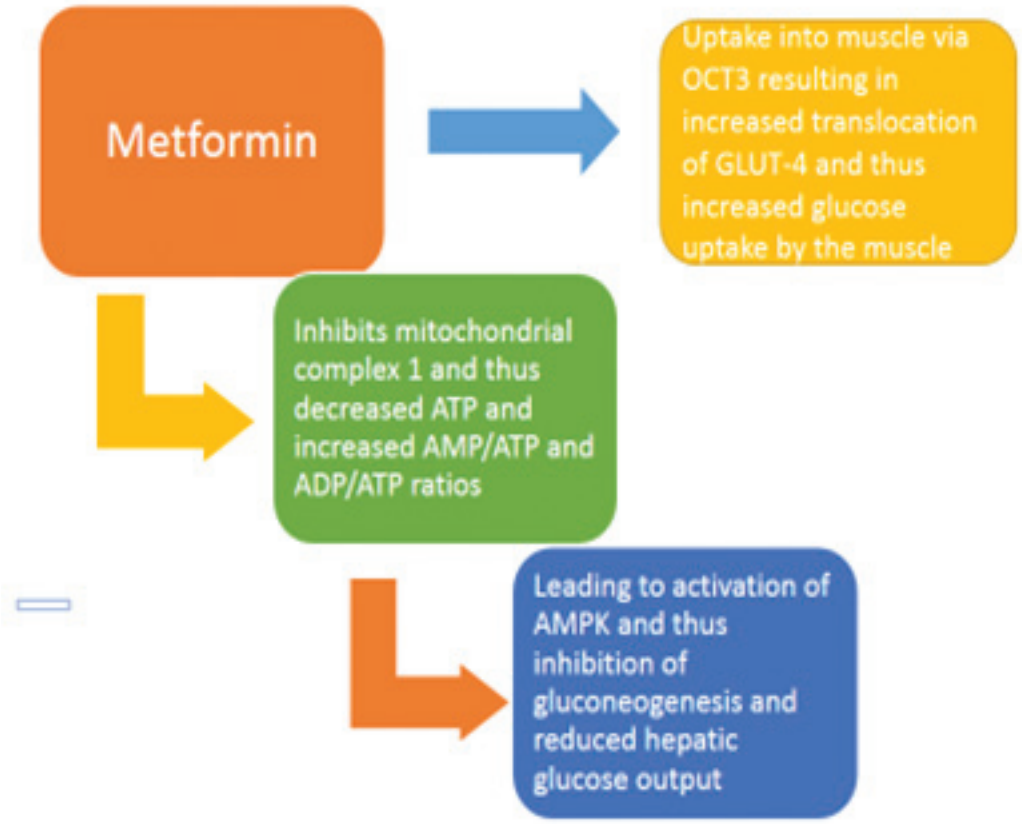


Figure 3: Metformin Pharmacodynamics.

Variable response of metformin observed in various studies

Treatment Options for T2D in Adolescents and Youth[15]

In this study, adolescents appear to have high metformin failure rates when compared with similar intervention studies in adults. In addition, metformin monotherapy was more effective in Hispanics and non-Hispanic whites compared with non- Hispanic blacks. Taken together, these observations suggest there are significant gaps in our ability to select the most efficacious medication for individuals in some of the populations at the highest risk for T2D and its complications.

U.K. Diabetes Audit and Research in Tayside Scotland Study[16]

This study utilized the extensive electronic health record (EHR) system in Scotland, allowing the inclusion of 10,000 patients with diabetes and 8,000 control patients who had electronic health information. Of these, 3,200 metformin-treated patients underwent genotyping on a genome-wide single nucleotide polymorphism (SNP) chip or other arrays. Of note in this study was a considerable interindividual variation in metformin response, with some patients experiencing lowering of their percent A1C by close to 4%, while other patients exhibited no change or substantial increases in A1C after treatment. the strongest association with metformin response was found in a variant lying in a region on chromosome 11 containing seven genes, and has been replicated in additional meta-analyses (30,31). One potential candidate gene is the ataxia telangiectasia mutated gene (ATM), which encodes a serine/threonine kinase and may regulate enzymes involved in response to metformin. Although the investigators presented *in vitro* data showing ATM was involved in metformin's activation of AMPK in cell cultures, it has since been shown that the small molecule used to inhibit ATM in the *in vitro* cellular studies is actually an inhibitor of OCT1. As OCT1 is the major metformin transporter in the liver and in hepatic cell lines, the ATM inhibitor reduced metformin's activation

of ATM by preventing the drug from getting into the cells, greatly complicating the interpretation of the experiments.

Table 1: List of the known metformin pharmacokinetic genes and select pharmacodynamic genes for which there are associations with a clinical response of metformin

Gene	Note	Summary of effects	References
SLC22A1	OCT1	Decreased function alleles linked to reduction in metformin effect on initial A1C and lipid responses; incidence of diabetes	10
SLC22A2	OCT2	No associations with clinical outcomes, only changes in metformin PK reported	4
SLC22A3	OCT3	No associations with clinical outcomes, only changes in metformin PK reported	4
SLC47A1	MATE1	Increased metformin response to A1C; incidence of diabetes	10, 11
SLC47A2	MATE2	Poorer response to metformin; changes in A1C	11
SRR	Serine racemase	Associated with changes in FPG, PPG, and CHO	12
ATM	Serine/threonine kinase	Metformin treatment success by A1C	13,14
LKB/STK11	AMPK upstream kinase	Decrease in ovulation in women with polycystic ovarian syndrome on metformin; incidenceof diabetes	10

Future work will be necessary to fully explore the genic and intergenic regions around this locus and to understand differences between cohorts where this pharmacogenomic association with metformin response has not been replicated.

DPP and DPP Outcomes Study[17]

Variability in the ability of metformin to prevent diabetes was seen, with it being less effective in the older participants but more effective in the more obese participants. An intriguing mechanistic insight comes from the observation that metformin-associated weight loss can account for a substantial fraction of the benefit in obese subjects. The reduction in diabetes incidence persisted for at least 10 years of follow-up, even after metformin washout, and may be partly due to some persistent weight loss. Metformin was effective in decreasing diabetes incidence in women with a history of gestational diabetes mellitus. Metformin also improved HDL levels and LDL particle size, but had insignificant effects on blood pressure or triglyceride levels.

A candidate gene analysis has been reported with several variants in genes showing a nominally significant effect on the response of metformin . Of particular note were variants in genes in the AMPK pathway, supporting the relevance of that pathway in metformin's clinical action. Variants in the genes encoding the transporters OCT1 and MATE1 were also nominally associated with metformin response. Shu *et al*.[18] showed reduced metformin uptake into transfected cells expressing naturally occurring amino acid altering variants of OCT1. Translating these *in vitro* studies to the clinic, the investigators also showed that healthy volunteers heterozygous for these OCT1 variants had reduced response to the drug and altered pharmacokinetics (Table 1).

Metformin Pharmacodynamics

Its primary action is through its insulin-sensitizing effect in the liver resulting in a decrease of hepatic glucose output, mainly through inhibition of gluconeogenesis.[4] In isolated hepatocytes, metformin action requires the enzyme AMP-activated protein kinase (AMPK), a master sensor, integrator, and regulator of cell and body energy homeostasis. AMPKs are activated by an increased AMP/ATP ratio and by upstream kinases (e.g., LKB1). AMPK activation affects many pathways, generally causing

conservation and generation of ATP. How metformin activates AMPK, such as through an upstream kinase or by altering the cell's energy status and thus AMP/ATP ratio, is not yet clear (Figure 3).[8]

Metformin can be taken up by the muscle via OCT3 where it results in increased translocation of the facilitated glucose transporter 4 (SLC2A4) and a concomitant increase in glucose uptake by the muscle. Additionally, metformin inhibits lipogenesis and promotes free fatty acid oxidation.

Table 1 shows list of known metformin pharmacokinetic genes and select pharmacodynamic genes for which there are associations with clinical response of metformin.

Practical hurdles of pharmacogenomics today

There appears to be a strong desire among patients and physicians to use pharmacogenomic guidance to help select medications and dose. However, uptake in the real world is slow. In a recent survey of U.S. physicians, only 13% of physicians reported having ordered or recommended a pharmacogenetic test in the previous 6 months, and only 29% of physicians reported that they received graduate or postgraduate training in pharmacogenomics.[19] There is a lack of prospective randomized clinical trials to address whether pharmacogenomic testing improves patient outcomes, what the optimal clinical algorithm for its application is, and whether it is cost-effective. The logistics of genetic testing can also be a hurdle in terms of turnaround time, point-of-care relative to patient encounters, and the availability of Clinical Laboratory Improvement Amendments– certified laboratories to perform such testing.[4] One of the most transforming efforts to advance implementation of pharmacogenomics in patient care to date has been the National Institutes of Health Pharmacogenomic Research Network–supported Clinical Pharmacogenomics Implementation Consortium (CPIC).[20] This consortium has coauthored a number of publications that inform how to use genetic information in selecting drugs and doses that are beginning to be implemented across diverse health care systems.[21]

CONCLUSION

Although significant progress has been made in T2DM pharmacogenetics, the field is still in its infancy. Much work is needed in performing comprehensive assessments of genetic variation across well phenotyped, which can typically be attained only in the setting of international collaborations. There is lack of prospective randomized clinical trials to address whether pharmacogenomic testing improves patient outcomes, what the optimal clinical algorithm for its application is, and whether it is cost-effective. We do hope the use of individual genetic information can help guide intelligent medication choices in the future: public and private funding bodies should support clinical trials with large sample sizes in an effort to show improved outcomes and cost effectiveness before this promise can be delivered to clinical practice.

ACKNOWLEDGEMENT

NIL.

REFERENCES

1. Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007;55(Y):323-4.
2. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J. 2013;6(10):524-31.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(3):1047-53.
4. Aaron C. Pawlyk, Kathleen M. Giacomini, Catherine McKeon, *et al*. Metformin Pharmacogenomics: Current Status and Future Directions. Diabetes. 2014;63(8):2590-9.
5. Hermann LS. Biguanides and sulfonylureas as combination therapy in NIDDM. Diabetes Care. 1990;13(Suppl. 3):37-41.
6. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996;334:574-9.
7. Kahn SE, Haffner SM, Heise MA, *et al*.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427-43
8. Marc L. Reitman, Eric E. Schadt. Pharmacogenetics of metformin response: a step in the path toward personalized medicine. The Journal of Clinical Investigation. 2007;117(5):1226-9.
9. Available from http://www.ama-assn.org/ama/pub/physician as accessed on 12/03/2016
10. Jablonski KA, McAteer JB, de Bakker PI, *et al*.; Diabetes Prevention Program Research Group. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. Diabetes. 2010;59(10):2672-81.
11. Stocker SL, Morrissey KM, Yee SW, *et al*. The effect of novel promoter variants in MATE1 and MATE2 on the pharmacokinetics and pharmacodynamics of metformin. Clin Pharmacol Ther. 2013;93(2):186-94.
12. Dong M, Gong ZC, Dai XP, *et al*. Serine racemase rs391300 G/A polymorphism influences the therapeutic efficacy of metformin in Chinese patients with diabetes mellitus type 2. Clin Exp Pharmacol Physiol. 2011;38(12):824-9.
13. Van Leeuwen N, Nijpels G, Becker ML, *et al*. A gene variant near ATM is significantly associated with metformin treatment response in type 2 diabetes: a replication and meta-analysis of five cohorts. Diabetologia. 2012;55(7):1971-7.

14. Tkac I. Replication of the association of gene variant near ATM and response to metformin. Pharmacogenomics. 2012;13(12):1331-2.
15. Zeitler P, Hirst K, Pyle L, *et al*.; TODAY Study Group. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012;366:2247-56.
16. Morris AD, Boyle DI, MacAlpine R, et al.; DARTS/MEMO Collaboration. The Diabetes Audit and Research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. BMJ. 1997;315:524-8.
17. The Diabetes Prevention Program Research Group. Ten-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677-86.
18. Shu Y, Sheardown SA, Brown C, et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. J Clin Invest. 2007;117:1422-31.
19. Stanek EJ, Sanders CL, Taber KA, et al. Adoption of pharmacogenomics testing by US physicians: results of a nationwide survey. Clin Pharmacol Ther. 2012;91(3):450-8.
20. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther. 2011;89(3):464-7.
21. Shuldiner AR, Relling MV, Peterson JF, et al.; Pharmacogenomics Research Network Translational Pharmacogenetics Program Group. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. Clin Pharmacol Ther. 2013;94(2):207-10.