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# Metformin Pharmacogenomics: Current Status and Future Directions



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The incidence of type 2 diabetes (T2D) and its costs to the health care system continue to rise. Despite the availability of at least 10 drug classes for the treatment of T2D, metformin remains the most widely used first-line pharmacotherapy for its treatment; however, marked interindividual variability in response and few clinical or biomarker predictors of response reduce its optimal use. As clinical care moves toward precision medicine, a variety of broad discovery-based “omics” approaches will be required. Technical innovation, decreasing sequencing cost, and routine sample storage and processing has made pharmacogenomics the most widely applied discovery-based approach to date. This opens up the opportunity to understand the genetics underlying the interindividual variation in metformin responses in order for clinicians to prescribe specific treatments to given individuals for better efficacy and safety: metformin for those predicted to respond and alternative therapies for those predicted to be nonresponders or who are at increased risk for adverse side effects. Furthermore, understanding of the genetic determinants of metformin response may lead to the identification of novel targets and development of more effective agents for diabetes treatment. The goals of this workshop sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases were to review the state of research on metformin pharmacogenomics, discuss the scientific and clinical hurdles to furthering our knowledge of the variability in patient responses to metformin, and consider how to

effectively use this increased understanding to improve patient outcomes.

Metformin is recommended as the initial medication for treatment of type 2 diabetes (T2D) (1–4). Additionally, it has been demonstrated to prevent or delay the onset of T2D in those with prediabetes (5,6). The rising incidence of diabetes, including in children, makes it particularly relevant to both the clinical and research communities today. 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 (7–10). Over time, many patients become less responsive to metformin, which may be due to a variety of causes (8,11). Metformin acts as an insulin sensitizer, and although widely regarded as efficacious and safe, the precise mechanisms by which it enhances insulin sensitivity are still elusive (8,12). Emerging evidence reviewed at this workshop indicates that genetic variation may be one of the important determinants of an individual’s responses to metformin. A variety of approaches can be used to understand metformin’s pharmacologic action and interindividual differences in response, with pharmacogenomics providing a unique and powerful clinically relevant tool. An enhanced understanding of genes and pathways that determine response to metformin also has the potential to reveal new drug targets for the treatment of diabetes.

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The overall objective of the “Workshop on Metformin Pharmacogenomics” sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases was to assess the state of the field of metformin pharmacogenomics and identify key gaps and opportunities in scientific knowledge to further our understanding of metformin’s clinical responses. Ultimately, this increased knowledge base around the causative factors underlying interindividual response to metformin will enable improved, tailored treatment for diabetes (“precision medicine”), and provide a more solid bedrock for continued study of nongenomic factors contributing to the understanding of metformin’s responses.

## USES AND RESPONSES OF METFORMIN

### Metformin Background

#### *Efficacy and Side Effects*

Metformin is the only currently approved member of the class of drugs known as the biguanides (8). It is available in standard and extended-release formulations and it is widely accepted that its maximum effect is exhibited at 2,000 mg/day, although earlier studies indicate that some individual patients may respond better to higher doses (13). The most frequent side effects associated with metformin are gastrointestinal, with over half of patients being able to tolerate the maximum daily dose; however, it has been reported that ~5% of patients are unable to tolerate any dose (8). The rare event of lactic acidosis with metformin occurs approximately three times in 100,000 patient-years and appears to be linked to renal insufficiency, which by impairing metformin clearance results in extremely high plasma levels of the drug (8). Thus, metformin is contraindicated in patients with substantial renal dysfunction. Anemia due to vitamin B<sub>12</sub> malabsorption and deficiency is also noted as a rare event (8).

The first and best known large trial demonstrating the efficacy of metformin is the UK Prospective Diabetes Study (UKPDS) (14). UKPDS demonstrated that, particularly in obese subjects, there was an average reduction in percent glycosylated hemoglobin (A1C) of 1%. Metformin was shown not to result in weight gain, and in fact, many participants lost a modest amount of weight on metformin. Importantly, overall risk of diabetes-related death and other negative end points were reduced. Reduction in cardiovascular-related deaths in patients on metformin in comparison with patients on other antidiabetes agents with similar levels of glycemic control was confirmed in meta-analyses. It was also observed that metformin’s effects on A1C waned over time (11). The international A Diabetes Outcome Progression Trial (ADOPT) also demonstrated the efficacy and concomitant deterioration of metformin efficacy over time (9). These findings suggest that distinct mechanisms may underlie early and late failure of metformin efficacy, both of which are likely to be multifactorial.

In comparison with other oral agents, metformin is regarded as the best initial choice, resulting in a decrease in A1C better or equipotent to sulfonylureas but without a risk of hypoglycemia (2). The position statement of the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) in 2012 recommends metformin as the foundation treatment for T2D along with diet and exercise (3), as also embraced by the American Association of Clinical Endocrinologists (15).

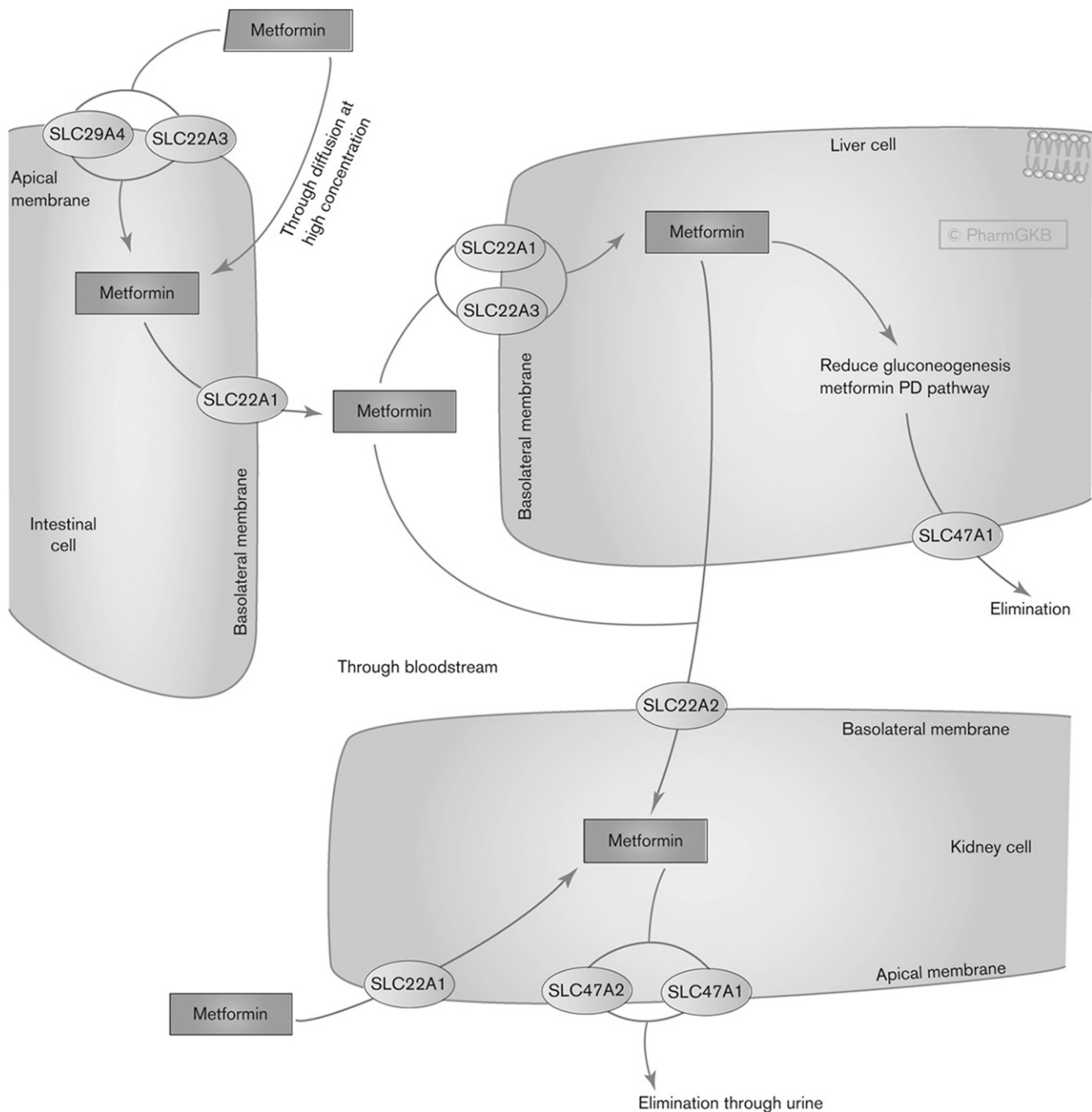
#### *Metformin Pharmacokinetics*

Metformin is not metabolized in the liver or kidney but rather excreted intact in the urine (Fig. 1). The transport of metformin has been recently reviewed elsewhere (12,16). 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. 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.

#### *Metformin Pharmacodynamics*

It is now believed that metformin may exert its therapeutic effects in people with T2D through pleiotropic mechanisms and physiologic pathways (12). 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 (Fig. 2). This action is believed to occur via alterations in cellular energetics that involve inhibition of mitochondrial complex 1, resulting in lower ATP levels and consequently higher ratios of AMP/ATP and ADP/ATP. The increased levels of AMP and ADP result in activation of AMP-activated protein kinase (AMPK), which for many years has been thought to be responsible for the beneficial effects of metformin on hepatic glucose output. Recent studies in conditional *Ampk* knockout mice challenge the notion that AMPK activation is required for the effects of metformin on glycemia (17), although genetic variants in AMPK subunits in humans have now been associated with metformin clinical responses at the nominal significance level (18). A recent report suggests that metformin interferes with glucagon action, resulting in a decrease of cAMP leading to reductions in hepatic glucose output (19).

Beyond its primary role in decreasing hepatic glucose output, metformin may exert additional beneficial effects in people with T2D. Metformin can be taken up by the muscle via OCT3 where it results in increased translocation

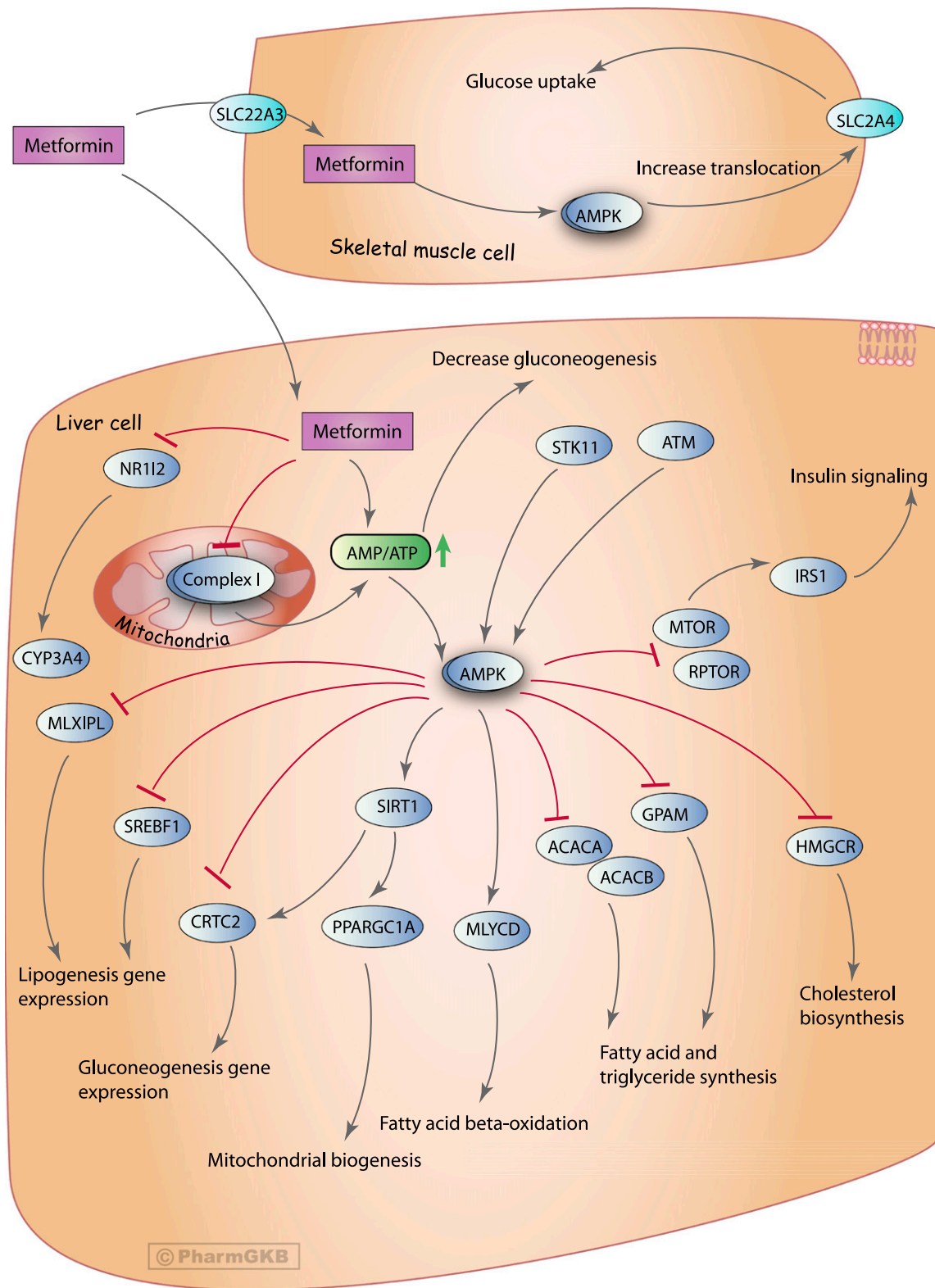


**Figure 1**—Illustration showing transport of metformin from the gastrointestinal tract into the bloodstream, disposition into the liver, and secretion intact by the kidneys. Additional information is described in the text. This figure is copyrighted by Pharmacogenomics Knowledge Base (PharmGKB) and used by permission of PharmGKB and Stanford University. An interactive version is available online at <http://www.pharmgkb.org/pathway/PA165948259>. PD, pharmacodynamic.

of the facilitated glucose transporter 4 (*SLC2A4*) and a concomitant increase in glucose uptake by the muscle (20). Additionally, metformin inhibits lipogenesis and promotes free fatty acid oxidation. In the Diabetes Prevention Program (DPP), metformin reduced C-reactive protein and other inflammatory biomarkers (21). Recent evidence has also shown that metformin has anti-inflammatory effects on vascular walls and improves lipid metabolism in macrophages (22). This provides possible mechanisms for a

reduction in the cardiovascular complications of diabetes. Metformin may also increase gut glucose utilization (23). Overall, the drug appears to have pleiotropic effects on both glycemic control and other end points relevant to the treatment of T2D and its complications.

The exact contributions and interactions of these mechanisms have been and are likely to continue to be a matter of much debate. It is hoped that gaining an understanding of the pharmacogenomics of metformin



**Figure 2**—Illustration depicting pharmacodynamic effects of metformin. The primary action of metformin is to decrease gluconeogenesis in the liver, and this is believed to occur through inhibition of mitochondrial complex 1, resulting in changes in the ratio of AMP/ATP and ADP/ATP and the concomitant activation of AMPK. Activation of AMPK results in the activation or inhibition of numerous downstream pathways affecting liver metabolism, including gluconeogenesis. AMPK activity may also be modulated by metformin through kinases such as ATM or STK11. Metformin may also alter muscle glucose utilization through activation of muscle cell AMPK. This figure is copyrighted by Pharmacogenomics Knowledge Base (PharmGKB) and used by permission of PharmGKB and Stanford University. An interactive version is available online at <http://www.pharmgkb.org/pathway/PA165948566>.

responses will help elucidate the mechanisms responsible for metformin's clinical actions. Furthermore, the pleiotropic effects of metformin provide a fertile ground for both explanations of its interindividual variations in response and the elucidation of new drug targets.

#### **Understanding Individual Responses to Metformin**

While numerous clinical trials and studies demonstrating interindividual variation in metformin are present in the literature, many with associated genetics studies, we focus the discussion below on four studies presented at the workshop that represent the diverse approaches to studying metformin's variable responses.

#### **Treatment Options for T2D in Adolescents and Youth**

Prevalence of T2D among different racial and ethnic groups in the U.S. varies. For example, individuals of African or American Indian/Alaska Native ancestries have a high prevalence of the disease (12.9% and 16.3%, respectively), whereas European and Asian Americans have lower prevalence rates (8.2% and 9.1%, respectively) (24). Furthermore, with the epidemic of childhood obesity in the U.S., there has been a marked increase in T2D at younger ages (25). In the recent Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, adolescents appear to have high metformin failure rates when compared with similar intervention studies in adults (26). In addition, metformin monotherapy was more effective in Hispanics and non-Hispanic whites compared with non-Hispanic blacks (26). 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**

The first and only genome-wide association study (GWAS) conducted in metformin-treated patients thus far is the Diabetes Audit and Research in Tayside Scotland (DARTS) study (27). 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 (28). Surprisingly, publication of detailed analyses of interindividual variation of metformin and other antidiabetes agents appears to be uncommon; the increased inclusion of data in this manner in publications may help increase our understanding of the magnitude and causes of interindividual variation in drug response. The broader availability of such data will be integral to

setting reasonable expectations for improving individual drug response using precision medicine guidance for metformin.

From the GWAS in the Genetics of DARTS (GoDARTS) study (29), 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 (29), 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 (32,33). 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. 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**

The largest diabetes prevention trial conducted is the DPP and its extension into the DPP Outcomes Study (DPPOS) (5,34). Variability in the ability of metformin to prevent diabetes was seen, with it being less effective in the older participants (35) but more effective in the more obese participants (36). 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 (6). Metformin was effective in decreasing diabetes incidence in women with a history of gestational diabetes mellitus (37). Metformin also improved HDL levels and LDL particle size, but had insignificant effects on blood pressure or triglyceride levels (38).

A candidate gene analysis has been reported with several variants in genes showing a nominally significant effect on the response of metformin (18). Of particular note were variants in genes in the AMPK pathway, supporting the relevance of that pathway in metformin's clinical action. Genes encoding subunits of the sulfonylurea receptor were associated with the metformin response, an intriguing observation given the data from the UKPDS showing an increase in diabetes-related mortality when metformin was added to sulfonylureas. Variants in the genes encoding the transporters OCT1 and MATE1 were also nominally associated with metformin response. The variant associated with *ATM* in the GoDARTS study was not replicated in this cohort (39), highlighting the differences

between the two studies (e.g., cohort ethnicity, prospective trial vs. retrospective EHR study, prevention vs. treatment) and the need for meta-analyses to account for such differences.

### Pharmacogenomics Guided by Pharmacokinetics

Another approach taken to understand the pharmacogenomics of metformin has focused on looking at the coupled pharmacokinetics and pharmacodynamics of metformin in individuals from varied ethnic groups with known variations in transporter genes. Shu et al. (40) 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 (40,41). In *SLC47A1* (MATE1), a common variant in the promoter region (−66T>C; rs2252281) present with minor allele frequency (MAF) >25% was identified. The −66C allele disrupts an enhancer element and creates a repressor binding site, presumably resulting in decreased MATE1 expression and higher metformin levels in hepatocytes. The C allele of rs2252281 was associated with significantly better glucose-lowering response to metformin during an oral glucose tolerance test (42). Variants in *SLC47A2* (MATE2), particularly a promoter region variant rs12943590, have also been associated with altered glucose-lowering response to metformin in humans (42,43).

### Variability and Commonalities in Approaches to Metformin Pharmacogenomics

The described studies highlight human pharmacogenomics approaches using both long-term clinical studies of metformin as well as short-term studies focusing on pharmacokinetics and acute drug responses. Preliminary results suggest that metformin response genes occur in pathways including AMPK or novel pathways such as ATM. A well-powered multicohort meta-analysis should be able to confirm as well as identify additional clinically relevant pathways and genetic variants. Numerous differences among the described studies highlight both the power of multiple approaches as well as the confounding variables that must be explored as the field moves forward, such as ethnicity, study design, patient age, environmental factors, and clinical end points.

In summary, there have been few genes associated with glycemic control by metformin (Table 1), and the most reproducible associations have been in known transporter genes. Many questions remain regarding the genetic architecture of the metformin response, and more studies are required to understand the genetic factors that underlie variation in the transport of and the response to metformin. It also must be recognized that nongenetic factors contribute to response to metformin and that broader system biology approaches will be required to model the combined effects of multiple gene variants in the same or converging pathways and their interaction with nongenetic factors.

**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
<i>SLC22A1</i>	OCT1	Decreased function alleles linked to reduction in metformin effect on initial A1C and lipid responses; incidence of diabetes	18, 40, 41, 52–56
<i>SLC22A2</i>	OCT2	No associations with clinical outcomes, only changes in metformin PK reported	
<i>SLC22A3</i>	OCT3	No associations with clinical outcomes, only changes in metformin PK reported	
<i>SLC47A1</i>	MATE1	Increased metformin response to A1C; incidence of diabetes	18, 42, 52
<i>SLC47A2</i>	MATE2	Poorer response to metformin; changes in A1C	42, 43
<i>SRR</i>	Serine racemase	Associated with changes in FPG, PPG, and CHO	57
<i>ATM</i>	Serine/threonine kinase; SNP in large LD block with 6 other genes	Metformin treatment success by A1C	29–31
<i>LKB/STK11</i>	AMPK upstream kinase	Decrease in ovulation in women with polycystic ovarian syndrome on metformin; incidence of diabetes	18, 58
<i>PRKAA1, PRKAA2, PRKAB2</i>	AMPK subunits	Incidence of diabetes	18
<i>ABCC8-KCNJ11</i>	Subunit of $\beta$ -cell potassium channel	Incidence of diabetes	18

CHO, cholesterol; FPG, fasting plasma glucose; LD, linkage disequilibrium; PK, pharmacokinetics; PPG, postprandial plasma glucose.

## FUTURE LANDSCAPE OF METFORMIN PHARMACOGENOMICS AND PRECISION MEDICINE

The afternoon component of the workshop consisted of breakout sessions addressing various unresolved issues and future models for understanding better metformin pharmacogenomics and its role in precision antidiabetes therapy. At the conclusion of the meeting, the key points from each breakout session were presented and followed by a discussion, which are summarized here.

### Defining and Deepening Phenotypes

Clinical trials of metformin interventions performed to date have focused on a diverse array of efficacy end points. Other studies have attempted to extract end points from EHRs of patients in the course of their routine medical care. The diversity of study designs, interventions, and phenotype definitions present challenges when trying to perform pooled or meta-analysis of data sets. The generation of agreed-upon common core phenotyping that can be applied across future metformin studies, either controlled clinical trials or data collection by health care systems, will allow for pooling of data sets to obtain larger sample sizes with increased power and/or data sets for replication of promising findings across studies.

The costs associated with deep phenotyping and broad discovery-based “omics” technologies currently prevent their implementation in very large cohorts. The careful selection of patients with extreme responses to metformin would make these studies more feasible (e.g., strong vs. weak responders, the metformin intolerant). Alternatively, more detailed characterization of patients with particular genotypes could serve to identify mechanisms for SNPs discovered in GWAS. Given our current understanding of the importance of metformin’s transport to drug response, inclusion based upon specific transporter genotypes can be considered as a way to use emerging pharmacogenomics knowledge to select patients for more comprehensive multi-omics studies leading to broader precision medicine guidance. Additional measurements could include deep phenotyping of the metabolic status of patients on metformin as well as discovery-based metabolomic and proteomics approaches to identify nongenomic markers of metformin response. Comprehensive pharmacokinetic–pharmacodynamic models incorporating multiple types of data should be developed to optimize selection of metformin dosing regimens.

### Primary Versus Secondary Failure of Metformin

Another interesting question in the field addresses the differences between primary and secondary failure of metformin. Frequently, patients who do not show an initial robust response to metformin undergo slow dose escalation and addition of a cotherapy without understanding if metformin is having a significant effect. Additionally, for patients whose glycemia was controlled by metformin for a time and then required cotherapy, it is not known if metformin stopped working for some reason

or if the disease progressed beyond the point where metformin alone could be efficacious. These issues will require an increased understanding of the intersection of the natural history of T2D and the responses of metformin through a variety of genomic and nongenomic approaches as well as mechanistic insights into interactions of metformin with other diabetes medications when given in combination.

The academic community, pharmaceutical industry, payers, providers, patients, and public health sector all have a strong interest in understanding metformin’s mechanism and the potential for developing precision prescription guidance for antidiabetes treatment. The long-term goal of developing a thorough evidence base to support the precision prescribing of metformin, and other antidiabetes agents, will likely require the cooperation of these different parties. Pharmacogenomic studies are often underpowered because of difficulties in accruing patients and samples. This is particularly true for studies of individuals from under-represented racial and ethnic groups. The field has advanced enormously by the formation of consortia (44). A “metformin consortium” with multiple research groups contributing expertise and samples from various ethnic groups will greatly advance the field.

Another avenue for conducting studies on metformin-treated patients comes from networks of health care systems such as the Electronic Medical Records and Genomics (eMERGE) Network, which is a national consortium of biobanks linked to the EHRs from over a dozen academic-affiliated and private health care systems with the long-term goal of applying genetics in a clinical setting (45). The outpatient pharmacy systems in the U.S. also have extensive records, with the single prescription benefit manager Express Scripts, for example, covering over 100 million people (46).

The pharmaceutical industry has an interest in understanding the precision prescribing of metformin as a means to identify novel pathways through which metformin functions that can be leveraged for new therapies as well as to identify patients likely to benefit from cotreatment with another antidiabetes agent. Thus, some members of the pharmaceutical industry may be willing to contribute stored samples from metformin comparator arms from diabetes clinical trials.

## CLINICAL TRANSLATION OF FINDINGS

### Need and Outcomes of Metformin Pharmacogenomics in Precision Medicine

The interindividual variation in metformin ranging from improvement in percent A1C up to 4% to worsening of A1C following treatment (28) and estimates of a close to 35% failure rate for metformin monotherapy (7–10) clearly indicate that there are aspects of individuals that lead them to respond differently to metformin. The overall challenge to the field of precision medicine as it relates to antidiabetes treatment is to identify the individualized factors that can lead to improved glycemic control and ultimately quality and length of life. There are numerous

scientific and practical hurdles, many of which have been touched upon here, that limit the conceptual delivery of idealized precision medicine for diabetes treatment. Although it is likely that precision medicine will ultimately involve metabolomic panels, genomic information, imaging results, etc., the potential to use genetic information that may be incorporated into a patient's health record is a compelling, practical, and first step forward. Furthermore, the use of pharmacogenetic information will provide one key level of patient stratification in which to study further the individualized response of medications.

The interactions of the natural disease progression of T2D and comorbid conditions in patients with the pleiotropic pharmacodynamics and complex pharmacokinetics of metformin present a complex, multifaceted clinically relevant puzzle that changes over time and with drug treatment. These interactions also emphasize the potential difference between pharmacokinetic and short-term drug response studies compared with long-term outcomes in clinical trials. One possibility to meld these two aspects is to conduct longitudinal pharmacokinetic and response studies within longer clinical trials. Nevertheless, progress is being made to identify genetic polymorphisms that influence both short-term effects and long-term clinical outcomes associated with metformin treatment (Table 1), including analyses incorporating polymorphisms at multiple transporter alleles (42). Additional pharmacogenomics and metabolic studies to understand metformin's response are under way and the knowledge from extant and ongoing studies will be used to guide future multi-omics studies of metformin's response. The refinement of the knowledge base underlying potential precision medicine approaches for metformin is likely to be an iterative process by which existing knowledge is used to identify subpopulations for further elucidation of markers associated with interindividual response to metformin. For example, identification of clinical responders and nonresponders to metformin who have variants associated with robust metformin transport to target tissues may help identify pharmacodynamic markers that could not be identified in the population at large.

For all its potential, it remains impossible to predict this early in the field of antidiabetes precision medicine what exactly the impact may be to individuals and how much interindividual variation can be explained by genetics alone. The greatest individual benefit may be in identifying those who are predisposed to be intolerant or poor responders to metformin so that an alternative primary therapy or initial cotherapy can be considered. While it can be argued that individuals who do not tolerate metformin or for whom it is not efficacious will eventually achieve a treatment paradigm effective for them, in practice this can take several months during which the individual is unnecessarily receiving suboptimal treatment and perhaps becoming frustrated with a process perceived to be "trial and error." Interestingly, there have been recent reports that pharmacogenomic testing alone can increase

medicine compliance (47,48), suggesting that the incorporation of testing in prescribing decisions may provide validity or reemphasis of medical importance to patients. It is even harder to predict how this will translate to population health, but it may be that optimizing each individual's glycemic control will result in significant long-term health benefits at the population level.

### **Practical Hurdles to Translational of Pharmacogenomics**

One of the ultimate goals of studying pharmacogenomics in precision medicine for metformin is to realize guidance that can improve the prescribing of metformin and choice of cotherapy. 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 (49).

Lessons on why pharmacogenomics guidance may not be used can be drawn from existing pharmacogenetic-guided prescribing for other medications. For example, why are not many cardiologists performing *CYP2C19* genetic testing to individualize antiplatelet therapy? Foremost, 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. Reimbursement at multiple levels also needs to be addressed in terms of testing services and implementation of results (e.g., prescribing physician, pharmacogenomic counselors, etc.).

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) (50). 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 (51). This implementation process is identifying barriers and developing and disseminating a toolbox of real-world solutions to enhance pharmacogenomics-guided prescribing. Such efforts and tools will ensure that once the pharmacogenomics determinants of metformin are established, they can be readily implemented in clinical practice.

### **CONCLUSIONS**

In this article, the workshop summarized the importance and challenges in determining the pharmacogenomic and



other drivers for interindividual variation in metformin's responses. Not only will the exploration of the clinical omics of metformin lead to improved prescribing, but it will assist in clarifying the pleiotropic mechanisms via which metformin functions. One clear message from the discussions at the workshop was the importance of concerted efforts to use data from existing studies and to introduce standard paradigms to enhance the integration of future studies. Although not discussed in this article due to space limitations, the emerging potentials of metformin for therapeutic treatment outside of glycemic control were also highlighted, in particular for the prevention of cancer and treatment of fertility issues in polycystic ovarian syndrome.

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## References

- Holman R. Metformin as first choice in oral diabetes treatment: the UKPDS experience. *Journ Annu Diabetol Hotel Dieu* 2007;13–20
- Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193–203
- Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012;35:1364–1379
- American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care* 2014;37(Suppl. 1):S14–S80
- 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;374:1677–1686
- Knowler WC, Fowler WC, Hamman RF, et al.; Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012;35:731–737
- Hermann LS. Biguanides and sulfonylureas as combination therapy in NIDDM. *Diabetes Care* 1990;13(Suppl. 3):37–41
- Bailey CJ, Turner RC. Metformin. *N Engl J Med* 1996;334:574–579
- Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355:2427–2443
- Cook MN, Gorman CJ, Stein PP, Alexander CM. Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care. *Diabet Med* 2007;24:350–358
- U.K. Prospective Diabetes Study Group. U.K. Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44:1249–1258
- Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics* 2012;22:820–827
- Garber AJ, Duncan TG, Goodman AM, Mills DJ, Rohlf JL. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med* 1997;103:491–497
- Turner RC. The U.K. Prospective Diabetes Study. A review. *Diabetes Care* 1998;21(Suppl. 3):C35–C38
- Rodbard HW, Jellinger PS, Davidson JA, et al. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr Pract* 2009;15:540–559
- Zolk O. Disposition of metformin: variability due to polymorphisms of organic cation transporters. *Ann Med* 2012;44:119–129
- Foretz M, Hébrard S, Leclerc J, et al. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. *J Clin Invest* 2010;120:2355–2369
- 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;59:2672–2681
- Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. *Nature* 2013;494:256–260
- Chen L, Pawlikowski B, Schlessinger A, et al. Role of organic cation transporter 3 (SLC22A3) and its missense variants in the pharmacologic action of metformin. *Pharmacogenet Genomics* 2010;20:687–699
- Haffner S, Temprosa M, Crandall J, et al.; Diabetes Prevention Program Research Group. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes* 2005;54:1566–1572
- Anfossi G, Russo I, Bonomo K, Trovati M. The cardiovascular effects of metformin: further reasons to consider an old drug as a cornerstone in the therapy of type 2 diabetes mellitus. *Curr Vasc Pharmacol* 2010;8:327–337
- Mithieux G, Rajas F, Zitoun C. Glucose utilization is suppressed in the gut of insulin-resistant high fat-fed rats and is restored by metformin. *Biochem Pharmacol* 2006;72:1757–1762
- Schiller JS, Lucas JW, Ward BW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview Survey, 2010. *Vital Health Stat* 10;2012:1–207
- Santoro N. Childhood obesity and type 2 diabetes: the frightening epidemic. *World J Pediatr* 2013;9:101–102
- 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;366:2247–2256
- 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;315:524–528
- Rena G, Pearson ER, Sakamoto K. Molecular action and pharmacogenetics of metformin: current understanding of an old drug. *Diabetes Management* 2012;2:439–452
- Zhou K, Bellenguez C, Spencer CC, et al.; GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group; Wellcome Trust Case Control Consortium 2;

- MAGIC Investigators. Common variants near *ATM* are associated with glycemic response to metformin in type 2 diabetes. *Nat Genet* 2011;43:117–120
30. 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;55:1971–1977
31. Tkáč I. Replication of the association of gene variant near *ATM* and response to metformin. *Pharmacogenomics* 2012;13:1331–1332
32. Yee SW, Chen L, Giacomini KM. The role of *ATM* in response to metformin treatment and activation of AMPK. *Nat Genet* 2012;44:359–360
33. Woods A, Leiper JM, Carling D. The role of *ATM* in response to metformin treatment and activation of AMPK. *Nat Genet* 2012;44:360–361
34. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
35. Crandall J, Schade D, Ma Y, et al.; Diabetes Prevention Program Research Group. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci* 2006;61:1075–1081
36. The Diabetes Prevention Program Research Group. Relationship of body size and shape to the development of diabetes in the Diabetes Prevention Program. *Obesity (Silver Spring)* 2006;14:2107–2117
37. Ratner RE, Christophi CA, Metzger BE, et al.; Diabetes Prevention Program Research Group. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. *J Clin Endocrinol Metab* 2008;93:4774–4779
38. Ratner R, Goldberg R, Haffner S, et al.; Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care* 2005;28:888–894
39. Florez JC, Jablonski KA, Taylor A, et al.; Diabetes Prevention Program Research Group. The C allele of *ATM* rs11212617 does not associate with metformin response in the Diabetes Prevention Program. *Diabetes Care* 2012;35:1864–1867
40. 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;117:1422–1431
41. Shu Y, Brown C, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1, *OCT1*, on metformin pharmacokinetics. *Clin Pharmacol Ther* 2008;83:273–280
42. 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;93:186–194
43. Choi JH, Yee SW, Ramirez AH, et al. A common 5'-UTR variant in *MATE2-K* is associated with poor response to metformin. *Clin Pharmacol Ther* 2011;90:674–684
44. Relling MV, Gardner EE, Sandborn WJ, et al.; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther* 2011;89:387–391
45. Gottesman O, Kuivaniemi H, Tromp G, et al.; eMERGE Network. The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genet Med* 2013;15:761–771
46. Topol EJ. Pharmacy benefit managers, pharmacies, and pharmacogenomic testing: prescription for progress? *Sci Transl Med* 2010;2:44cm22
47. Charland SL, Agatep BC, Herrera V, et al. Providing patients with pharmacogenetic test results affects adherence to statin therapy: results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. *Pharmacogenomics J* 2014;14:272–280
48. Haga SB, LaPointe NM. The potential impact of pharmacogenetic testing on medication adherence. *Pharmacogenomics J* 2013;13:481–483
49. Stanek EJ, Sanders CL, Taber KA, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. *Clin Pharmacol Ther* 2012;91:450–458
50. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther* 2011;89:464–467
51. 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;94:207–210
52. Becker ML, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in the organic cation transporter 1 is associated with metformin response in patients with diabetes mellitus. *Pharmacogenomics J* 2009;9:242–247
53. Christensen MM, Brasch-Andersen C, Green H, et al. The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c. *Pharmacogenet Genomics* 2011;21:837–850
54. Gambineri A, Tomassoni F, Gasparini DI, et al. Organic cation transporter 1 polymorphisms predict the metabolic response to metformin in women with the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2010;95:E204–E208
55. Shikata E, Yamamoto R, Takane H, et al. Human organic cation transporter (*OCT1* and *OCT2*) gene polymorphisms and therapeutic effects of metformin. *J Hum Genet* 2007;52:117–122
56. Tzvetkov MV, Vormfelde SV, Balen D, et al. The effects of genetic polymorphisms in the organic cation transporters *OCT1*, *OCT2*, and *OCT3* on the renal clearance of metformin. *Clin Pharmacol Ther* 2009;86:299–306
57. 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;38:824–829
58. Legro RS. Impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women: do we need a new drug? *J Clin Endocrinol Metab* 2008;93:4218–4220