Pharmacogenomics

Pharmacogenetics of oral antidiabetic therapy

Journal:	*Pharmacogenomics*
Manuscript ID	PGS-2017-0195.R1
Manuscript Type:	Review
Keywords:	Type 2 Diabetes (T2D), oral antidiabetic drugs (OAD), interindividual differences

Abstract

Type 2 diabetes prevalence is still on the rise worldwide. Antidiabetic drugs are widely prescribed to patients with type 2 diabetes. Most patients start with metformin which is mostly well tolerated. However, a high percentage of patients fail to achieve glycaemic control. The effectiveness of metformin as well as most other antidiabetic drugs depends among other factors on interindividual genetic differences that are up to now ignored in the treatment of type 2 diabetes. Interestingly, many genes influencing the effectiveness of antidiabetic drugs are type 2 diabetes risk genes making matters worse. Here, we shed light on these interindividual genetic differences.

Keywords: Type 2 Diabetes (T2D), oral antidiabetic drugs (OAD), interindividual differences

Executive Summary:

- The treatment success of most oral antidiabetic drugs depends among other factors on polymorphisms in classic pharmacogenomics genes but also in known T2D risk genes
- Even though many patients don't achieve desired blood glucose levels with metformin treatment and there are many polymorphisms known to influence treatments outcome in most cases it is not replaced but merely supplemented by one or more antidiabetic drugs
- Pharmacogenomic testing would lead to reduced costs for medication and hospitalization but also to personal health benefits for the patients

Introduction

Type 2 Diabetes (T2D) comprises a group of heterogeneous disorders with the common trait of peripheral insulin resistance combined with pancreatic beta-cell impairment leading to hyperglycaemia (**1**). A high percentage of patients with T2D remain undiagnosed and among those treated for the disease many have poorly controlled diabetes prompting neurological as well as renal complications and peripheral vascular disease, leading to increased health care expenditures (**2**). T2D prevalence is still on the rise worldwide especially in the developing world with serious health-related and socioeconomic consequences (**3**), making more effective T2D management to be desired. Genetics play a role in disease development but also in oral antidiabetic drug (OAD) treatment outcomes and may help define individually tailored therapies. The first T2D risk genes to be identified were *PPARG* (rs1801282), *KCNJ11/ABCC8* (rs5219/rs757110) and *TCF7L2* (rs7903146) (**4**), respectively. Shortly after, it was discovered that polymorphisms in *KCNJ11* and *PPARG* act in additive manner to increase T2D risk (**5**). However there are also polymorphisms that can rescue T2D-provoking traits of polymorphisms like it is the case in TCF7L2 and Nor-1 as we were able to show (**6**), leading to a complicated interaction of different polymorphisms. Aggravatingly, it gets more and more obvious that the treatment outcome of OADs depends on polymorphisms in a plethora of genes. This review will discuss well-studied polymorphisms.

T2D medication

Currently there are 12 drug classes available for T2D management: biguanides (metformin), thiazolidinediones (glitazones), α-glucosidase inhibitors, sulfonylureas (SU), meglitinides (glinides), dipeptidyl peptidase 4 (*DPP4*) inhibitors (gliptins), incretin mimetics (aka GLP-1 receptor agonists), sodium/glucose cotransporter 2 (*SGLT2*) inhibitors (gliflozins), amylin mimetics, bile acid sequestants, dopamine agonists and insulin/insulin analogues. This review will focus on oral antidiabetic drugs rather than injectable antidiabetic drugs due to a lack of pharmacogenetics data to date on the latter. Apart from amylin mimetics, incretin mimetics and insulin/insulin analogues, all are administered orally. Together with lifestyle intervention, metformin is usually prescribed as first-line therapy. Only when metformin is not well tolerated or the treatment goal is still not achieved after several months of treatment a combination therapy of metformin and one or more other antidiabetic drugs are prescribed. The extent to which these drugs are efficient or cause side effects significantly varies within the T2D population. This is due to physiological (age, sex, BMI) and pathological (liver or

kidney diseases) conditions, as well as lifestyle-related factors (alcohol and drug use, smoking) (**7**). A major factor, however, are interindividual genetic differences. The relatively new field in diabetes research, pharmacogenomics, is addressing this issue. By understanding interindividual variations in DNA sequence related to drug treatment outcomes, this field of research aims at developing a more personalized T2D management.

It is estimated that 20% to 40% of interindividual differences in metabolism and response to pharmacological drugs is accounted for by genetic factors (**8**). Even though the field of pharmacogenomics has existed for decades, the implementation of genetic testing in patient care has been very slow. In the field of diabetes, only testing for monogenic diabetes is already standard. Test results are crucially influencing further treatment (**9**). Pharmacogenetic testing in T2D is in its infancy even though evidence is accumulating that distinct common polymorphisms may robustly influence oral antidiabetic drug treatment outcomes.

Biguanides (Metformin)

Most patients with T2D needing pharmacological intervention start on metformin (**10**). By now metformin is the only available biguanide since other drugs in this class were shown to increase the risk for lactic acidosis, e.g. phenformin and buformin. Metformin might induce lactic acidosis in patients with renal insufficiency, therefore it is not prescribed in this subgroup of patients with T2D (**11**). Metformin is in clinical use since 1959 but its molecular mechanisms of action are still not entirely understood. One proposed mode of action is AMP-activated protein kinase (AMPK) activation (**12**). Metformin works as an insulin sensitizer, enhancing insulin sensitivity in liver, skeletal muscle and adipose tissue (**13**). Metformin shows benefits in patients with T2D beyond glucose lowering, like reduced cancer incidence and mortality (**14**) and reduced cardiovascular risk (**15;16**). This drug is also used in reproduction management in women with polycystic ovary syndrome where it reduces the risk of miscarriage (**17**).

Metformin reduces hepatic glucose output, therefore reducing blood glucose levels and HbA1c by 1-2% (**18**). However, there is considerable variation in response to metformin monotherapy, with about 35% of the patients failing to achieve glycaemic control (**19**) and many patients becoming less responsive to metformin over time (**20**). In addition, side effects like nausea, vomiting, stomach upset, diarrhoea and metallic taste in the mouth can occur, leading to discontinuance of the treatment in some cases (**21**). Glycaemic response to

metformin is heritable and is thus, in part, attributed to genetics (**22**). The genetic contribution to this variability in response to metformin treatment has been studied with a focus on pharmacokinetics and pharmacodynamics. Metformin is not metabolized in the liver (**23**), but its efficacy is highly dependent on several transport proteins, including organic cation transporter (OCT) family members OCT1-3 (solute carrier (SLC) family members 22A1-3, *SCL22A1-3*), the equilibrative nucleoside transporter 4 (ENT4, aka *SLC29A4*), and the multidrug and toxin extrusion transporters 1 and 2-K (MATE1 and MATE2-K, aka *SLC47A1* and *SLC47A2*) (**19**). Metformin is absorbed in the gut by ENT4 and OCT3 expressed on enterocytes and passed on into the blood stream via OCT1. Metformin is excreted via bile or urine. In the liver, OCT1 and OCT3 transport metformin into the hepatocyte while MATE1 excrete it into the bile. In the kidney, OCT2 is responsible for the uptake of metformin into renal tubular cells, and it is excreted into the urine via MATE2-K, MATE1 and OCT1. Polymorphisms in these transporter proteins may influence the uptake as well as the excretion of metformin. We recently published a very detailed account of these polymorphisms and their reported effects (**24**). Polymorphisms in the highly polymorphic OCT1 gene are reported to predominantly reduce metformin release from the enterocyte into the bloodstream compared with the attenuation of hepatic metformin uptake. Research focuses on the following polymorphisms: Arg61Cys, Gly401Ser, Met420del, Gly465Arg and Ser189Leu. The more polymorphisms one subject carries, the lower is the effect of metformin on blood glucose and HbA1c reduction. Additionally, metformin intolerance was seen in carriers of two reduced-function alleles compared to carriers of one or none allele (**25**). The exact localisation of OCT1 in the enterocyte is still debated. It is not clear whether OCT1 polymorphisms lead to increased intra-enterocyte concentrations or whether reduced absorption of metformin leads to increased luminal metformin concentration. Increased metformin concentrations in the gut may affect intestinal serotonin concentration, bile salt absorption or alter the microbiome potentially leading to gastrointestinal side effects. One factor also leading to metformin intolerance is concomitant treatment with OCT1 inhibiting drugs like citalopram, PPIs, verapamil, doxazosin, and codeine (**25**).

Renal excretion of metformin is mainly mediated by OCT2 (**26;27**). It harbours an interesting polymorphism, Ala270Ser (rs316019): in Caucasian and African American subjects it is associated with enhanced clearance of metformin (**28**), while in Asian subjects it is associated with higher plasma metformin levels and reduced renal clearance (**29;30**). Another OCT2 variant, Thr201Met, is associated to higher HbA1c, fasting glucose levels, insulin resistance

and insulin secretion during metformin treatment (**31**). Latest research indicates a role for OCT3 polymorphisms in metformin action (**32**). Two polymorphisms in the 5'-flanking region of *SCL22A2* (OCT2), rs3119309 and rs7757336, and one in the 5'-flanking region of *SCL22A3* (OCT3), rs2481030, were associated with short-term response to metformin monotherapy in patients with T2D (**32**). Several polymorphisms in *SLC47A1* (MATE1) (rs2252281 (**33**), rs2289669 (**34**), rs8065082 (**35**)) were identified to be associated with metformin performance. They were however not confirmed in the South Danish Diabetes Study (**36**). A-allele carriers of rs12943590 in *SLC47A2* (MATE2-K) show higher renal metformin clearance and higher glucose levels during oral glucose tolerance test (OGTT) (**33**). Finally, ENT4 gene (*SLC29A4*) polymorphisms rs2685753, rs3889348, rs4720572, rs4299914, and rs6971788 were associated with lower metformin concentrations in blood possibly due to impaired enterocytic metformin uptake (**36**).

However, a vast number of these associations were not replicated in a large-scale meta-analysis across the cohorts of the Metformin Genetics (MetGen) Consortium, questioning the impact transporter gene variants have on the variability of glycemic response to metformin in T2D (**37**). Whether kinds of transporter gene variants not assessed yet, such as rare variants, copy number variants or epigenetic modifications, may play a role in the variation of treatment response to metformin has to be addressed in future studies.

Obvious pharmacogenetic candidates for metformin action are the genes encoding for AMPK subunits. An interesting large-scale candidate gene genotyping study in 2010 analysed the association of polymorphisms in 40 genes associated to T2D with metformin treatment outcome. Among others, they found SNPs in the AMPK subunit genes *PRKAA1* and *PRKAA2* to interact with metformin response (**35**). Other interesting polygenic genes in this context were the AMPK upstream regulatory kinase serine/threonine kinase 11 (*STK11*, aka liver kinase B1 (LKB1); rs741765 C>T), the AMPK downstream transcription factors myocyte-specific enhancer factor (MEF) 2A and *MEF2D* (rs4424892 A>G and rs6666307 A>T, respectively), and in the T2D risk genes *HNF1B* (rs11868513 G>A), *HNF4A* (rs11086926 T>G), *ABCC8* (rs4148609 G>A), *KCNJ11* (rs7124355 G>A), *GCK* (rs2908289 G>A), and *CAPN10* (rs3792269 A>G) (**35**). Among the aforementioned SNPs, Tkac *et al.* tested SNPs in *PRKAA1*, *STK11*, *HNF4A*, and *CAPN10* for association with treatment success (HbA1c <7 %) and absolute reduction in HbA1c after six months of metformin monotherapy in 148 drug-naïve patients with T2D but could only show less treatment success

in G-allele carriers of *CAPN10* SNP rs3792269 A>G (**38**). However this population was much smaller than the at-risk population of the Diabetes Prevention Program (DPP) with 990 participants on metformin. Using a large Scottish observational genetic cohort of European ancestry the GoDARTS (Genetics of Diabetes and Audit Research Tayside Study) identified a common polymorphism at a locus containing the ataxia telangiectasia mutated (*ATM*) gene to be associated with metformin treatment success. The well powered GWA study identified rs11212617 to increase the treatment success 1.35-fold, and reduced the HbA1c by 0.11% per minor C-allele (**39**). In this case, GWAS was very useful since *ATM* does not harbour an established candidate gene and would have been missed in a hypothesis-led approach. The MetGen Consortium identified rs8192675 in the intron of *SLC2A2*, encoding the facilitated glucose transporter GLUT2, to be associated with greater metformin-induced HbA1c reduction in 10,577 participants of European ancestry. The same SNP was associated with GLUT2 expression in the liver. The transporter is thought to be one target of metformin by which hepatic glucose output reduction is achieved (**40**). GLUT2 also represents a T2D risk allele (**41**). Another approach taken was to analyse transcription factors controlling transport gene expression revealing polymorphisms in SP1, AP2, HNF4-α, and PPAR-α to be associated with metformin action (**42**). SP1 is probably regulating the expression of several transport proteins in the liver involved in metformin elimination. The role of PPAR-α on the other hand is less clear. However these transcription factors are also implicated in the pharmacogenomics of other drugs. For example *PPARA Leu162Val* (rs1800206) is implicated in the efficacy of gemfibrozil and fenofibrate, two drugs prescribed for hypertriglyceridemia and dyslipidaemia (**43**), common metabolic disorders in T2D. These pharmacogenetic data at least partly explain why metformin does not work in all patients. Still, metformin in most cases is not substituted by a different OAD when treatment goals are not achieved but is further prescribed even though it might not be effective at all in the first place.

Genome-wide analyses of the MetGen consortium that provided with *SLC2A2* rs8192675 a very robust and mechanistically very plausible result were unable to replicate any of the other candidate gene variants affecting metformin pharmacodynamics (40). However, the small effect size of the GLUT2 variant is insufficient to explain a relevant part of the variation in treatment response. It therefore remains to be shown whether kinds of candidate gene variants not investigated yet (e.g., rare variants, copy number variants or epigenetic modifications) may play a role in the variation of treatment response.

Hence, even though metformin is still the drug of choice for starting pharmacological T2D management (**10;44;45**), there are more and more publications demanding more personalized approaches (**46;47**). Additionally many patients initially on metformin require escalation of therapy (**48**) and about 20% of patients fail to meet glycaemic goals in the first 5 years of metformin therapy (**20**). In young patients with newly diagnosed T2D the failure rate even exceeds 50% (**49**). Therefore, a substantial part of patients with T2D requires one or more oral antidiabetic drugs in addition to metformin. The list of oral antidiabetic drugs might seem long, however it is shortened by the fact that glitazones are no longer marketed in some European countries and are put under selling restrictions in the US due to a possibly increased risk of myocardial infarction and increased risks of distal fractures of long bones, bladder cancer and heart failure (**50**). Additionally, 12% to 45% of patients with T2D receiving pioglitazone or rosiglitazone failed to achieve sufficient HbA1c reduction (**51**). Polymorphisms in *PPARG*, *ADIPOQ1*, *CYP2C8*, *CYP2C9* and *CYP3A4* (**52**) are associated with effectiveness of glitazones. Among others, polymorphisms in *CYP2P9* are also associated with the effectiveness of ACE inhibitors often prescribed to patients with T2D (**53**). Treatment with α-glucosidase inhibitors often leads to adverse gastrointestinal side-effects like flatulence and diarrhoea and are rarely prescribed (**54**). Until now no pharmacogenetic data emerged for α-glucosidase inhibitors. Bile acid sequestants and dopamine agonists are rarely prescribed for T2D management. Remaining are sulfonylurea, meglitinides, DPP4 inhibitors and SGLT2 inhibitors that are prescribed for T2D management.

Sulfonylureas

Sulfonylureas lower blood glucose by blocking the K_{ATP} channels in the ß cells and thereby increasing insulin secretion. Additionally SU limit hepatic gluconeogenesis (due to increased insulin levels) and the clearance of insulin in the liver. They are prescribed as second-line or add-on treatment in T2D management (**55**). However, sulfonylureas are β-cell stressors and are suspected to accelerate the exhaustion of endogenous insulin secretion (**56**). Further unwanted side effects are weight gain, increased risk of hypoglycaemia (**57**) and increased risk of cardiovascular events and mortality (**58**). *KCNJ11/ABCC8* and *TCF7L2* belong to a long list of genetic markers predicting sulfonylurea treatment outcomes. Other genes associated with SU treatment outcomes are *IRS1*, *CDKAL1*, *CDKN2A/2B* and *KCNQ1* (**59**). Interestingly, all these genes are also T2D susceptibility genes. Polymorphisms in *KCNJ11*

and *ABCC8* affect the pharmacodynamics of sulfonylureas. They encode for the inward-rectifier potassium ion channels (Kir6.2) and ATP-binding cassette transporters known as sulfonylurea receptors (SUR-1). Four of each form the K_{ATP} channel (ATP-sensitive K^+ channel). SU bind directly to the K_{ATP} channel on SUR-1 resulting in their closure and depolarisation which in turn leads to a cascade of events leading to insulin release from the ß cells (**60**). Latest studies on polymorphisms in *KCNJ11* and *ABCC8* and their effect on OAD treatment outcomes strongly vary in SU concentration used, duration and ethnicity of the population. The most widely studied *KCNJ11* polymorphism to date is rs5219 that leads to the replacement of glutamine (E) by lysine (K) in the amino-acid sequence of the protein. It seems that the E23K polymorphism in long-term SU treatment is associated with secondary failure to SU (**61**), while there is a report showing an improvement of HbA1c after only 2 months of SU treatment in E23K carriers (**62**). *ABCC8* harbours three polymorphisms associated to SU response (rs757110 (S1369A), rs1799854 (intron) and rs1799859 (AGG1273AGA)). Carriers of the rs757110 missense polymorphism in the SUR-1 protein seem to have higher odds of responding to gliclazide treatment. However, after short-term treatment there doesn't seem to be an association (**63**). E23K in *KCNJ11* and S1369A in *ABCC8*, are in strong linkage disequilibrium.

The evidence for the involvement of *TCF7L2* polymorphisms in sulfonylurea action is more compelling. There are several well-powered studies showing under similar conditions an increased risk of sulfonylurea failure in T-allele carriers of the rs7903146 variant. Patients were treated over a period of six months with SU in combination with metformin, and sulfonylurea failure was defined as failure to lower HbA1c below 7%. Interestingly, between 25% and 30% of the world population are T-allele carriers while the proportion in East Asian populations is below 5%. As a common T2D risk allele, it is by nature even higher in patients with T2D. *TCF7L2* harbours a second polymorphism, rs12255372, associated with reduced response to SU treatment and increased T2D risk, which is in strong linkage disequilibrium with rs7903146 (**64**).

IRS1 gene polymorphism rs1801278 is strongly associated with insulin resistance but also with sulfonylurea failure as was shown in an Italian as well as in an Egyptian population (**59**). As for many other drugs SU action is affected by CYP450 enzymes. In this context, *CYP2C9* and *CYP2C19* are of interest. Individuals with variants in these genes are labelled poor metabolizers. It was found that Dutch carriers of CYP2C9*1/3, *2/3 or *3/3 needed significantly lower tolbutamide dose compared to CYP2C9*1/*1, *1/*2 or *2/*2 carriers

probably due to higher blood concentrations of the drug accounted for by lower metabolism by the CYP2C9 enzyme in the risk allele carriers (**65**). Interestingly the *CYP2C19* variants are very common in Asians (19%) compared to Caucasians (2%) which is clinically relevant (**65**).

According to FDA black-box warnings on drug labels, certain sulfonylureas (https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm) should be prescribed with precaution in patients with underlying *glucose-6-phosphate dehydrogenase* (G6PD) deficiency since haemolytic acute anaemia can occur depending of G6PD enzymatic activity (**66**). The gene for G6PD is on the X chromosome and G6PD deficiency is caused by various mutations and polymorphisms in this gene (**67**). G6PD activity is tested by quantitative spectrophotometric assay in red blood cells or with commercially available kits (**67**). Interestingly, G6PD deficiency is also associated with an increased prevalence of diabetes in 45-65-year-old patients with this deficiency (**68**). G6PD is most prevalent in sub-Saharan Africa, Asia and the Mediterranean but also in the United States and South America (**69**). But, with people migrating to all parts of the world the lines get more and more blurred.

Taken all these data together, it might explain why the use of sulfonylureas is more and more discontinued due to adverse effects with the UK being an exception (**10**). This trend started around the year 2000 in Germany, Belgium and Sweden (**70**).

Meglitinides

Meglitinides (glinitides) are short-acting (in contrast to SU) insulin secretagogues stimulating insulin secretion by blocking ATP-dependent potassium channels and causing calcium influx to pancreatic β cells. Most of the drugs in this class show a weak binding to SUR1, however, repaglinide might also bind to Kir6.2 (**71**). The response to meglitinides was associated to SNPs in *SLCO1B1*, *OATP1B1*, *CYP2C9*, *CYP2C8* and *CYP3A4* (**72**).

DPP4 inhibitors

In response to food intake, the intestinal L- and K-cells secrete the incretin hormones glucagon- like peptide 1 (GLP1) and gastric inhibitory peptide (GIP). Their natural half-life is short (1.5-2min) because the enzyme dipeptidyl peptidase 4 (DPP4) cleaves and inactivates the incretins rapidly (**73**). DPP4 inhibitors inhibit the degradation of incretins and therefore

prolong incretin-stimulated insulin secretion by pancreatic ß cells (**73**). Even though DPP4 inhibitors are in general well tolerated and prescribed as a second-line therapy on a regular basis (**10**), there is still a considerable inter-individual variance in the responsiveness to these drugs (**74**). TCF7L2 acts downstream of the incretin receptors and is involved in the exocytosis of insulin. Homozygous T2D risk allele carriers of the rs7903146 variant showed reduced responsiveness to linagliptin in regard to HbA1c lowering (**75**). Using a genotyping array designed for genetic studies, a locus near *CTRB1/2* rs7202877, which is a known susceptibility gene for T2D, was identified to associate with reduced lowering of HbA1c in minor G-allele carriers (**76**). The gene encoding for DPP4 also harbours a locus (rs6741949) associated with markedly reduced glucose-induced GLP1 levels, reduced insulin secretory capacity, and increased fasting and 2-hour glucose concentrations during an OGTT (**77**). DPP4 gene polymorphism rs12617656 is associated to T2D in Malaysian subjects (**78**). Latest research has revealed several new genes involved in DPP4 inhibitor responsiveness. In a Korean cohort of patients with T2D, a variant in the *GLP-1R* gene, encoding the GLP1 receptor, was associated with better response to DPP4 inhibitors. Among the carriers of the minor A-allele were more responders compared to the major genotype (GG) (**79**). Another polymorphism rs6923761 (Gly168Ser) in *GLP-1R* was identified in 140 European patients with T2D after 6 months of gliptin treatment. Here reduced HbA1c was the main outcome of the study (**80**). A polymorphism in the T2D risk gene *KCNQ1* (rs163184) was found to associate with less HbA1c reduction in the minor G-allele homozygotes compared to TT-major allele carriers (**81**). In a small Taiwanese T2D population, several genes were identified using an assumption-free genome-wide association study as possible genes involved in DPP4 inhibitor response (*PRKD1*, *CNTN3*, *ASK*, and *LOC10537792*). PRKD1 (rs57803087) was strongly associated to DPP4 inhibitor response, however results did not reach statistical significance after Bonferroni correction and therefore need to be replicated in larger cohorts (**82**). Even though to this day there are no studies published yet analysing the pharmacogenomics of incretin mimetics, it is conceivable that polymorphisms affecting incretin action like those in *TCF7L2* and *WFS1* might be of interest (**83**) as are polymorphisms in GLP-1R that lead to loss of peptide-induced response (**84**). But it also needs to be taken into account that there are polymorphisms counteracting the effect of other polymorphisms as it is the case for Nor-1 (*NR4A3*): we were able to show rs12686676 in *NR4A3* fully rescues incretin resistance provoked by *TCF7L2* rs7903146 (**6**). This makes things more complicated, but of course explains why there is no absolute effect of single polymorphisms.

SGLT2 inhibitors

SGLT2 inhibitors lower blood glucose by increasing glucose excretion via the urine. SGLT2 and SGTL1 are expressed in the proximal convoluted tubule of the nephron and are reabsorbing 90% and 3% of the glucose from the urine, respectively (**85**). Therefore, inhibition of the cotransporters significantly lowers blood glucose. SGLT2 was also shown to be expressed in the pancreatic islets of Langerhans and inhibition induced glucagon secretion (**86**). Co-treatment of mice with metformin and SGLT2 inhibitors exhibits beneficial effects by suppressing endogenous glucose production (**87**). SGLT2 inhibitors are well tolerated and show cardioprotective properties (**88**). However, there were some side effects reported like increased risk for ketoacidosis, urinary tract infections and hypoglycaemia (**88**). Also, an increased risk for lower limb amputation was reported for canagliflozin treatment (**88**). Common noncoding polymorphisms (rs9924771 G/A and rs9934336 G/A in intron 1 and rs3813008 G/A and rs3116150 G/A in intron 5) in SGLT2 did not show any effects on fasting nor glucose-suppressed plasma glucagon concentrations (**89**). But rs3116150 was associated with fasting glycaemia, glucose excursions during the 5-point OGTT (AUC glucose), and systolic blood pressure (**90**). In another study, rs9934336 was associated with 2-hour insulin concentrations during OGTT in two German cohorts (**91**). Since the SGLT2 inhibitors are a very novel class of drugs in T2D management, there are not many data available yet in regard to their pharmacogenomics. Four tested polymorphisms in SGLT2 don't seem to have any impact on SGLT2 inhibitor responsiveness (**90**).

It has to be noted that the variants shown in small studies to interact with treatment response to sulfonylureas, meglitinides, DPP4– and SGLT2 inhibitors clearly should be considered as hypothesis-generating candidates that need to be followed up in larger treatment studies and in meta-analyses thereof. Time will bring more clarity which gene-drug pairs will withstand large-scale replication efforts and, for instance, will have the potential to be integrated in electronic health records.

Conclusions & future perspective

It is becoming increasingly evident that the treatment outcome with OAD differs strongly between individuals and that a personalized approach would make sense. Among other factors influencing the effectiveness of OAD are gene polymorphisms. However, the current guidelines do not consider individual variation to therapeutic response yet. Since sequencing

costs are constantly decreasing genetic testing in T2D may become feasible in the future and could provide benefits for patients' outcome. One possibility could be a once-in-a-lifetime genome-wide genetic test the patients could benefit their entire life from not only with respect to T2D therapy (**92**). By avoiding inefficient or even adverse medication, genetic testing could not only lead to reduced costs for medication and hospitalization but also to personal health benefits for the patients (**8**). In other fields of medicine like breast cancer whole-genome analysis is more common and costs have declined over time due to reduced sequencing costs. However, they are still very costly to date and not expected to reach critical thresholds within the next 10 years (**93**). But whole-genome analysis would have the benefit over targeted sequencing in respect to the discovery of new polymorphisms in the future. No further testing would be needed (**94**). The interpretation of such pharmacogenetic data is not trivial and gene-gene (**95**) and gene-environment interaction for example must be taken into account and generated data would have to be presented in a comprehensible manner to health care providers.

Currently, it appears as if gene polymorphisms influencing the treatment outcome of OAD can be roughly divided into two groups: the classical pharmacogenomics genes influencing pharmacokinetics/pharmacodynamics (e.g., *SLC2A2*) and T2D risk genes. Like for many other drugs, the effectiveness of OAD depends on metabolizing enzymes and transport proteins (**96**). The former include drug transporters, CYP450 enzymes and transcription regulators. These are already included in existing pharmacogenomic chips like the DMET™ Microarray (**97**). If replicated in larger studies and meta-analyses thereof, interindividual variation in response to OADs could turn out to be associated with polymorphisms with the highest odds ratio for T2D (**98**) (Table 1). The latter include polymorphisms in the T2D risk genes *TCF7L2*, *KCNJ11*, *IRS1* and *PPARG*. If corroborated, these T2D risk genes involved in OAD treatment outcome would have to be included in novel pharmacogenetic chips or in the case of a genome-wide test would be needed to be taken into consideration.

These T2D risk genes represent a double edges sword. *TCF7L2* polymorphism rs7903146 for example with an allele frequency of up to 30% (Europeans and South Asians) has a negative impact on various aspects of β-cell function like impaired proinsulin conversion and insulin secretion (**99;100**) and influences the treatment outcome of SU (**59**) and DPP4 inhibitors (**75**) as discussed above. Therefore, not only do these genes increase the risk for developing T2D and have an increased allele frequency in this patient group but they additionally influence

the treatment outcome of the very drugs intended to treat the disease. This could in part explain the poor overall treatment success of OAD.

Disclosures: The authors have no conflicts of interest related to this work.

Author contributions: A.-M.O. wrote the manuscript. H.-U.H., M.H.d.A. and H.S. commented on and edited the manuscript.

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Table 1: OAD and pharmacogenetically relevant target genes (T2D risk genes in bold)

Drug class	Metabolic drug effects	Pharmacogenetically relevant genes
Biguanides	Insulin sensitization	*SCL22A1-3, SLC29A4, SLC47A1, SLC47A2, PRKAA1, PRKAA2, STK11, MEF2A, MEF2D,* ***HNF1B****,* ***HNF4A****,* ***ABCC8****,* ***KCNJ11****,* ***GCK****,* ***CAPN10****, ATM,* ***SLC2A2****, SP1, AP2,* ***PPARA***
Thiazolidinediones	Insulin sensitization	***PPARG****, ADIPOQ1, CYP2C8, CYP2C9, CYP3A4*
Sulfonylureas	Glucose-independent stimulation of insulin secretion	***KCNJ11****,* ***ABCC8****,* ***TCF7L2****,* ***IRS1****,* ***CDKAL1****,* ***CDKN2A/2B****,* ***KCNQ1****, CYP2C9, CYP2C19,* ***G6PD***
Meglitinides	Glucose-independent stimulation of insulin secretion	*SLCO1B1, OATP1B1, CYP2C9, CYP2C8, CYP3A4*
DPP4 inhibitors	Glucose-independent stimulation of insulin secretion, inhibition of glucagon secretion	***TCF7L2****,* ***CTRB1/2****, GLP-1R,* ***KCNQ1****, PRKD1, CNTN3, ASK, LOC10537792*
SGLT2 inhibitors	Renal glucose excretion	*SGLT2* (up to date no SNPs with relevant effects on treatment response described)