From Pharmacogenetics to Gene Expression: Implications for Precision Medicine in Diabetes

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Abstract

Approximately 25–60% of patients show specific pharmacological responses to a particular drug. We call this interindividual variability (IV) response to drugs affecting their efficacy and the appearance of side effects in individuals. This IV may be due to multifactorial components such as genetic factors (single nucleotide polymorphisms, SNPs; and copy number variations, CNV), environmental stimuli, epigenetic modulation, disease/health conditions, or drug interactions, among others. Therefore, these factors can influence the response to the drug by modifying absorption, metabolism, pharmacokinetics (PK), and pharmacodynamics (PD), causing the loss of treatment efficacy or leading to adverse drug reactions with negative consequences for patients. The knowledge in pharmacogenetics (study of pharmacological consequences of single gene mutations) and pharmacogenomics (study of the influence of many gene or gene patterns in the response to drugs), disciplines that seek to predict how a specific individual responds to the administration of a particular drug, has advanced by leaps and bounds thanks to “omics” technologies. Nonetheless, despite, the development of next-generation sequencing platforms and the mapping of the human genome have transformed the field of pharmacogenetics, the translational into clinical practice has been slow. Therefore, identification of SNPs that could affect the expression of pharmacogenes in order to make associations with PK and PD will improve our understanding of genetic effects on drug efficacy and transfer it to the clinic. Type 2 diabetes (T2D) represents a national public health problem, not only because of the high frequency of the disease reported worldwide, but also because of the poor adherence to therapeutic management, whose causes have not yet been clarified. One of the challenges in the management of diseases to reach optimal treatment is the complex genetic background. Hence, the integration of multiple levels of pharmacological information, including variation in gene sequence, impact in drug response, and function of drug targets, could help us to predict sources of interpatient variability in drug effects, laying the basis for precision therapy. Thus, the present chapter aims to collect all the available data about genetic variations in pharmacogenes affecting drug response in T2D and integrate it with their effect on gene expression to elucidate their impact in pharmacological efficacy.

Keywords: diabetes, pharmacogenetics, pharmacogenes, expression
1. Introduction

Although there is no consensus in the contribution of genetic component to drug response, many studies from the 1970s have estimated that could be between 20 and 95% of the variability in drug disposition and effects [1]. The difficulty in reaching a consensus is because the contribution of environmental and genetic components to pharmacogenetics cannot be evaluated, through only one approach, that is, analyzing only one drug or group of drugs, or only a SNP or a group of SNPs; we have to talk about PK, PD and related outcomes. In this context, there are a variety of studies focused on PK, or PD, but the convergence of all these concepts has been difficult, so the translation to the clinical practice has been challenging. Along with these barriers are additional factors, such as gene–environment interactions and gene–gene interactions [2]. Moreover, the different responses among ethnicities are another factor to add to this complex phenomenon.

The knowledge on which the participation of genetics in response to the action of drugs in an individual or group of individuals has been generated through various studies, applying different strategies such as those described below. In this regard, in past decades, different laboratories in four countries carried out twin studies with different drugs to determine the contribution of genetic and environmental factors to interindividual variations. The results from all studies converged in that PK variation were similar between monozygotic twins and was preserved within dizygotic twins, and even as similar as the monozygotic twins [3]. Researchers from these laboratories conclude that genetic factors primarily controlled interindividual variations in the metabolism of a wide range of drugs [3–8]. In the field of heritability of antidiabetics drug response, the studies are scarce, but one classic example is tolbutamide. In this context, an intravenous administration to 42 nondiabetic subjects, eight of their relatives, and to five sets of twins, the authors observed a monogenic control of tolbutamide revealed by a heritability value of 0.995 (this value means that considering a trait with 1.0 heritability, such as a Mendelian trait, the genetic factors have a great or complete influence in phenotype; in contrast, a trait with 0.0 heritability will not be influenced by genetic factors) [9]. In a more recent study by Gjesing et al., they found high heritabilities estimations for acute insulin secretion subsequent to glucose stimulation (0.88 ± 0.14), for insulin sensitivity (0.26 ± 0.12), disposition index (0.56 ± 0.14) and disposition index after tolbutamide administration (0.49 ± 0.14) in 284 non diabetic family members of patients with T2D after an intravenous injection of tolbutamide [10]. In another study of genome-wide complex trait analysis in patients in the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study, the heritability of glycaemic response to metformin varied by response phenotype, with a heritability of 34% (p = 0.022) for the absolute reduction in HbA1c in 2085 individuals in treatment with metformin [11]. Hence, these studies clearly show that the response to different types or classes of drugs is modulated by the individual’s genetics and can be passed on to their descendants showing a clearly genetic component.

2. Variability in drug response in T2D

Diabetes has become a health problem (by 2030, the number of individuals with diabetes is estimated to rise to 578 million and 700 million by 2045) [12]. Approximately, 90–95% of cases of diabetes correspond to T2D. T2D is a chronic metabolic disease characterized by hyperglycemia, resulting from insulin resistance and
reduced insulin secretion, which leads to impaired glucose utilization, dyslipidemia and hyperinsulinemia [13].

The great prevalence of T2D impacts both direct and indirect costs. In 2019, the International Diabetes Federation estimated that total diabetes-related health spending reached $ 760 billion. By the years 2030 and 2045, spending is forecast to reach $ 825 billion and $ 845 billion, respectively [12]. Moreover, approximately the 32% of annual costs per diabetic patient is destined to treatment [14]. Furthermore, approximately 50% of T2D patients have good glycemic control considering HbA1c < 7%, which means that ~50% have poor glycemic control [15]. Besides, as consequence of adverse drug reactions (approximately 20–30%) there is a high prevalence of treatment abandonment [16–18] All these facts denote the need for new drugs or strategies to improve glycemic control. Current treatment to control diabetes is aimed at specific key targets in glucose metabolism such as: adipose and muscle tissue to reduce insulin resistance, or act on the liver to inhibit glucose production, as well as stimulate the pancreas to release insulin. However, it is necessary to go beyond lowering glucose levels. In clinical practice it is often observed that T2D patients who receive identical antidiabetic regimens have significant variability in drug response, hence interindividual variation may be caused by numerous factors, such as genetic factors, physical inactivity, hypertension, age, gender and others [19]. Particularly, the genetic variability of therapy response was recently shown in several independent studies for the common drugs used for T2D treatment. Therefore, identification of genetic variants and their impact in drug response may improve our knowledge in the field, in order to be able of translate it into clinical practice. This could help in decision making on the therapeutic approach, reducing the rates of side effects and improving the adherence to treatment. Thus, the present chapter aims to collect all the available data about genetic variations in pharmacogenes affecting drug response in T2D and integrate them with their effect on gene expression, and to elucidate their impact on pharmacological efficacy.

In order to cover the objective, we compile all the available information about pharmacogenetics and epigenetics in T2D. We carried out a literature search using PubMed and Google Scholar. For this purpose, search words used were the following: diabetes + pharmacogenetics (826 studies); type 2 diabetes + pharmacogenetics (421 studies), diabetes + pharmacogenomics (1,184 studies); type 2 diabetes + pharmacogenomics (456 studies). When we added the words “drug response” the result was 338 and 267 papers, for pharmacogenomics and pharmacogenetics, respectively; or when we added the words “personalized medicine” in the search, we retrieved 152 and 114 papers, for pharmacogenomics and pharmacogenetics, respectively. Table 1 shows all the studies considered significantly associated with antidiabetics drug response. Regarding the Epigenetics section, this was covered with a literature search using the words diabetes + drug response + epigenetics. Table 2 shows the reports of epigenetics variations that influence drug response in T2D treatment. All the studies were chosen taking into account glycemic control and significance.

2.1 Single nucleotide polymorphisms

SNPs, are modifications in the DNA sequence, that implies changes in single nucleotides, which are the most common variations and the main source of interindividual diversity [99]. Interindividual variability could be explained in part by SNPs in genes encoding drug-metabolizing enzymes, transporters, receptors and molecules involved in drug metabolism. In this context, many SNPs related with the metabolism of antidiabetic drugs have been described. In the following section we
| Drug group       | Gene (Encoded protein) | dbSNP ID  | Aminoacid change | Population     | Effect                                      | References          |
|------------------|------------------------|-----------|------------------|----------------|--------------------------------------------|---------------------|
| Biguanides       | *SLC22A1* (OCT1)       | rs12208357| Arg61Cys         | European       | Association with metformin intolerance     | [20–22]             |
|                  |                        | rs72552763| Met420del        |                |                                            |                     |
|                  |                        | rs34059508| Gly465Arg        |                |                                            |                     |
|                  |                        | rs34130495| Gly401Ser        |                | Lower decrease in HbA1c                    |                     |
|                  |                        | rs1867351 | Ser52Ser         | Asian          | Reductions in PPG and ΔHbA1c              | [23]                |
|                  |                        | rs622342  | Intron A > C     | South Indian   | Less response to metformin                | [24]                |
|                  |                        |           |                  | European       | Decreased reduction in HbA1c levels       | [25]                |
|                  |                        |           |                  | Mexican        | High ΔHbA1c values                         | [26]                |
|                  |                        | rs36056065| Indel GTAAGTGG   | European       | Association with metformin side effects    | [27]                |
|                  |                        | rs628031  | Val408Met        | Mexican        | High ΔHbA1c values                         | [26]                |
|                  |                        |           |                  | Chinese        | Reduction in ΔHbA1c and ΔFPG               | [23]                |
|                  |                        |           |                  | European       | Association with metformin side effects    | [27]                |
|                  |                        | rs594709  | 597 A > G        | Mexican        | Increase in HbA1c values                   | [26]                |
|                  |                        |           |                  | Chinese        | Increase in FINS decrease in HOMA-IS and in QUICKI | [28]                |
|                  |                        | rs145450955| Thr201Met        | Iranian        | High HbA1c values                          | [29]                |
| *SLC22A2* (OCT2)| rs316019               | Ala270Ser | Chinese          | Higher incidence of hyperlactacidemia     | [30–32]             |
|                  |                        |           | South Indian     | Better response                           |                     |
|                  | rs3119309              | Intergenic| European         | Association with metformin inefficiency    | [33]                |
|                  | rs7757336              |           |                  |                                            |                     |
|                  | rs2481030              |           |                  |                                            |                     |
| Drug group | Gene (Encoded protein) | dbSNP ID    | Aminoacid change          | Population            | Effect                                           | References |
|------------|------------------------|-------------|---------------------------|-----------------------|-------------------------------------------------|------------|
|            | **SLC47A1 (MATE1)**    | rs2252281   | g. – 66 T → C             | European              | Enhanced response                               | [34]       |
|            |                        | rs2289669   | g. – 130G → A             | African               | Association with reduction in HbA1c levels      | [35]       |
|            | **SLC47A2 (MATE2)**    | rs12943590  | Gly211Val                 | European              | Reduced response                                | [34]       |
|            |                        | rs34399035  | Gly393Arg                 | South Indian          | Better response                                 | [31]       |
|            | **SLC2A2 (GLUT2)**     | rs8192675   | Intron C > T              | European, African    | Reduction in HbA1c values                       | [36, 37]   |
|            |                        |             |                           | American              | Reduction in blood glucose                      |            |
|            |                        |             |                           | Asian American, Latino|                                                 |            |
|            | **C11orf65 (MFI)**     | rs11212617  | Intron C > A              | European              | Association with treatment success              | [38]       |
|            | **CPA6 (CBPA6)**       | rs2162145   | UTR variant T > A / C/G   | European              | Better response                                 | [39]       |
|            | **PRPF31 (PRP31)**     | rs254271    | Intron T > A / C/G        | European              | Worse response                                  |            |
|            | **STK11**              | rs2075604   | Intron G > T              | Chinese               | Better therapeutic efficacy                     | [32]       |
|            | **CAPN10 (CAN10)**     | rs3792269   | Arg197Gly                 | European              | Association with less treatment success and with smaller reduction in HbA1c | [40]       |
|            | **SPI**                | rs784892    | Intron G > A              | European              | Association with decreased efficacy             | [41]       |
| Drug group | Gene (Encoded protein) | dbSNP ID | Aminoacid change | Population | Effect | References |
|------------|------------------------|----------|------------------|------------|--------|------------|
| FMO5       | rs7541245              | Intron C > A | Not provided     | Association with decreased glycemic response (decrease response to metformin) | [42] |
| SLC22A3 (OCT3) | rs2076828       | C > G          | European, African, American | Association with reduced response | [43] |
| Sulfonylureas | CYP2C9        | rs1799853 (‘2) | Arg144Cys | European | Greater response to sulfonylureas | [44, 45] |
|            | rs1057910 (‘3)       | Ile359Leu | Mexican | Association with good glycemic control |          |
| ABCC8      | rs757110              | Ser1369Ala | Chinese | Association with FPG, 2 h plasma glucose and HbA1c decrease | [46, 47] |
|            | rs1799854              | Intron C > T | European | Association with therapeutic efficacy |          |
|            | rs1799859              | Arg1273Arg | European | Lower HbA1c concentration | [48] |
|            | rs1801261              | Thr759Thr | Chinese | Less reduction in FPG and HbA1c levels | [49] |
| KCNJ11 (KCJ11) | rs5219                  | Glu23Lys | European, Chinese | Better response | [50, 51] |
|            | rs5210                 | UTR G > A | Chinese | Association with FPG decrease | [46] |
| KCNQ1      | rs163184              | C > G          | European | Lower FPG response | [53] |
|            | rs2237892              | Intron C > T | Chinese | Association with treatment success | [54] |
|            | rs2237895              | Intron A > C, T | Association with treatment success |          |
| TCF7L2 (TF7L2) | rs7903146       | Intron C > T | European | Lower effect of gliclazide | [55] |
|            | rs12255372             | Intron G > T | Association with therapeutic failure | [56, 57] |
| NOSIAP (CAPON) | rs10494366           | Intron G > C/T | Less effectiveness of treatment | [58] |
| Drug group    | Gene (Encoded protein) | dbSNP ID | Aminoacid change | Population | Effect                                      | References |
|--------------|------------------------|----------|------------------|------------|---------------------------------------------|------------|
| Thiazolidinediones | IRS1                  | rs1801278| Gly972Arg        | African European | Association with increased risk for secondary failure | [59, 60] |
|               | ABCA1                  | rs9282541| Arg230Cys        | Mexican    | Association with decreased response to treatment | [61]      |
|               | PPARG2 (PPARγ2)        | rs1801282| Pro12Ala         | Chinese    | Association with better response             | [62, 63]  |
|               |                        |          | Intron A > G     | Mexican American | Association with response to troglitazone | [64]      |
|               |                        | rs880663 | Intron T > C     |            |                                             |            |
|               |                        | rs4135263| G > C            |            |                                             |            |
|               |                        | rs1152003| G > T            |            |                                             |            |
|               |                        | rs6806708| C > A/G          |            |                                             |            |
|               |                        | rs13065455| T > G            |            |                                             |            |
|               |                        | rs13088205| T > C            |            |                                             |            |
|               |                        | rs13073869| Intron G > A/C   |            |                                             |            |
|               | PPARGC1A (PGC-1α)      | rs8192678| Gly482Ser        | Chinese    | Reduced ΔFPG and ΔFINS                       | [65]      |
|               |                        | rs2970847| Thr394Thr        |            | Reduced ΔPINS                               |            |
|               | UCP2                   | rs659366 | ~866 G/A         | Chinese    | Smaller attenuated PINS and greater attenuated HbA1c | [66]      |
|               | CYP2C8                 | rs10509681| Lys399Arg        | European   | Association with reduced glycemic response  | [67]      |
|               | SLCO1B1                | rs4149056| Val174Ala        | European   | Association with enhanced glycemic response  | [67]      |
| Drug group | Gene (Encoded protein) | dbSNP ID | Aminoacid change | Population | Effect | References |
|------------|-----------------------|----------|------------------|------------|--------|------------|
|           | **KCNQ1**             | rs2237892| Intron C > T     | Chinese    | Larger augmentation in $\Delta_2h$ glucose | [54] |
|           |                       | rs2237895| Intron A > C/T   |            | Greater decrement in $\Delta HbA1c$        |       |
| ADIPOQ    | (ADPN)                | rs266729 | −11377 C > G    |            | Attenuated rosiglitazone effect            | [68] |
|           |                       | rs2241766| GLy15Gly        |            | Attenuated $\Delta FINS$                   | [69] |
|           |                       | rs1501299| SNP + 276 G > T | Korean     | Smaller reductions in FPG and HbA1c       | [70] |
|           |                       | rs182052 | −10068 G > A    | Chinese    | Increased reduction in HbA1c              | [71] |
| RETN      |                       | rs1862513| −420 C > G      | Japanese   | Correlation with reduction of HbA1c       | [72] |
| LEP       |                       | rs7799039| G-2548A         | Chinese    | High differential values of FINS and PINS  | [73] |
| TNFA      |                       | rs1800629| G-308A          |            | Lower values of FINS                      |       |
| PTPRD     |                       | rs1758449| Intron C > T    | Korean     | Higher $\Delta PPG$                       | [63] |
| DPP-4 inhibitors | **TCF7L2 (TF7L2)** | rs7903146| Intron C > T    | European   | Lower reduction of HbA1c                  | [74] |
|           |                       |          |                 | African    |                                              |       |
|           |                       |          |                 | Asian      |                                              |       |
| KCNJ11    | (KCNJ11)             | rs2285676| UTR A > G/T     | Asian      | Association with better response          | [75] |
| CTRB1/2   |                       | rs7202877| T > C/G         | European   | Smaller decrease of HbA1c                 | [76] |
| KCNQ1     |                       | rs163184 | Intron T > C/G  | European   | Association with a reduced glycemic response | [77] |
| GLP1R     |                       | rs3765467| Arg131Gln       | Korean     | Association with HbA1c reduction          | [78–80] |
|           |                       | rs6923761| Gly168Ser       | European   |                                              |       |
| DPP4      |                       | rs2909451| Intron C > T    | Not Provided| Association with DPP-4 activity           | [81] |
|           |                       | rs759717 | Intron G > C    |            |                                              |       |
|           |                       | rs6733162| Intron G > C/A  |            |                                              |       |
| Drug group          | Gene (Encoded protein) | dbSNP ID       | Aminoacid change | Population | Effect                                              | References |
|---------------------|------------------------|----------------|------------------|------------|-----------------------------------------------------|------------|
|                     | PRKD1                  | rs57803087     | Intron A > G     | Taiwanese  | Association with DPP-4 inhibitor response            | [82]       |
|                     | ABCB1 (MDR1)           | rs1128503      | Gly412Gly        | Asian      | Association with response to therapy                | [83]       |
|                     | CDKAL1                 | rs7754840      | Intron C > G     | Japanese   | Association with HbA1c reduction                    | [84]       |
|                     |                        | rs7756992      | Intron A > G     |            |                                                     |            |
| GLP-1 receptor agonists | GLP1R                | rs10305420     | Pro7Leu          | Chinese    |                                                     | [85]       |
|                     | TCF7L2 (TF7L2)         | rs7903146      | Intron C > T     | Brazilian  | Association with PINS                              | [86]       |
|                     |                        | rs761386       | Intron C > G/T   | Taiwanese  | Association with changes in the standard deviation of plasma glucose | [87]       |
|                     | SORCS1 (SORC1)         | rs1416406      | A > G/T          | Chinese    | Association with FINS                              | [88]       |
|                     | CNR1                   | rs1049353      | Thr453Thr        | European   | Association with improvement of insulin resistance  | [89]       |
| SGLT2 inhibitors    | UGT1A9                 | rs72551330     | Met33Thr         | Not Provided | Higher AUC (26%)                                    | [90, 91]  |
|                     | SLC5A2 (SGLT2)         | rs9934336      | Intron G > A     | European   | Association with reduced 30-min plasma glucose      | [92]       |

OR: Odd ratio; BG: Blood glucose; FINS: Fasting serum insulin; PINS: Postprandial serum insulin; PPG: Postprandial plasma glucose; HOMA-1S: Insulin sensitivity by homeostasis model assessment; HOMA-IR: Insulin resistance by homeostasis model assessment; HOMA-BCF: homeostatic index of percentage of β-cell function; FBG: fasting blood glucose; FG: fasting glucose; AUC: Area under the curve. The gray cells indicate a haplotype associated with metformin intolerance in the study of Dujic et al. in 2015 [21].

Table 1.
Changes in DNA sequence that influence T2D treatment.
described the most significant SNPs associated with drug response, specifically glycemic control, with antidiabetics treatment.

### 2.1.1 Biguanides (Metformin)

First-line drugs in T2D therapy are biguanides, however, when the patient is not obese, the sulfonylureas group is usually prescribed and the response to treatment will be evaluated after 3 months [100]. Guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with T2D [101]. Approximately 30% of patients with T2D do not respond to metformin and about 20 to 30% experience intolerable side effects [102]. There is considerable variability in the glycemic response and PK characteristics of metformin. In terms of PK, metformin

| Drug group | Gene /miRNA (Encoded protein) | CpG site | Effect | References |
|------------|-------------------------------|----------|--------|------------|
| Biguanides  | CFAP58 (CFA58)                | cg03529510| Association with glycemic metformin response | [93] |
|            | OR4S1                         | cg05402062|        |            |
|            | GPHA2                         | cg16704073|        |            |
|            | SAP130 (SP130)                | cg16240962|        |            |
|            | SEPT11 (SEP11)                | cg01070242|        |            |
|            | LRRN2                         | cg05151280|        |            |
|            | CSTT                          | cg07511259|        |            |
|            | SCYL1                         | cg27553780| Association with metformin intolerance |    |
|            | FOXA2 (HNF-3B)                | cg12356107|        |            |
|            | PGM1                          | cg02994863|        |            |
|            | FAM107A (F107A)               | cg08148545|        |            |
|            | SLC22A1 (OCT1)                | cg24864413| Lower DNA methylation and lower glucose levels | [94] |
|            | SLC22A3 (S22A3)               | cg06295784|        |            |
|            |                                | cg07883823|        |            |
|            | SLC47A1 (MATE1)               | cg01530032|        |            |
|            |                                | cg07829432|        |            |
|            |                                | cg12550399|        |            |
|            | miR-192                       | N. A.     | Decreased fasting glucose and HbA1c | [95, 96] |
|            | miR-140-5p                    |          |        |            |
|            | miR-222                       |          |        |            |
| Sulfonylureas| KCNJ11 (KCJ11)              | N.R.     | 26.2% vs. 27.2% | [97] |
|            | ABCC8                         |          | 0% vs. 7.2% |            |
| SGLT2 inhibitors | miR30e-5p                  | N. A.     | Upregulated | [98] |
|            |                                |          | Downregulated |            |
|            | miR199a3p                     |          |        |            |

*N.R. Not reported.*

Table 2. Epigenetics variations that influence T2D treatment.
is not metabolized, and is excreted unchanged in the urine, with a half-life of roughly 5 h. In particular, mean plasma concentrations of metformin fluctuate between 0.4 and 1.3 mg/L at a dose of 1,000 mg twice daily [103].

The disposition of metformin includes elimination and tissue distribution, which in turn involves organic transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs); both may contribute to the wide variation in metformin PK. Metformin response variability is important, in fact >30% of patients receiving metformin are classified as poor responders [102]. This drug is a polar molecule largely eliminated by the kidney without undergoing hepatic metabolization. The processes of uptake and secretion of metformin are highly dependent on membrane transporters, among which are solute carrier family 22A members 1 and 2 (SLC22A1/OCT1 and SLC22A2/OCT2, respectively), multidrug and toxin extrusion proteins MATE1 (SLC47A1) and MATE2 (SLC47A2) and the plasma membrane monoamine transporter PMAT (SLC29A4/hENT4). Therefore, impacting variants in any of these transporters may have an influence in metformin efficacy and adverse effects (Table 1). In this context, the most studied genes are SLC22A1/OCT1, SLC22A2/OCT2, SLC47A1/MATE1 and SLC47A2/MATE2. Genetic variants in SLC22A1/OCT1 are responsible for the adverse gastrointestinal effects experienced by many patients with T2D diabetes who use metformin. Dujic et al. found that 47% of participants with T2D, incident users of metformin, experienced gastrointestinal adverse effects. In the study the number of SLC22A1/OCT1 reduced-function alleles was highly correlated with over two-fold risk of gastrointestinal side effect development [20]. Consequently, the gastrointestinal adverse effects and in some cases intolerance to metformin could lead to treatment abandonment. In this same gene other variants associated to metformin response have been reported. As it can be seen in Table 1, most of the reported variants are related to a decrease in the effect of metformin, reflected in the less reduction in HbA1c levels (high concentration of HbA1c). In contrast variant rs316019 in SLC22A2/OCT2 is associated with lactic acidosis and better response to metformin, due to the evidence that this variant is related to a reduced level of metformin clearance [30, 104]. Therefore, patients with these variants may benefit receiving alternative therapy instead metformin.

The studies that evaluated the role of SLC47A1/MATE1 and SLC47A2/MATE2 SNPs in PK and PD in patients receiving metformin revealed that promoter variants in MATE1 (g.-66 T → C, rs2252281; g.-130G → A, rs2289669) are associated with a greater response to the drug in T2D patients [34, 35]. Interestingly, it is also reported that the MATE1 variant affects the PD but not the PK of metformin, a very important finding that reveals that the distribution of drugs occurs in response to the organ-specific location of the various transporters [34]. Most studies have associated variants in SLC47A2/MATE2 with contradictory effects. Concerning rs12943590, it was related to a reduced response in European populations and a better metformin response in South Indian populations; whilst rs34399035 was associated with a reduced response to metformin in European populations [31, 34]. It is important to mention that the studies were carried out in different populations, and that investigations in other ethnicities had not found associations between these variants and metformin response [105, 106]. In a recent meta-analysis by Dujic et al. there was no association between rs12943590 and glycemic response [107]. Nonetheless, it is important to note that SNP-drug interactions and SNP-SNP interactions cannot be ruled out, since the presence of other SNPs also modulate the response to drugs and are different in each individual, thus, genotyping of these SNPs should be considered if it is desired apply personalized medicine in diseases such as T2D [34].

Other SNPs in candidate genes such as SLC2A2/GLUT2 (solute carrier family 2/Glucose transporter 2) have been associated with reduction in HbA1c or treatment success, together with rs11212617 in C11orf65 (MFI, inhibitor of mitochondrial
fission), in rs2162145 CPA6 (encoded protein CBPA6, this peptidase may convert inactive angiotensin I into the biologically active angiotensin II) and rs2162145 in STK11 (serine/threonine-protein kinase involved in cell metabolism) [36–39]. In contrast, variants in genes PRPF31 (PRP31), CAPN10 (CAN10), SPI, FMO5 and SLC22A3 (OCT3) are related to reduced response to metformin. Nonetheless, these associations have not been replicated in other studies or populations.

2.1.2 Sulfonylureas

Sulfonylureas are a class of oral antidiabetic agents widely used for the management of T2D [108]. They are chosen in the first line of treatment if the patient does not present with obesity or with insulin resistance or if there is intolerance or contraindication to metformin. Also, they are used in the second line in combination with other oral hypoglycemic agents, such as metformin [109]. According to the 2003–2016 National Health and Nutrition Examination Survey (NHANES), sulfonylurea monotherapy decreased from 33–8%, nonetheless, the combination with insulin or metformin was used in 50% of patients in the mentioned period [110]. Patients with a short duration of diabetes with residual beta cell function (high C-peptide levels) are likely to be most responsive to sulfonylurea therapy [111]. The mechanism of action of sulfonylureas consists of promoting insulin secretion via binding to sulfonylurea receptor 1 (SUR1), an element of the ATP-sensitive K+ (KATP) channel. The link between sulfonylurea and SUR1 inhibits the K-ATP channel, depolarizing the β cells, increasing intracellular Ca²⁺, and consequently insulin granule exocytosis [112]. The rise of insulin levels regulates postprandial glycemia, stimulating peripheral glucose utilization [113]. Despite, sulfonylureas have a relatively short half-lifes (3 to 5 hours); they can cause hypoglycemia, which affects the quality of life and adherence to therapy in patients with T2D [114]. Two studies have reported hypoglycemia had occurred in 16–39% of patients treated with sulfonylureas [115, 116]. As a consequence, it has been estimated that 10–20% of individuals treated with sulfonylureas do not attain adequate glycemic control and 5–10% initially responding to sulfonylurea subsequently lose the ability to maintain normal glycemic level [117].

The most commonly used sulfonylureas, including the second-generation: glyburide, glipizide, and glimepiride are mainly metabolized through the cytochrome P450 (CYP) 2C9 enzyme. CYP2C9 belongs to the cytochrome P450 gene family and is the enzyme most abundantly expressed in liver. Indeed, CYP2C9 accounts for approximately 20% of total hepatic P450 protein, based on mass spectrometry quantitation [118]. It contributes to the metabolism of approximately 15% of all drugs that are subject to P450-catalyzed biotransformation, and it is responsible for >25% of metabolic clearance of oral hypoglycemic agents, such as chlorpropamide, glibenclamide, gliclazide, glimepiride, nateglinide and tolbutamide [119, 120]. Although CYP2C9 is highly polymorphic, however, only two polymorphisms have shown impact in enzyme expression and function, both allelic variants CYP2C9*2 (Arg144Cys, rs1799853) and CYP2C9*3 (Ile359Leu, rs1057910), encode proteins with less enzymatic activity for the metabolism of several substrates compared with the wild-type allele CYP2C9*1 (Arg144/Ile359). CYP2C9*2 and CYP2C9*3 are generally associated with more than 80% reduction in CYP2C9-mediated intrinsic clearance, while the effect of CYP2C9*2 is generally slightly smaller and varies considerably, depending on the substrate [120]. In both cases patients present more drug event reactions. Some studies have shown that CYP2C9 loss-of function alleles CYP2C9*2/*3 are associated with higher sulfonylurea levels and greater response to sulfonylureas. In the Go-DARTS study, patients with two copies of a loss-of-function allele were 3.4 times more probable to reach good glycemic control compared with patients with two wild-type CYP2C9 alleles,
corresponding with a 0.5% greater reduction in HbA1c [44, 45]. In several pharmacokinetic studies the two variants rs1799853 and rs1057910 in CYP2C9 have been associated with hypoglycemic events, suggesting identification of these variants as a tool to predict adverse effects of these drugs in the patients with T2D [121].

Polymorphisms in KCNJ11, ABCC8, NOS1AP, TCF7L2, CYP2C8, KCNQ1, and IRS1 genes have been associated with altered therapeutic response to sulfonylureas, which will be described below [122]. ABCC8 and KCNJ11 encode K-ATP channel proteins SUR1 and Kir6.2, respectively, both form the K-ATP channel, which controls glucose-dependent insulin secretion in pancreatic β-cells [123, 124]. It has been reported that 50% of cases of neonatal diabetes are caused by mutations in KCNJ11 or ABCC8 (SUR1) [125]. Therefore, genetic variants in ABCC8 and KCNJ11 genes could influence K-ATP channel function of beta cells, leading to changes in depolarization of the cell membrane and impact insulin secretion. Most studied SNPs in the ABCC8 gene include rs757110 (Ser1369Ala), rs1799854 (intronic variant) and rs1799859 (Arg1273Arg). Feng et al. demonstrated the association of the Ser1369Ala variant in the ABCC8 gene with fasting plasma glucose test (FPG) and two-hour plasma glucose after oral glucose tolerance test decreases after 8 weeks of gliclazide therapy. Additionally, the authors found a nominal association of the variant with levels of HbA1c, suggesting a role of this SNP on antidiabetic efficacy of gliclazides [46]. Several authors have attempted to associate this variant with insulin secretion; however, the findings have been contradictory. A study in the Diabetes Prevention Program population that includes Caucasian, African Americans, Hispanic Americans, American Indians and Asian Americans, found an association with a significantly lower insulin index, nevertheless, other studies failed to replicate this association [126–128]. Despite these data, it is interesting to mention that variant Ser1369Ala has been related with progression to diabetes [126]. Nikolac et al., found that rs1799854 and rs1799859 in the ABCC8 gene were associated with sulfonylurea efficacy in Caucasians, evidenced by significantly lower HbA1c concentrations in carriers compared with noncarriers [48].

As mentioned above, the KCNJ11 gene encodes the Kir6.2 subunit; four pore forming subunits assemble with four regulatory subunits of SUR1 to form the K-ATP channel of the β-cell [129]. Two SNPs have been associated with sulfonylureas response, rs5219 and rs5210. The rs5219 (Lys23Glu, p.E23K) A allele plays an important role in insulin secretion through reduction of ATP sensitivity of the K-ATP channel and suppression of insulin secretion. Previous studies, have demonstrated that carriers of a common variant, E23K, with normal glucose tolerance showed up to 40% reduction in glucose-stimulated insulin secretion [130, 131]. However, the mechanism of action of this locus in the insulin secretion pathway is still not completely understood. Although early observations have reported that E23K carriers exhibit higher predisposition to secondary failure when treated with sulfonylureas, other investigations have associated this variant with a better response to sulfonylureas [50, 51, 132, 133]. Additionally, some studies have suggested that the presence of the E23K variant is related to the severity of hypoglycemia in patients with sulfonylureas therapy or with lower response [52, 133].

Regarding rs5210, it has been reported that the G allele acts as a potential target for miR-1910, which is implicated in T2D; however, the mechanism of action of this miRNA in the development of T2D is unknown [134]. Moreover, variant rs5210, has been associated with gliclazide response, revealed by decreased levels of FPG test in carriers of this SNP [46].

The KCNQ1 gene belongs to a large family of voltage-gated K+ channels [135]. Although KCNQ1 is mainly expressed in the tissues or cells in the heart, it is also expressed in other tissues or organs such as pancreas islets [136]. Blocking the channels with KCNQ1 inhibitors, might stimulate secretion of insulin in pancreas, suggesting the association of KCNQ1 with the regulation of insulin secretion,
specifically with reduced insulin secretion [137]. The intronic SNPs rs2237892 and rs2237895 were shown to increase gliclazide efficacy, whereas the intronic variant rs163184, was reported to lower-sulfonylureas effects on FPG levels [53, 54].

The transcription-factor-7-like-2 (TCF7L2) gene encodes the transcription factor 7 like-2 [138]. TCF7L2 can act through GLP-1 protein (Glucagon Like Peptide 1), which plays a central role in glucose homeostasis and is involved in the regulation of insulin secretion [139]. Several studies have suggested that TCF7L2 stimulates the proliferation of β-cells in the pancreas and facilitate the production of GLP-1 in intestinal cells. In this context, it is postulated that the SNP rs7903146 could decrease the expression levels of TCF7L2 in the pancreas and lead to lower secretion of insulin due to the decreased levels of GLP1. However, the association between TCF7L2 and T2D is more complex and is not limited to the decrease in GLP1, but also to alterations in other processes regulated by TCF7L2 such as the differentiation of pancreatic beta cells, in the normal metabolism of cholesterol and in the production of other incretins [140]. Pearson et al. determined the association of two genetic variants rs1225372 and rs7903146 in TCF7L2 with the treatment success of sulfonylurea therapy in T2D patients. It was shown that 12% of the diabetic population are homozygous carriers of SNP rs1225372 and were twice as unlikely to achieve good glycemic control within 1 year of treatment initiation compared to 42% of the population with wild type [56]. These findings were replicated in Indian and European populations among others [57, 141]. Therefore, carriers of these variants are at high risk of therapy failure with sulfonylureas.

The rest of SNPs that were associated with decreased response to sulfonylurea treatment and are found in the following genes: nitric oxide synthase 1 adaptor protein (NOS1AP), insulin receptor substrate 1 (IRS-1) and ATP binding cassette subfamily A member 1 (ABCA1). NOS1AP binds to neuronal nitric oxide synthase (nNOS). This enzyme plays a role in the electrical current of the heart and in insulin release from pancreatic β cells [142, 143]. Some polymorphisms in the NOS1AP gene have been described as predictive markers of cardiovascular mortality in diabetics treated with sulfonylureas. In patients with the rs10494366 TG/GG genotypes, glibenclamide is less effective in reducing glucose levels and mortality rates compared with the wild type TT genotype. By contrast, mortality risk was lower in tolbutamide and glimepiride users who carried a G allele compared with the T/T genotype [58]. Of note, no genotype differences in mortality were observed in metformin or insulin users. The mechanisms through which this polymorphism influenced mortality risk and the reason why this association differed based on the type of sulfonylurea used are unclear. Moreover, it was shown that in users of glibenclamide the TG and GG genotypes were associated with an increased risk of mortality; in tolbutamide and glimepiride users, the TG or GG genotypes were associated with a reduced risk of mortality [144]. Conversely, in a Korean study no significance was found between rs10494366 in the NOS1AP gene and response on glimepiride treatment [145].

Regarding rs1801278 in the ISR-1 gene, this variant has been associated with increased risk for secondary failure in African an European populations [59, 60]. In case of rs9282541, T2D patients carriers of variant needed a higher dose of glyburide in order to achieve the same glucose lowering effect that persons with the wild type variant [61].

2.1.3 Thiazolidinediones

Thiazolidinediones (TZDs) are pharmacologic agents that specifically treat insulin resistance. TZDs are effective at lowering HbA1c by ~1–1.25% on average [146]. Despite durability in action, TZDs show weight gain which has limited their clinical utility [147, 148]. For every 1% reduction in HbA1c, an estimated 2–3%
weight gain is reported [149]. TZDs are transported into the liver by OATP1B1 (encoded by SLCO1B1 gene) and metabolized by CYP450 2C8 enzyme (encoded by CYP2C8 gene) [150, 151]. The most studied variant allele in the CYP2C8 gene is CYP2C8*3, which comprises two linked polymorphisms at codon 139 and codon 399 (Arg139Lys; Lys399Arg) [152].

TZDs decrease insulin resistance directly through activation of peroxisome proliferator-activated receptors-γ (PPARγ) receptors, which facilitate differentiation of mesenchymal stem cells into adipocytes, promote lipogenesis in peripheral adipocytes, decrease hepatic and peripheral triglycerides, decrease activity of visceral adipocytes, and increase adiponectin. These primary effects of TZDs markedly ameliorate insulin resistance and decrease insulin requirements [153, 154]. Individuals differ in drug response, and ~20–30% of diabetic patients fail to respond to thiazolidinediones [155]. To date, numerous case–control studies have been conducted to identify the possible relationship between PPARG gene polymorphisms with the risk of T2D in various ethnic populations [156]. The most common variant is located at exon-2 of PPARG, rs1801282, and consists of a non-synonym change Pro12Ala. This substitution leads to a change in the structure of PPARγ protein, which in turn decreases the binding effect of target genes, and reducing transcriptional activity [157]. PPARγ is also the target of antidiabetic TZD drugs, which have a unique and powerful insulin-sensitizing effect [158].

2.1.4 DPP-4 inhibitors/GLP-1 receptor agonists

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are enzyme inhibitors that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4). Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins which play an important role in insulin secretion and blood glucose regulation [159]. DPP-4 is a 766 amino acid transmembrane glycoprotein, which is also known as adenosine deaminase or CD26, is a ubiquitously expressed glycoprotein of 110 kDa, which was first characterized by Hopsu-Havu and Glenner [160].

The DPP4 gene encodes a serine aminopeptidase enzyme, which inactivates GLP-1, GIP and other proteins via dipeptide cleavage of the N-terminal amino acid. Other DPP-4 substrates include peptides containing proline or alanine, such as growth factors, chemokines, neuropeptides, and vasoactive peptides [161].

Inhibitors of DPP-4 reversibly inhibit the hydrolysis of endogenous incretins, which increases plasma levels of GIP and GLP-1, producing an increase in insulin response and a decrease in glucagon secretion. Therefore, the increase in the concentration of GLP-1 in plasma is the pharmacological effect of DPP-4 inhibitors, which increases insulin synthesis in β cells of the pancreas, stimulates the growth of these cells and prevents apoptosis [162]. Hence, DPP4 inhibition leads to greater exposure to incretins and therefore prolongs the half-life of insulin action. Because of this, DPP4 became a major target for the treatment of T2D [163].

However, it has recently been reported that some patients taking DPP-4 inhibitors are at increased risk of heart failure. It has been suggested that DPP-4 polymorphisms could potentially lead to a change in gene expression in renal cells in patients with T2D; these changes would be related to the renin-angiotensin-aldosterone system causing cardio-renal damage or myocardial hypertrophy, however further studies are needed to clarified the impact of these polymorphisms in DPP-4 inhibitors response [164].

2.1.5 SGLT-2 inhibitors

Sodium-glucose cotransporter inhibitors are adjunctive medications in the treatment of T2D. These drugs decrease HbA1c concentrations in diabetic patients,
with few adverse effects seen to date. In a healthy adult, the kidneys filter approximately 180 g of glucose per day, this is almost entirely reabsorbed into the circulation and less than 1% of glucose is excreted in the urine filtered. This reabsorption is possible thanks to the action of a family of transmembrane proteins called sodium-glucose cotransporters (SGLT, sodium glucose co-transporter) [165]. So far, seven types of sodium-glucose transporters have been identified. Particularly, type 2 (SGLT2) is responsible for glucose renal reabsorption; and is mainly found in the epithelial cells of the proximal convoluted tubule.

Glycosuria, which was initially observed as an etiopathogenic component of some renal and urinary complications in patients with T2D, has been proposed as a means to lower glucose concentrations through the pharmacological use of SGLT2 inhibitors [166]. Some SGLT-2 inhibitors can be glucuronidated by UGT enzymes (UDP-glucuronosyltransferase), thereby polymorphisms like UGT1A9*3 allele (rs72551330), in the genes encoding these drug-metabolizing enzymes could potentially influence its response. Despite, higher values of area under the curve (AUC) of canagliflozina in carriers if UGT1A9*3, the studies have not found clinical implications [90, 91]. Recently Zimdahl et al. found that common genetic variants in the SLC5A2 gene do not affect diabetes-related metabolic traits and they do not have a clinically relevant impact on response to treatment with the SGLT2 inhibitor emagliflozin [167]. Nonetheless, a study in a Caucasian population showed that rs9934336 carriers presented increased 30-min glucose concentrations after oral glucose tolerance test [92]. Studies on these drugs are few, because SGLT2 inhibitors are relatively recent. Thus, the efficacy and safety evaluation of these drugs in various clinical settings has not yet been fully established.

2.2 Epigenetics

Despite, the major contribution in drug response can be attributed to genetic components, common genetic polymorphisms explain only less than half of this genetically encoded variability, thus it is important to address other factors of drug response, such as pharmacoepigenomics [168].

Pharmacoepigenomics combines the analysis of genetic variations and epigenetic modifications in an effort to advance personalized medicine [169]. Epigenetic modification refers to processes that modify DNA or chromatin structure in a manner that alters the level of expression of genes but not the DNA sequence itself. Chemical processes that fall into the realm of epigenetics include DNA methylation and post-translational modifications of histones such as the addition of methyl, phosphate, and acetyl groups. These modifications influence the overall chromatin structure and the availability of gene regulatory regions to transcription machinery [170].

On the other hand, regulatory processes involve molecules such as miRNAs. Although miRNAs do not directly interact with DNA, they inhibit mRNA translation, therefore it is considered as having epigenetic effects [158].

Specific genes can be expressed or silenced depending on specific stimulators, such as hormone levels, dietary components or drug exposure, and can also accommodate gene-expression changes in response to gene–environment interactions [171]. Although, the cellular machinery responsible for the secretion of miRNA is not fully understood yet, it is recognized that miRNAs are packaged into microvesicles, exosomes, lipid drops and apoptotic bodies by a broad range of cell types and can be found in various types of body fluids, such as serum, plasma, and urine [172]. The miRNAs participate as negative regulators in post-transcriptional processes inhibiting mRNA translation or degrading the mRNA via the seed sequence region at the 5’ end of the miRNA, which allows the binding to its
3'-untranslated region (3'-UTR) of mRNA. miRNAs are estimated to affect approximately 30% of the process of protein coding genes [173]. A single miRNA is responsible for the expression of hundreds of proteins, and a protein-coding gene can be modulated by more than one miRNA, this is therefore a highly complex mechanism, but its results largely contribute to inter-individual variability in response to drugs. Although the study of miRNAs has focused on their involvement in the genesis of some complex diseases [174, 175] there is some evidence about their participation in the response to treatment in T2D. Interestingly the treatment with dapagliflozin (an inhibitor of sodium-glucose co-transporter 2, SGLT2), but not with hydrochlorothiazide (useful in treating high blood pressure), significantly up-regulated miR30e-5p and downregulated miR199a-3p (P < 0.05). These miRNAs are involved in the pathophysiology of heart failure and suggest a cardioprotective effect of SGLT2 inhibitor response [165].

Metformin can also interfere with the levels of miRNAs in the blood, which results in a change in the expression of the genes that are controlled by these. Ortega et al. have shown that increasing the dose of metformin modifies the levels of circulating miRNAs (started at a 425 mg/day and increased progressively during the first week to reach 1,700 mg/day), increased miR-192 (49.5%; P = 0.022) and decreased miR-140-5p (−15.8%; P = 0.004), and miR-222 (−47.2%; P = 0.03), in parallel to decreased fasting glucose and HbA1c. Revealing the response of circulating miRNAs to metformin therapy [95].

The information generated on miRNAs and their molecular actions place these molecules as innovative applications in the industry. Among the most promising prospects is the use of miRNA in medical therapy. Future studies of miRNAs that allow the generation of knowledge about their probable role in the modulation of pharmacogene expression will undoubtedly contribute to personalizing the treatment of T2D. miRNA-based therapies offer advantages over other nucleic acid therapies, because miRNAs are efficient silencers and, in contrast to plasmid DNA or synthetic oligonucleotides, miRNAs are naturally found in the bloodstream. As they target multiple mRNAs, the resulting synergistic effects could be positive for therapy, however, there are still multiple aspects that must be addressed before application to clinical trials in various human pathologies, among them, to identify the best miRNA candidates of miRNA targets for each disease type, the design of more efficient vehicles for the targeted delivery of oligonucleotides to specific organs, as well as avoiding potential toxicities and off-target effects. Low toxicity and good tolerance in patients treated with antagoniR a 15-nucleotide locked nucleic acid–modified antisense oligonucleotide whose action is sequestering mature miR-122 in a highly stable heteroduplex, thereby inhibiting its function avoiding the stability and propagation of hepatitis C virus (HCV), supporting the beneficial role of miRNAs in therapy [176]. miRNAs are naturally endogenous regulators of cell processes that are often dysregulated in diabetes restoration of any given miRNA function to normal levels will be the ultimate therapeutic goal. Several miRNAs appear to affect the function of the differentiated state of the pancreatic β-cell, while miRNAs in skeletal muscle, the liver, and adipose tissue constitute sets of different miRNAs, which is why the choice of the best molecules to treat this disease becomes very complex. Several challenges will need to be overcome in the field of pharmacotherapy with miRNA in the control of diabetes, but they will undoubtedly contribute to personalizing the treatment of this disease.

It has been suggested that epigenomics may act synergistically with pharmacogenomics towards optimization of drug therapy [177]. In addition, epigenomic somatic alterations represent an emerging class of biomarkers that hold promise for personalized therapy particularly to overcome drug resistance [178].
Regarding methylation, García-Calzón et al. evaluated the potential blood epigenetic markers associated with metformin glycemic and intolerance response. They analyzed DNA methylation in blood from newly diagnosed patients with T2D after 1.5 years of metformin treatment. According to the authors, the methylation risk scores explain 68–73% of the variation in glycemic response to metformin. In addition, the methylation risk scores explain 50–51% of the variation in metformin tolerance. In the same study, the researchers also assessed whether any of 26 SNPs previously associated with metformin response were associated with DNA methylation of any of the identified epigenetic markers. They identified one significant association between a SNP in SCL22A1 (rs628031) and DNA methylation of cg05151280 (P = 0.001, q = 0.028). The A/A genotype carriers had lower methylation (83.6 ± 2.3%) compared to carriers of the G/G (85.3 ± 1.9%, P = 0.002) and G/A (85 ± 1.8%, P = 0.006) genotypes in 132 participants from the discovery and replication cohorts. Lower methylation of this CpG site was associated with a better glycemic response to metformin (Table 2) [93]. In previous work from the same group, they assessed the DNA methylation in OCT1 encoded by SLC22A1, OCT3 encoded by SLC22A3, and MATE1 encoded by SLC47A1 liver biopsies from gastric bypass surgery. Lower promoter DNA methylation of SLC22A1, SLC22A3, and SLC47A1 were found in diabetic subjects receiving metformin. These findings suggest that metformin decreases DNA methylation of metformin transporter genes in the human liver, in contrast with the higher methylation levels in these genes associated with hyperglycemia and obesity. These findings show how a drug is capable of modulating gene expression however, the presence of genetic variants in these genes would be interfering with the methylation process with unexpected results [94].

Methylation in KCNJ11 and ABCC8 gene promoters in T2D patients receiving sulfonylurea therapy have been assessed by Karaglani et al., their results show that epigenetic changes such as methylation influence interindividual variability in treatment with sulfonylureas. They considered hypoglycemia as an outcome of the treatment. KCNJ11 methylation was detected in 21.6% of hypoglycemic individuals and in 27.7% of non-hypoglycemic patients (P = 0.353) in this study, while ABCC8 methylation in 7.2% of non-hypoglycemic and none of the hypoglycemic patients (P = 0.012). These findings suggest that ABCG8 methylation is associated with hypoglycemic events in sulfonylurea-treated T2D patients [97].

3. Conclusions

The interindividual variability in the response to a drug is the consequence of various factors, including pharmacokinetic causes: absorption, distribution, metabolism and excretion of the drug that affects the intensity and duration of the response, or to pharmacodynamic causes in drug-receptor interaction. Each of these PK and PD factors is different in each individual due to genetic, environmental or pathological determinants, and also depends on the severity or intensity of the disease to be treated.

One of the main obstacles to transferring findings from pharmacogenetics to the clinic is the impact of ethnicity on genetic variation. The highly significant associations between SNPs and the response modulated by pharmacogenetics can differ considerably between populations, which has a direct impact on drug use and dosage decisions. It is necessary then that the studies to evaluate pharmacological efficacy and pharmacogenetics, have uniformity in research designs, dosage regimens, study populations, and analytical methods.
The epidemic of T2D has forced the use of drugs that aim at glycemic control and avoid secondary complications that cause very high medical costs and decrease the quality of life of patients. However, it has been observed that even though many patients carefully follow medical guidelines, the glycemic control so desired is not achieved. Thus, with the advent of pharmacogenomics, various studies are carried out to achieve personalized medicine in this field having an impact on a better quality of life and also reducing the costs of treatment of this disease by the Health services.

In this review, the main drugs used for the treatment of T2D were analyzed and the implications that the various SNPs have on their target genes, which will affect their pharmacological response. All this opens the way for us to apply these genomic findings in daily clinical practice, in search of personalized medicine that impacts adequate glycemic control in patients with T2D in search of a better quality of life.
References

[1] Kalow W, Endrenyi L, Tang B. Repeat administration of drugs as a means to assess the genetic component in pharmacological variability. Pharmacology. 1999 Jun;58(6):281–4.

[2] Gamazon ER, Perera M. Genome-wide approaches in pharmacogenomics: heritability estimation and pharmacoethnicity as primary challenges. Vol. 13, Pharmacogenomics. 2012. p. 1101–4.

[3] Vesell ES. Genetic and environmental factors causing variation in drug response. Vol. 247, Mutation Research. 1991.

[4] Rasmussen BB, Brix TH, Kyvik KO, Brøsen K. The interindividual differences in the 3-demthylation of caffeine alias CYP1A2 is determined by both genetic and environmental factors. Pharmacogenetics. 2002 Aug;12(6):473–8.

[5] Matthaei J, Tzvetkov M V, Strube J, Sehrt D, Sachse-Seeboth C, Hjelmborg JB, et al. Heritability of Caffeine Metabolism: Environmental Effects Masking Genetic Effects on CYP1A2 Activity but Not on NAT2. Clin Pharmacol Ther. 2016 Dec;100(6):606–16.

[6] Matthaei J, Brockmöller J, Tzvetkov M V, Sehrt D, Sachse-Seeboth C, Hjelmborg JB, et al. Heritability of metoprolol and torsemide pharmacokinetics. Clin Pharmacol Ther. 2015 Dec;98(6):611–21.

[7] Matthaei J, Tzvetkov M V, Gal V, Sachse-Seeboth C, Sehrt D, Hjelmborg JB, et al. Low heritability in pharmacokinetics of talinolol: a pharmacogenetic twin study on the heritability of the pharmacokinetics of talinolol, a putative probe drug of MDR1 and other membrane transporters. Genome Med. 2016 Nov;8(1):119.

[8] Jensen O, Matthaei J, Blome F, Schwab M, Tzvetkov M V, Brockmöller J. Variability and Heritability of Thiamine Pharmacokinetics With Focus on OCT1 Effects on Membrane Transport and Pharmacokinetics in Humans. Clin Pharmacol Ther. 2020 Mar;107(3):628–38.

[9] Scott J, Poffenbarger PL. Pharmacogenetics of tolbutamide metabolism in humans. Diabetes. 1979 Jan;28(1):41–51.

[10] Gjesing AP, Hornbak M, Allin KH, Ekstrøm CT, Urhammer SA, Eiberg H, et al. High heritability and genetic correlation of intravenous glucose- and tolbutamide-induced insulin secretion among non-diabetic family members of type 2 diabetic patients. Diabetologia. 2014 Jun;57(6):1173–81.

[11] Zhou K, Donnelly L, Yang J, Li M, Deshmukh H, Van Zuydam N, et al. Heritability of variation in glycaemic response to metformin: a genome-wide complex trait analysis. lancet Diabetes Endocrinol. 2014 Jun;2(6):481–7.

[12] Online version IDF Diabetes Atlas [Internet]. [cited 2020 Dec 17]. Available from: www.diabetesatlas.org

[13] Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009 Jan;32 Suppl 1(Suppl 1):S62-7.

[14] Lorenzoni V, Baccetti F, Genovese S, Torre E, Turchetti G. Cost-consequence analysis of sitagliptin versus sulfonylureas as add-on therapy for the treatment of diabetic patients in Italy. Clinicoecon Outcomes Res. 2017;9:699–710.

[15] Cowie CC. Diabetes Diagnosis and Control: Missed Opportunities to Improve Health. Diabetes Care [Internet]. 2019 Jun 1;42(6):994 LP
[16] Shrestha J, Prajapati M, Karkee A, Shrestha H, Maharjan A. Adverse Effects of Oral Hypoglycemic Agents and Adherence to them among Patients with Type 2 Diabetes Mellitus in Nepal. J Lumbini Med Coll. 2017 Jun 29;5:6.

[17] Chahal H. Oral hypoglycemics (Review) – Adults. 19th Expert Committee on the Selection and Use of Essential Medicines. 2013.

[18] Edridge CL, Dunkley AJ, Bodicoat DH, Rose TC, Gray LJ, Davies MJ, et al. Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies. PLoS One. 2015;10(6):e0126427.

[19] Mannino GC, Andreozzi F, Sesti G. Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. Diabetes Metab Res Rev. 2019 Mar;35(3):e3109.

[20] Dujic T, Causevic A, Bego T, Malenica M, Velija-Asimi Z, Pearson ER, et al. Organic cation transporter 1 variants and gastrointestinal side effects of metformin in patients with Type 2 diabetes. Diabet Med [Internet]. 2016; 33(4):511–4. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/dme.13040

[21] Dujic T, Zhou K, Donnelly LA, Tavendale R, Palmer CNA, Pearson ER. Association of Organic Cation Transporter 1 With Intolerance to Metformin in Type 2 Diabetes: A GoDARTS Study. Diabetes [Internet]. 2015 May 1;64(5):1786 LP – 1793. Available from: http://diabetes.diabetesjournals.org/content/64/5/1786.abstract

[22] Christensen MMH, Brasch-Andersen C, Green H, Nielsen F, Damkier P, Beck-Nielsen H, et al. The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c. Pharmacogenet Genomics. 2011 Dec;21(12):837–50.

[23] Zhou Y, Ye W, Wang Y, Jiang Z, Meng X, Xiao Q, et al. Genetic variants of OCT1 influence glycemic response to metformin in Han Chinese patients with type-2 diabetes mellitus in Shanghai. Int J Clin Exp Pathol. 2015;8(8):9533–42.

[24] Umamaheswaran G, Praveen RG, Damodaran SE, Das AK, Adithan C. Influence of SLC22A1 rs622342 genetic polymorphism on metformin response in South Indian type 2 diabetes mellitus patients. Clin Exp Med. 2015 Nov;15(4):511–7.

[25] Becker ML, Visser LE, van Schaik RHN, Hofman A, Uitterlinden AG, Stricker BHC. Genetic variation in the organic cation transporter 1 is associated with metformin response in patients with diabetes mellitus. Pharmacogenomics J. 2009 Aug;9(4):242–7.

[26] Reséndiz-Abarca CA, Flores-Alfaro E, Suárez-Sánchez F, Cruz M, Valladares-Salgado A, Del Carmen Alarcón-Romero L, et al. Altered Glycemic Control Associated With Polymorphisms in the SLC22A1 (OCT1) Gene in a Mexican Population With Type 2 Diabetes Mellitus Treated With Metformin: A Cohort Study. J Clin Pharmacol. 2019 Oct;59(10):1384–90.

[27] Tarasova L, Kalhina I, Geldnere K, Bumbure A, Ritenberga R, Nikitina-Zake L, et al. Association of genetic variation in the organic cation transporters OCT1, OCT2 and multidrug and toxin extrusion 1 transporter protein genes with the gastrointestinal side effects and lower
BMI in metformin-treated type 2 diabetes patients. Pharmacogenet Genomics. 2012 Sep;22(9):659–66.

[28] Xiao D, Guo Y, Li X, Yin J-Y, Zheng W, Qiu X-W, et al. The Impacts of SLC22A1 rs594709 and SLC47A1 rs2289669 Polymorphisms on Metformin Therapeutic Efficacy in Chinese Type 2 Diabetes Patients. Int J Endocrinol. 2016;2016:4350712.

[29] Kashi Z, Masoumi P, Mahrooz A, Hashemi-Soteh MB, Bahar A, Alizadeh A. The variant organic cation transporter 2 (OCT2)-T201M contribute to changes in insulin resistance in patients with type 2 diabetes treated with metformin. Diabetes Res Clin Pract. 2015 Apr;108(1):78–83.

[30] Li Q, Liu F, Zheng T, Tang J, Lu H, Jia W. SLC22A2 gene 808 G/T variant is related to plasma lactate concentration in Chinese type 2 diabetics treated with metformin. Acta Pharmacol Sin. 2010 Feb;31(2):184–90.

[31] Phani NM, Vohra M, Kakar A, Adhikari P, Nagri SK, D’Souza SC, et al. Implication of critical pharmacokinetic gene variants on therapeutic response to metformin in Type 2 diabetes. Pharmacogenomics. 2018 Jul;19(11):905–11.

[32] Li Q, Li C, Li H, Zeng L, Kang Z, Mao Y, et al. STK11 rs2075604 Polymorphism Is Associated with Metformin Efficacy in Chinese Type 2 Diabetes Mellitus. Int J Endocrinol. 2017;2017:3402808.

[33] Zaharenko L, Kalnina I, Geldnere K, Konrade I, Grinberga S, Židzik J, et al. Single nucleotide polymorphisms in the intergenic region between metformin transporter OCT2 and OCT3 coding genes are associated with short-term response to metformin monotherapy in type 2 diabetes mellitus patients. Eur J Endocrinol. 2016 Dec;175(6):531–40.

[34] Stocker SL, Morrissey KM, Yee SW, Castro RA, Xu L, Dahlin A, et al. The effect of novel promoter variants in MATE1 and MATE2 on the pharmacokinetics and pharmacodynamics of metformin. Clin Pharmacol Ther. 2013 Feb;93(2):186–94.

[35] Tkáč I, Klimčáková L, Javorský M, Fabianová M, Schroner Z, Hermanová H, et al. Pharmacogenomic association between a variant in SLC47A1 gene and therapeutic response to metformin in type 2 diabetes. Diabetes Obes Metab. 2013 Feb;15(2):189–91.

[36] Zhou K, Yee SW, Seiser EL, van Leeuwen N, Tavendale R, Bennett AJ, et al. Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin. Nat Genet. 2016 Sep;48(9):1055–9.

[37] Rathmann W, Strassburger K, Bongaerts B, Kuss O, Müssig K, Burkart V, et al. A variant of the glucose transporter gene SLC2A2 modifies the glycaemic response to metformin therapy in recently diagnosed type 2 diabetes. Diabetologia. 2019 Feb;62(2):286–91.

[38] van Leeuwen N, Nijpels G, Becker ML, Deshmukh H, Zhou K, Stricker BHC, 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 Jul;55(7):1971–7.

[39] Rotroff DM, Yee SW, Zhou K, Marvel SW, Shah HS, Jack JR, et al. Genetic Variants in CPA6 and PRPF31 Are Associated With Variation in Response to Metformin in Individuals With Type 2 Diabetes. Diabetes. 2018 Jul;67(7):1428–40.

[40] Tkáč I, Javorský M, Klimčáková L, Židzik J, Gaša I, Babjaková E, et al. A pharmacogenetic association between a
variation in calpain 10 (CAPN10) gene and the response to metformin treatment in patients with type 2 diabetes. Eur J Clin Pharmacol. 2015 Jan;71(1):59–63.

[41] Goswami S, Yee SW, Stocker S, Mosley JD, Kubo M, Castro R, et al. Genetic variants in transcription factors are associated with the pharmacokinetics and pharmacodynamics of metformin. Clin Pharmacol Ther. 2014 Sep;96(3):370–9.

[42] Breitenstein MK, Wang L, Simon G, Ryu E, Armasu SM, Ray B, et al. Leveraging an Electronic Health Record-Linked Biorepository to Generate a Metformin Pharmacogenomics Hypothesis. AMIA Jt Summits Transl Sci proceedings AMIA Jt Summits Transl Sci. 2015;2015:26–30.

[43] Chen EC, Liang X, Yee SW, Geier EG, Stocker SL, Chen L, et al. Targeted disruption of organic cation transporter 3 attenuates the pharmacologic response to metformin. Mol Pharmacol. 2015 Jul;88(1):75–83.

[44] Zhou K, Donnelly L, Burch L, Tavendale R, Doney ASF, Leese G, et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a GoDARTS study. Clin Pharmacol Ther. 2010 Jan;87(1):52–6.

[45] Castelán-Martínez OD, Hoyo-Vadillo C, Bazán-Soto TB, Cruz M, Tesoro-Cruz E, Valladares-Salgado A. CYP2C9*3 gene variant contributes independently to glycaemic control in patients with type 2 diabetes treated with glibenclamide. J Clin Pharm Ther. 2018 Dec;43(6):768–74.

[46] Feng Y, Mao G, Ren X, Xing H, Tang G, Li Q, et al. Ser1369Ala variant in sulfonylurea receptor gene ABCC8 is associated with antidiabetic efficacy of gliclazide in Chinese type 2 diabetic patients. Diabetes Care. 2008 Oct;31(10):1939–44.

[47] Zhang H, Liu X, Kuang H, Yi R, Xing H. Association of sulfonylurea receptor 1 genotype with therapeutic response to gliclazide in type 2 diabetes. Diabetes Res Clin Pract. 2007 Jul;77(1):58–61.

[48] Nikolac N, Simundic A-M, Katalinic D, Topic E, Cipak A, Zjacic Rotkvic V. Metabolic control in type 2 diabetes is associated with sulfonylurea receptor-1 (SUR-1) but not with KCNJ11 polymorphisms. Arch Med Res. 2009 Jul;40(5):387–92.

[49] Zhou X, Chen C, Yin D, Zhao F, Bao Z, Zhao Y, et al. A Variation in the ABCC8 Gene Is Associated with Type 2 Diabetes Mellitus and Repaglinide Efficacy in Chinese Type 2 Diabetes Mellitus Patients. Intern Med. 2019 Aug;58(16):2341–7.

[50] Javorsky M, Klimcakova L, Schroner Z, Zidzik J, Babjakova E, Fabianova M, et al. KCNJ11 gene E23K variant and therapeutic response to sulfonylureas. Eur J Intern Med. 2012 Apr;23(3):245–9.

[51] Li Q, Chen M, Zhang R, Jiang F, Wang J, Zhou J, et al. KCNJ11 E23K variant is associated with the therapeutic effect of sulphonylureas in Chinese type 2 diabetic patients. Clin Exp Pharmacol Physiol. 2014 Oct;41(10):748–54.

[52] Sanchez-Ibarra HE, Reyes-Cortes LM, Jiang X-L, Luna-Aguirre CM, Aguirre-Trevino D, Morales-Alvarado IA, et al. Genotypic and Phenotypic Factors Influencing Drug Response in Mexican Patients With Type 2 Diabetes Mellitus. Front Pharmacol. 2018;9:320.

[53] Schroner Z, Dobrikova M, Klimcakova L, Javorsky M, Zidzik J, Kozarova M, et al. Variation in KCNQ1 is associated with therapeutic response
to sulphonylureas. Med Sci Monit Int Med J Exp Clin Res. 2011 Jul;17(7): CR392-6.

[54] Li Q, Tang T-T, Jiang F, Zhang R, Chen M, Yin J, et al. Polymorphisms of the KCNQ1 gene are associated with the therapeutic responses of sulfonylureas in Chinese patients with type 2 diabetes. Acta Pharmacol Sin. 2017 Jan;38(1): 80–9.

[55] Javorský M, Babjaková E, Klimčáková L, Schroner Z, Zidzik J, Stolfová M, et al. Association between TCF7L2 Genotype and Glycemic Control in Diabetic Patients Treated with Gliclazide. Int J Endocrinol. 2013; 2013:374858.

[56] Pearson ER, Donnelly LA, Kimber C, Whitley A, Doney ASF, McCarthy MI, et al. Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDART’s study. Diabetes. 2007 Aug;56(8):2178–82.

[57] Holstein A, Hahn M, Körner A, Stumvoll M, Kovacs P. TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes. BMC Med Genet. 2011 Feb;12:30.

[58] Becker ML, Aarnoudse A-JLHJ, Newton-Cheh C, Hofman A, Witteman JCM, Uitterlinden AG, et al. Common variation in the NOS1AP gene is associated with reduced glucose-lowering effect and with increased mortality in users of sulfonylurea. Pharmacogenet Genomics. 2008 Jul;18(7):591–7.

[59] El-Sisi AE, Hegazy SK, Metwally SS, Wafa AM, Dawood NA. Effect of genetic polymorphisms on the development of secondary failure to sulfonylurea in Egyptian patients with type 2 diabetes. Ther Adv Endocrinol Metab. 2011 Aug;2(4):155–64.

[60] Sesti G, Marini MA, Cardellini M, Sciacqu a A, Frontoni S, Andreozzi F, et al. The Arg972 variant in insulin receptor substrate-1 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes. Diabetes Care. 2004 Jun;27(6): 1394–8.

[61] Aguilar-Salinas CA, Muñoz-Hernandez LL, Cobos-Bonilla M, Ramírez-Márquez MR, Ordoñez-Sanchez ML, Mehta R, et al. The R230C variant of the ATP binding cassette protein A1 (ABCA1) gene is associated with a decreased response to glyburide therapy in patients with type 2 diabetes mellitus. Metabolism. 2013 May;62(5): 638–41.

[62] Hsieh M-C, Lin K-D, Tien K-J, Tu S-T, Hsiao J-Y, Chang S-J, et al. Common polymorphisms of the peroxisome proliferator-activated receptor-gamma (Pro12Ala) and peroxisome proliferator-activated receptor-gamma coactivator-1 (Gly482Ser) and the response to pioglitazone in Chinese patients with type 2 diabetes mellitus. Metabolism. 2010 Aug;59(8):1139–44.

[63] Pei Q, Huang Q, Yang G, Zhao Y, Yin J, Song M, et al. PPAR-γ2 and PTPRD gene polymorphisms influence type 2 diabetes patients’ response to pioglitazone in China. Acta Pharmacol Sin. 2013 Feb;34(2):255–61.

[64] Wolford JK, Yeatts KA, Dhanjal SK, Black MH, Xiang AH, Buchanan TA, et al. Sequence Variation in PPARG May Underlie Differential Response to Troglitazone. Diabetes [Internet]. 2005; 54(11):3319–25. Available from: https://diabetes.diabetesjournals.org/content/54/11/3319

[65] Zhang K-H, Huang Q, Dai X-P, Yin J-Y, Zhang W, Zhou G, et al. Effects of the peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α) Thr394Thr and Gly482Ser polymorphisms on rosiglitazone response in Chinese patients with type 2 diabetes mellitus. J Clin Pharmacol. 2010 Sep;50(9):1022–30.
[66] Yang M, Huang Q, Wu J, Yin J-Y, Sun H, Liu H-L, et al. Effects of UCP2-866 G/A and ADRB3 Trp64Arg on rosiglitazone response in Chinese patients with Type 2 diabetes. Br J Clin Pharmacol. 2009 Jul;68(1):14–22.

[67] Dawed AY, Donnelly L, Tavendale R, Carr F, Leese G, Palmer CNA, et al. CYP2C8 and SLCO1B1 Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes. Diabetes Care. 2016 Nov;39(11):1902–8.

[68] Sun H, Gong Z-C, Yin J-Y, Liu H-L, Liu Y-Z, Guo Z-W, et al. The association of adiponectin allele 45T/G and –11377C/G polymorphisms with Type 2 diabetes and rosiglitazone response in Chinese patients. Br J Clin Pharmacol. 2008;65(6):917–26.

[69] Yang H, Ye E, Si G, Chen L, Cai L, Ye C, et al. Adiponectin gene polymorphism rs2241766 T/G is associated with response to pioglitazone treatment in type 2 diabetic patients from southern China. PLoS One. 2014;9(11):e112480.

[70] Kang ES, Park SY, Kim HJ, Ahn CW, Nam M, Cha BS, et al. The influence of adiponectin gene polymorphism on the rosiglitazone response in patients with type 2 diabetes. Diabetes Care. 2005 May;28(5):1139–44.

[71] Li Z, Peng X, Wu Y, Xia Y, Liu X, Zhang Q. The influence of adiponectin gene polymorphism on the pioglitazone response in the Chinese with type 2 diabetes. Vol. 10, Diabetes, obesity & metabolism. England; 2008. p. 794–802.

[72] MAKINO H, SHIMIZU I, MURAO S, KONDO S, TABARA Y, FUJIYAMA M, et al. A Pilot Study Suggests that the G/G Genotype of Resistin Single Nucleotide Polymorphism at -420 May Be an Independent Predictor of a Reduction in Fasting Plasma Glucose and Insulin Resistance by Pioglitazone in Type 2 Diabetes. Endocr J. 2009;56(9):1049–58.

[73] Liu H-L, Lin Y-G, Wu J, Sun H, Gong Z-C, Hu P-C, et al. Impact of genetic polymorphisms of leptin and TNF-alpha on rosiglitazone response in Chinese patients with type 2 diabetes. Eur J Clin Pharmacol. 2008 Jul;64(7):663–71.

[74] Zimdahl H, Ittrich C, Graefe-Mody U, Boehm BO, Mark M, Woerle H-J, et al. Influence of TCF7L2 gene variants on the therapeutic response to the dipeptidylpeptidase-4 inhibitor linagliptin. Diabetologia. 2014 Sep;57(9):1869–75.

[75] Jamaluddin JL, Huri HZ, Vethakkan SR. Clinical and genetic predictors of dipeptidyl peptidase-4 inhibitor treatment response in Type 2 diabetes mellitus. Pharmacogenomics. 2016 Jun;17(8):867–81.

[76] ’t Hart LM, Fritsche A, Nijpels G, van Leeuwen N, Donnelly LA, Dekker JM, et al. The CTRB1/2 locus affects diabetes susceptibility and treatment via the incretin pathway. Diabetes. 2013 Sep;62(9):3275–81.

[77] Gotthardová I, Javorský M, Klimčáková L, Kvařil M, Schroner Z, Kozárová M, et al. KCNQ1 gene polymorphism is associated with glycaemic response to treatment with DPP-4 inhibitors. Diabetes Res Clin Pract. 2017 Aug;130:142–7.

[78] Han E, Park HS, Kwon O, Choe EY, Wang HJ, Lee Y-H, et al. A genetic variant in GLP1R is associated with response to DPP-4 inhibitors in patients with type 2 diabetes. Medicine (Baltimore). 2016 Nov;95(44):e5155.

[79] Javorský M, Gotthardová I, Klimčáková L, Kvařil M, Židzik J, Schroner Z, et al. A missense variant in
GLP1R gene is associated with the glycaemic response to treatment with gliptins. Diabetes Obes Metab. 2016 Sep;18(9):941–4.

[80] Ūrgeová A, Javorský M, Klímčáková L, Židzik J, Šalagovič J, Hubáček JA, et al. Genetic variants associated with glycemic response to treatment with dipeptidylpeptidase 4 inhibitors. Pharmacogenomics. 2020 Apr;21(5):317–23.

[81] Wilson JR, Shuey MM, Brown NJ, Devin JK. Hypertension and Type 2 Diabetes Are Associated With Decreased Inhibition of Dipeptidyl Peptidase-4 by Sitagliptin. J Endocr Soc. 2017 Sep;1(9):1168–78.

[82] Liao W-L, Lee W-J, Chen C-C, Lu CH, Chen C-H, Chou Y-C, et al. Pharmacogenetics of dipeptidyl peptidase 4 inhibitors in a Taiwanese population with type 2 diabetes. Oncotarget. 2017 Mar;8(11):18050–8.

[83] Iskakova A, Aitkulova A, Sikhayeva N, Romanova AA, Maratkyzy L, Akanov Z, et al. Dipeptidyl peptidase-4 inhibitors: sensitivity markers. Biotechnol Theory Pract. 2017 Sep 18;13:20.

[84] Osada UN, Sunagawa H, Terauchi Y, Ueda S. A Common Susceptibility Gene for Type 2 Diabetes Is Associated with Drug Response to a DPP-4 Inhibitor: Pharmacogenomic Cohort in Okinawa Japan. PLoS One. 2016;11(5):e0154821.

[85] Yu M, Wang K, Liu H, Cao R. GLP1R variant is associated with response to exenatide in overweight Chinese Type 2 diabetes patients. Pharmacogenomics. 2019 Mar;20(4):273–7.

[86] Ferreira MC, da Silva MER, Fukui RT, do Carmo Arruda-Marques M, Azhar S, Dos Santos RF. Effect of TCF7L2 polymorphism on pancreatic hormones after exenatide in type 2 diabetes. Diabetol Metab Syndr. 2019;11:10.

[87] Lin C-H, Lee Y-S, Huang Y-Y, Hsieh S-H, Chen Z-S, Tsai C-N. Polymorphisms of GLP-1 receptor gene and response to GLP-1 analogue in patients with poorly controlled type 2 diabetes. J Diabetes Res. 2015;2015:176949.

[88] Zhou LM, Xu W, Yan XM, Li MXY, Liang H, Weng JP. [Association between SORCS1 rs1416406 and therapeutic effect of exenatide]. Zhonghua Yi Xue Za Zhi. 2017 May;97(18):1415–9.

[89] de Luis DA, Aller R, Izaola O, de la Fuente B, Romero E. Genetic variation in the beta-3-adrenoceptor gene (Trp64Arg polymorphism) and their influence on anthropometric parameters and insulin resistance after a high protein/low carbohydrate versus a standard hypocaloric diet. Nutr Hosp. 2015 Aug;32(2):487–93.

[90] Francke S, Mamidi RNVS, Solanki B, Scheers E, Jadwin A, Favis R, et al. In vitro metabolism of canagliflozin in human liver, kidney, intestine microsomes, and recombinant uridine diphosphate glucuronosyltransferases (UGT) and the effect of genetic variability of UGT enzymes on the pharmacokinetics of canagliflozin in humans. J Clin Pharmacol. 2015 Sep;55(9):1061–72.

[91] Hoeben E, De Winter W, Neyens M, Devineni D, Vermeulen A, Dunne A. Population Pharmacokinetic Modeling of Canagliflozin in Healthy Volunteers and Patients with Type 2 Diabetes Mellitus. Clin Pharmacokinet. 2016 Feb;55(2):209–23.

[92] Enigk U, Breitfeld J, Schleinitz D, Dietrich K, Halbritter J, Fischer-Rosinsky A, et al. Role of genetic variation in the human sodium-glucose cotransporter 2 gene (SGLT2) in glucose...
homeostasis. Pharmacogenomics. 2011 Aug;12(8):1119–26.

[93] García-Calzón S, Perfilyev A, Martinell M, Ustinova M, Kalamajski S, Franks PW, et al. Epigenetic markers associated with metformin response and intolerance in drug-naïve patients with type 2 diabetes. Sci Transl Med. 2020 Sep;12(561).

[94] García-Calzón S, Perfilyev A, Männistö V, de Mello VD, Nilsson E, Pihlajamäki J, et al. Diabetes medication associates with DNA methylation of metformin transporter genes in the human liver. Clin Epigenetics. 2017;9:102.

[95] Ortega FJ, Mercader JM, Moreno-Navarrete JM, Rovira O, Guerra E, Esteve E, et al. Profiling of circulating microRNAs reveals common microRNAs linked to type 2 diabetes that change with insulin sensitization. Diabetes Care. 2014;37(5):1375–83.

[96] Coleman CB, Lightell DJJ, Moss SC, Bates M, Parrino PE, Woods TC. Elevation of miR-221 and -222 in the internal mammary arteries of diabetic subjects and normalization with metformin. Mol Cell Endocrinol. 2013 Jul;374(1–2):125–9.

[97] Karaglani M, Ragia G, Panagopoulou M, Balgkouranidou I, Nena E, Kolios G, et al. Search for Pharmacoepigenetic Correlations in Type 2 Diabetes Under Sulfonylurea Treatment. Exp Clin Endocrinol diabetes Off journal, Ger Soc Endocrinol [and] Ger Diabetes Assoc. 2019 Apr;127(4):226–33.

[98] Solini A, Seghieri M, Giannini L, Biancalana E, Parolini F, Rossi C, et al. The Effects of Dapagliflozin on Systemic and Renal Vascular Function Display an Epigenetic Signature. J Clin Endocrinol Metab. 2019;104(10):4253–63.

[99] Shastry BS. SNPs: impact on gene function and phenotype. Methods Mol Biol. 2009;578:3–22.

[100] 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021 Jan;44(Supplement 1):S111 LP-S124.

[101] Rojas LBA, Gomes MB. Metformin: an old but still the best treatment for type 2 diabetes. Diabetol Metab Syndr. 2013 Feb;5(1):6.

[102] Cook MN, Girman 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 Apr;24(4):350–8.

[103] Graham GG, Punt J, Arora M, Day RO, Doogue MP, Duong JK, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011 Feb;50(2):81–98.

[104] Yoon H, Cho H-Y, Yoo H-D, Kim S-M, Lee Y-B. Influences of organic cation transporter polymorphisms on the population pharmacokinetics of metformin in healthy subjects. AAPS J. 2013 Apr;15(2):571–80.

[105] Menjivar M, Sánchez-Pozos K, Jaimé-Santoyo J, Monroy-Escutia J, Rivera-Santiago C, de Los Ángeles Granados-Silvestre M, et al. Pharmacogenetic Evaluation of Metformin and Sulphonylurea Response in Mexican Mestizos with Type 2 Diabetes. Curr Drug Metab. 2020;21(4):291–300.

[106] Raj GM, Mathaiyam J, Wyawahare M, Priyadarshini R. Lack of effect of the SLC47A1 and SLC47A2 gene polymorphisms on the glycemic response to metformin in type 2 diabetes mellitus patients. Drug Metab Pers Ther. 2018 Dec;33(4):175–85.

[107] Dujic T, Zhou K, Yee SW, van Leeuwen N, de Keyser CE, Javorský M,
et al. Variants in Pharmacokinetic Transporters and Glycemic Response to Metformin: A Metgen Meta-Analysis. Clin Pharmacol Ther. 2017 Jun;101(6):763–72.

[108] Sola D, Rossi L, Schianca GPC, Maffioli P, Bigliocca M, Mella R, et al. Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015 Aug;11(4):840–8.

[109] Tahrani AA, Barnett AH, Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. Nat Rev Endocrinol. 2016 Oct;12(10):566–92.

[110] Le P, Chaitoff A, Misra-Hebert AD, Ye W, Herman WH, Rothberg MB. Use of Antihyperglycemic Medications in U.S. Adults: An Analysis of the National Health and Nutrition Examination Survey. Diabetes Care. 2020 Jun;43(6):1227–33.

[111] DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Vol. 133, Annals of internal medicine. United States; 2000. p. 73–4.

[112] Seino S, Sugawara K, Yokoi N, Takahashi H. β-Cell signalling and insulin secretagogues: A path for improved diabetes therapy. Diabetes, Obes Metab. 2017;19(S1):22–9.

[113] Dunkley AJ, Fitzpatrick C, Gray LJ, Waheed G, Heller SR, Frier BM, et al. Incidence and severity of hypoglycaemia in type 2 diabetes by treatment regimen: A UK multisite 12-month prospective observational study. Diabetes Obes Metab. 2019 Jul;21(7):1585–95.

[114] Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycaemia and risks of vascular events and death. N Engl J Med. 2010 Oct;363(15):1410–8.

[115] Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM.

Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med. 2001 Jul;161(13):1653–9.

[116] Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia. 2007 Jun;50(6):1140–7.

[117] Aquilante CL. Sulfonylurea pharmacogenomics in Type 2 diabetes: the influence of drug target and diabetes risk polymorphisms. Expert Rev Cardiovasc Ther. 2010 Mar;8(3):359–72.

[118] Zhang H-F, Wang H-H, Gao N, Wei J-Y, Tian X, Zhao Y, et al. Physiological Content and Intrinsic Activities of 10 Cytochrome P450 Isoforms in Human Normal Liver Microsomes. J Pharmacol Exp Ther. 2016 Jul;358(1):83–93.

[119] Isvoran A, Louet M, Vladoiu DL, Craciun D, Loriot M-A, Villoutreix BO, et al. Pharmacogenomics of the cytochrome P450 2C family: impacts of amino acid variations on drug metabolism. Drug Discov Today. 2017 Feb;22(2):366–76.

[120] Daly AK, Rettie AE, Fowler DM, Miners JO. Pharmacogenomics of CYP2C9: Functional and Clinical Considerations. J Pers Med. 2017 Dec;8(1).

[121] Ragia G, Petridis I, Tavridou A, Christakidis D, Manolopoulos VG. Presence of CYP2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics. 2009 Nov;10(11):1781–7.

[122] Nasykhova YA, Tonyan ZN, Mikhailova AA, Danilova MM, Glotov AS. Pharmacogenetics of Type 2 Diabetes-Progress and Prospects. Int J Mol Sci. 2020 Sep;21(18).

[123] McTaggart JS, Clark RH, Ashcroft FM. The role of the KATP
channel in glucose homeostasis in health and disease: more than meets the islet. J Physiol. 2010 Sep;588(Pt 17):3201–9.

[124] Emdin CA, Klarin D, Natarajan P, Florez JC, Kathiresan S, Khera A V. Genetic Variation at the Sulfonylurea Receptor, Type 2 Diabetes, and Coronary Heart Disease. Diabetes. 2017 Aug;66(8):2310–5.

[125] Cordiner RLM, Pearson ER. Reflections on the sulphonylurea story: A drug class at risk of extinction or a drug class worth reviving? Diabetes Obes Metab. 2019 Apr;21(4):761–71.

[126] Florez JC, Jablonski KA, Kahn SE, Franks PW, Dabelea D, Hamman RF, et al. Type 2 diabetes-associated missense polymorphisms KCNJ11 E23K and ABCC8 A1369S influence progression to diabetes and response to interventions in the Diabetes Prevention Program. Diabetes. 2007 Feb;56(2):531–6.

[127] Hansen T, Echwald SM, Hansen L, Møller AM, Almind K, Clausen JO, et al. Decreased tolbutamide-stimulated insulin secretion in healthy subjects with sequence variants in the high-affinity sulfonylurea receptor gene. Diabetes. 1998 Apr;47(4):598–605.

[128] Rissanen J, Markkanen A, Kärkkäinen P, Pihlajamäki J, Kekäläinen P, Mykkänen L, et al. Sulfonylurea receptor 1 gene variants are associated with gestational diabetes and type 2 diabetes but not with altered secretion of insulin. Diabetes Care. 2000 Jan;23(1):70–3.

[129] Quan Y, Barszczyk A, Feng Z, Sun H. Current understanding of K ATP channels in neonatal diseases: focus on insulin secretion disorders. Acta Pharmacol Sin. 2011 Jun;32(6):765–80.

[130] Villareal DT, Koster JC, Robertson H, Akrouh A, Miyake K, Bell GI, et al. Kir6.2 variant E23K increases ATP-sensitive K+ channel activity and is associated with impaired insulin release and enhanced insulin sensitivity in adults with normal glucose tolerance. Diabetes. 2009 Aug;58(8):1869–78.

[131] Florez JC, Burtt N, de Bakker PIW, Almgren P, Tuomi T, Holmkvist J, et al. Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. Diabetes. 2004 May;53(5):1360–8.

[132] Sesti G, Laratta E, Cardellini M, Andreozzi F, Del Guerra S, Irace C, et al. The E23K variant of KCNJ11 encoding the pancreatic beta-cell adenine 5'-triphosphate-sensitive potassium channel subunit Kir6.2 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes. J Clin Endocrinol Metab. 2006 Jun;91(6):2334–9.

[133] Holstein A, Hahn M, Stumvoll M, Kovacs P. The E23K variant of KCNJ11 and the risk for severe sulfonylurea-induced hypoglycemia in patients with type 2 diabetes. Horm Metab Res = Horm und Stoffwechsel = Horm Metab. 2009 May;41(5):387–90.

[134] Haghvirdizadeh P, Mohamed Z, Abdullah NA, Haghvirdizadeh P, Haerian MS, Haerian BS. KCNJ11: Genetic Polymorphisms and Risk of Diabetes Mellitus. J Diabetes Res. 2015;2015:908152.

[135] Ohshige T, Tanaka Y, Araki S, Babazono T, Toyoda M, Umezono T, et al. A single nucleotide polymorphism in KCNQ1 is associated with susceptibility to diabetic nephropathy in japanese subjects with type 2 diabetes. Diabetes Care. 2010 Apr;33(4):842–6.

[136] Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M, Romey G. K(V) LQT1 and IsK (minK) proteins associate...
to form the I(Ks) cardiac potassium current. Nature. 1996 Nov;384(6604): 78–80.

[137] Ullrich S, Su J, Ranta F, Wittekindt OH, Ris F, Rössler M, et al. Effects of I(Ks) channel inhibitors in insulin-secreting INS-1 cells. Pflugers Arch. 2005 Dec;451(3):428–36.

[138] Grant SFA, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet. 2006 Mar;38(3):320–3.

[139] da Silva Xavier G, Loder MK, McDonald A, Tarasov AI, Carzaniga R, Kronenberger K, et al. TCF7L2 regulates late events in insulin secretion from pancreatic islet beta-cells. Diabetes. 2009 Apr;58(4):894–905.

[140] Zhou Y, Park S-Y, Su J, Bailey K, Ottosson-Laakso E, Shcherbina L, et al. TCF7L2 is a master regulator of insulin production and processing. Hum Mol Genet. 2014 Dec;23(24):6419–31.

[141] Dhawan D, Padh H. Genetic variations in TCF7L2 influence therapeutic response to sulfonylureas in Indian diabetics. Diabetes Res Clin Pract. 2016 Nov;121:35–40.

[142] Gunawardana SC, Rocheleau J V, Head WS, Piston DW. Mechanisms of time-dependent potentiation of insulin release: involvement of nitric oxide synthase. Diabetes. 2006 Apr;55(4):1029–33.

[143] Schulz R, Rassaf T, Massion PB, Kelm M, Balligand J-L. Recent advances in the understanding of the role of nitric oxide in cardiovascular homeostasis. Pharmacol Ther. 2005;108(3):225–56.

[144] Treuer A V, Gonzalez DR. NOS1AP modulates intracellular Ca(2+) in cardiac myocytes and is up-regulated in dystrophic cardiomyopathy. Int J Physiol Pathophysiol Pharmacol. 2014;6(1):37–46.

[145] Cho H-J, Lee S-Y, Kim Y-G, Oh S-Y, Kim J-W, Huh W, et al. Effect of genetic polymorphisms on the pharmacokinetics and efficacy of glimepiride in a Korean population. Clin Chim Acta. 2011 Sep;412(19–20): 1831–4.

[146] Sherifali D, Nerenberg K, Pullenayegum E, Cheng JE, Gerstein HC. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010 Aug;33(8):1859–64.

[147] Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006 Dec;355(23):2427–43.

[148] Bailey CJ. Safety of antidiabetes medications: An update. Clin Pharmacol Ther. 2015 Aug;98(2):185–95.

[149] Yki-Järvinen H. Thiazolidinediones. N Engl J Med. 2004 Sep;351(11):1106–18.

[150] Baldwin SJ, Clarke SE, Chenery RJ. Characterization of the cytochrome P450 enzymes involved in the in vitro metabolism of rosiglitazone. Br J Clin Pharmacol. 1999 Sep;48(3):424–32.

[151] Chang C, Pang KS, Swaan PW, Ekins S. Comparative pharmacophore modeling of organic anion transporting polypeptides: a meta-analysis of rat Oatp1a1 and human OATP1B1. J Pharmacol Exp Ther. 2005 Aug;314(2):533–41.

[152] Aquilante CL, Bushman LR, Knutsen SD, Burt LE, Rome LC, Kosmiski LA. Influence of SLCO1B1 and CYP2C8 gene polymorphisms on rosiglitazone pharmacokinetics in
healthy volunteers. Hum Genomics. 2008 Sep;3(1):7–16.

[153] Lebovitz HE, Banerji MA. Insulin resistance and its treatment by thiazolidinediones. Recent Prog Horm Res. 2001;56:265–94.

[154] Olefsky JM, Saltiel AR. PPAR gamma and the treatment of insulin resistance. Trends Endocrinol Metab. 2000 Nov;11(9):362–8.

[155] Sears DD, Hsiao G, Hsiao A, Yu JG, Courtney CH, Ofrecio JM, et al. Mechanisms of human insulin resistance and thiazolidinedione-mediated insulin sensitization. Proc Natl Acad Sci U S A. 2009 Nov;106(44):18745–50.

[156] Sarhangi N, Sharifi F, Hashemian L, Hassani Doabsari M, Heshmatzad K, Rahbaran M, et al. PPARG (Prot12Ala) genetic variant and risk of T2DM: a systematic review and meta-analysis. Sci Rep. 2020 Jul;10(1):12764.

[157] Tamori Y, Masugi J, Nishino N, Kasuga M. Role of peroxisome proliferator-activated receptor-gamma in maintenance of the characteristics of mature 3T3-L1 adipocytes. Diabetes. 2002 Jul;51(7):2045–55.

[158] Vasilatou D, Papageorgiou SG, Dimitriadis G, Pappa V. Epigenetic alterations and microRNAs: new players in the pathogenesis of myelodysplastic syndromes. Epigenetics. 2013 Jun;8(6):561–70.

[159] Green BD, Flatt PR, Bailey CJ. Dipeptidyl peptidase IV (DPP IV) inhibitors: A newly emerging drug class for the treatment of type 2 diabetes. Diabetes Vasc Dis Res. 2006 Dec;3(3):159–65.

[160] Hopsu-Havu VK, Glenner GG. A new dipeptide naphthylamidase hydrolyzing glycy1-proly1-betanaphthylamide. Histochemie. 1966;7(3):197–201.

[161] Jose T, Inzucchi SE. Cardiovascular effects of the DPP-4 inhibitors. Diabetes Vasc Dis Res. 2012 Apr;9(2):109–16.

[162] Brown DX, Evans M. Choosing between GLP-1 Receptor Agonists and DPP-4 Inhibitors: A Pharmacological Perspective. J Nutr Metab. 2012;2012:381713.

[163] Röhrborn D, Wronkowitz N, Eckel J. DPP4 in Diabetes. Front Immunol. 2015;6:386.

[164] Krittanawong C, Xanthopoulos A, Kitai T, Branis N, Zhang H, Kukin M. DPP-4 inhibitors and heart failure: a potential role for pharmacogenomics. Heart Fail Rev. 2018 May;23(3):355–61.

[165] Neumiller JJ, White JRJ, Campbell RK. Sodium-glucose co-transport inhibitors: progress and therapeutic potential in type 2 diabetes mellitus. Drugs. 2010 Mar;70(4):377–85.

[166] Nair S, Wilding JPH. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. J Clin Endocrinol Metab. 2010 Jan;95(1):34–42.

[167] Zimdahl H, Haupt A, Brendel M, Bour L, Machico F, Salsali A, et al. Influence of common polymorphisms in the SLC5A2 gene on metabolic traits in subjects at increased risk of diabetes and on response to empagliflozin treatment in patients with diabetes. Pharmacogenet Genomics. 2017 Apr;27(4):135–42.

[168] Lauschke VM, Ingelman-Sundberg M. Prediction of drug response and adverse drug reactions: From twin studies to Next Generation Sequencing. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2019 Mar;130:65–77.

[169] Ingelman-Sundberg M, Gomez A. The past, present and future of pharmacoepigenomics. Pharmacogenomics. 2010 May;11(5):625–7.
[170] Harvey ZH, Chen Y, Jarosz DF. Protein-Based Inheritance: Epigenetics beyond the Chromosome. Mol Cell. 2018 Jan;69(2):195–202.

[171] Delcuve GP, Rastegar M, Davie JR. Epigenetic control. J Cell Physiol. 2009 May;219(2):243–50.

[172] Diehl P, Fricke A, Sander L, Stamm J, Bassler N, Htun N, et al. Microparticles: major transport vehicles for distinct microRNAs in circulation. Cardiovasc Res. 2012 Mar;93(4):633–44.

[173] Sekar D, Venugopal B, Sekar P, Ramalingam K. Role of microRNA 21 in diabetes and associated/related diseases. Gene. 2016 May;582(1):14–8.

[174] Rottiers V, Näär AM. MicroRNAs in metabolism and metabolic disorders. Nat Rev Mol Cell Biol. 2012 Mar;13(4):239–50.

[175] Fu X, Dong B, Tian Y, Lefebvre P, Meng Z, Wang X, et al. MicroRNA-26a regulates insulin sensitivity and metabolism of glucose and lipids. J Clin Invest. 2015 Jun;125(6):2497–509.

[176] Janssen HLA, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, et al. Treatment of HCV infection by targeting microRNA. N Engl J Med. 2013 May;368(18):1685–94.

[177] Ingelman-Sundberg M, Sim SC. Pharmacogenetic biomarkers as tools for improved drug therapy; emphasis on the cytochrome P450 system. Biochem Biophys Res Commun. 2010 May;396(1):90–4.

[178] Lauschke VM, Barragan I, Ingelman-Sundberg M. Pharmacoepigenetics and Toxicopigenetics: Novel Mechanistic Insights and Therapeutic Opportunities. Annu Rev Pharmacol Toxicol. 2018 Jan;58:161–85.