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Trends and challenges in managing diabetes mellitus-personalized medicine

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***Abstract*---Background**: Diabetes Mellitus (DM) is a major global health issue, contributing to significant morbidity, mortality, and economic burden. The World Health Organization reported an increase in DM diagnoses, with 422 million adults affected globally by 2014. Despite a decline in newly diagnosed cases in the U.S., DM remains prevalent, significantly impacting cardiovascular health and incurring substantial healthcare costs. **Aim**: This article aims to explore the trends and challenges in managing DM through personalized medicine, focusing on genetic insights and pharmacogenomics to improve treatment strategies. **Methods**: The review encompasses recent advancements in genetic research and pharmacogenomics relevant to DM. It discusses the genetic underpinnings of both Type 1 and Type 2 DM, including monogenic forms like MODY and NDM.

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Various methodologies, such as genome-wide association studies (GWAS) and candidate gene studies, are evaluated for their contributions to understanding DM susceptibility and treatment responses. **Results**: The findings highlight significant progress in identifying genetic variants associated with DM risk and treatment response. Key genes, including TCF7L2, KCNJ11, and PPAR-γ, have been implicated in susceptibility and drug response. Monogenic forms like MODY and NDM present distinct genetic profiles that necessitate tailored treatment approaches. Advances in pharmacogenomics offer potential for personalized therapies based on genetic predispositions. **Conclusion**: Personalized medicine in DM management has evolved with improved genetic insights and pharmacogenomics. Tailoring treatment based on genetic profiles can enhance efficacy and reduce adverse effects, although challenges remain in integrating these advances into clinical practice.

***Keywords*---**Diabetes Mellitus, Personalized Medicine, Pharmacogenomics, Genetic Research, Type 1 Diabetes, Type 2 Diabetes, MODY, NDM, GWAS.

Introduction

Diabetes mellitus (DM) represents a major global health challenge and is recognized as a leading cause of premature mortality and disability [1]. The World Health Organization's Global Report highlights a rising incidence of DM worldwide, with diagnoses reaching 422 million adults by 2014 and leading to 1.5 million deaths [2]. In the United States, while newly diagnosed cases of DM are showing a downward trend, the prevalence remains alarmingly high, with 29 million cases reported in 2016 (https://www.cdc.gov/chronicdisease/resources/publications/aag/diabetes.htm) . In 2013, DM was ranked as the seventh leading cause of death, and evidence shows that individuals with diabetes are at a significantly increased risk of developing cardiac complications at a younger age compared to those without the disease [3]. The financial impact of DM is substantial, with direct and indirect costs estimated at $245 billion, and the annual medical expenses for individuals with DM amounting to $17,000, which is approximately 2.3 times higher than those without the condition [4].

Effective prevention, early diagnosis, and management of DM are essential to mitigate life-threatening complications. Current guidelines stress the need for personalized care in DM treatment, advocating for tailored pharmacotherapy strategies [5]. A structured approach to managing DM involves identifying the type of diabetes, setting glycemic targets, using medications with established efficacy and safety profiles, and addressing cardiovascular comorbidities, along with promoting healthy lifestyle changes. Advances in genetic research related to DM risk, pathophysiology, and pharmacogenetics of common oral glucose-lowering agents contribute to the development of patient-specific therapies [Figure 1]. This article reviews genetic insights into DM pathophysiology and risk, and the role of pharmacogenomics in enhancing personalized treatment strategies.

Diabetes mellitus (DM) is frequently accompanied by various comorbid conditions that complicate its management and significantly impact overall health. One of the primary comorbidities associated with DM is cardiovascular disease. Individuals with DM are at a heightened risk of developing heart conditions such as coronary artery disease, myocardial infarction, and stroke due to the adverse effects of prolonged hyperglycemia on vascular structures. Hypertension, or high blood pressure, is another common comorbidity, which further exacerbates cardiovascular risk and complicates blood sugar control.

Chronic kidney disease (CKD) is also prevalent among those with DM, often resulting from diabetic nephropathy. Persistent hyperglycemia damages the kidneys' filtering units, leading to progressive renal impairment. Peripheral neuropathy is another significant concern, characterized by nerve damage in the extremities that manifests as numbness, tingling, or pain. Additionally, diabetic retinopathy, a condition caused by damage to the retinal blood vessels, can result in serious visual impairment or blindness if not properly managed. Foot problems are common among diabetic patients, including infections, ulcers, and deformities, attributed to compromised circulation and nerve damage. Obesity, which is both a risk factor for developing DM and a prevalent comorbidity, can exacerbate insulin resistance and complicate glycemic management. Sleep apnea, specifically obstructive sleep apnea, is more frequently observed in individuals with DM and can adversely affect glycemic control and increase cardiovascular risks. Furthermore, gastrointestinal disorders such as gastroparesis, where stomach emptying is delayed, and constipation are notable among DM patients. Psychological comorbidities, including depression and anxiety, are also common and can adversely impact disease management and quality of life. Lastly, hearing loss has been identified as a possible complication of DM, potentially due to nerve and blood vessel damage affecting auditory functions. Addressing these comorbidities is crucial for improving health outcomes and managing DM effectively.

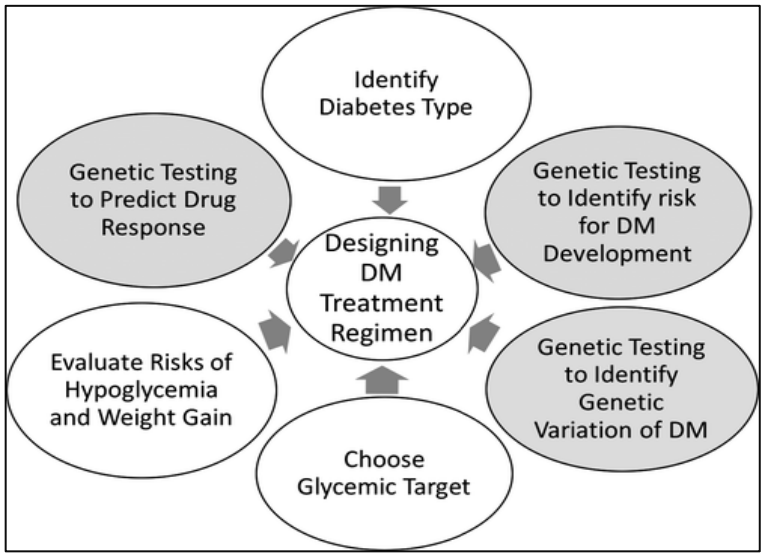

Figure 1: Designing DM Treatment Regimen

Pharmacogenomic Landscape of Diabetes Mellitus

Diabetes mellitus (DM) is broadly categorized into four types based on underlying pathophysiological mechanisms, yet further classification based on genetic factors is also feasible. This discussion will center on the polygenic form of type 2 diabetes mellitus (T2DM), with additional consideration given to the monogenic forms, including maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM). Type 1 DM, which comprises 5–10% of cases, is characterized by the presence of autoantibodies targeting pancreatic islet cells and insulin, leading to the destruction of pancreatic β-cells and resulting in insulin deficiency. This type is primarily associated with genetic variations in the HLA genes, which play a crucial role in immune system function and pancreatic β-cell integrity. Other genetic factors are also implicated in type 1 DM [a]. Type 2 DM, representing 90–95% of DM cases, involves increased glucose production by the liver, insulin resistance in target tissues, and β-cell dysfunction, which impairs insulin secretion. The genetic components associated with this form include mutations in genes linked to glucose homeostasis disorders.

Monogenic forms of diabetes, such as neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY), account for less than 5% of cases each. In NDM, insulin is produced but is not secreted effectively due to mutations in genes encoding KATP channels in pancreatic β-cells. Conversely, MODY presents with different genetic mutations depending on the subtype: MODY 1 and MODY 3 are associated with hyperglycemia due to partial β-cell dysfunction and involve mutations in the HNF4α and HNF1α genes, respectively. MODY 2 is characterized by hyperglycemia resulting from impaired glucose-level monitoring by pancreatic β-cells, linked to mutations in the GCK gene and other transcription factors important for β-cell development.

Type 2 Diabetes Mellitus: A Polygenic, Multifactorial Disease

Type 2 diabetes mellitus (T2DM) is the most widespread form of diabetes, characterized by its polygenic nature as evidenced by familial aggregation and the absence of Mendelian inheritance patterns [6]. The pathophysiology of T2DM involves multiple disruptions in glucose homeostasis regulation (**Figure 2**). Over the years, extensive research has sought to identify susceptibility genes associated with T2DM and its phenotypic manifestations. Various methodologies have been employed, including linkage studies, candidate gene studies, genome-wide association studies (GWAS), and exome-wide association studies [9]. More recent strategies, such as reverse genetics phenome-wide approaches, have emerged, which involve examining clinically validated phenotypes in relation to known susceptibility gene variants to confirm diabetes-related genes and pathways [10].

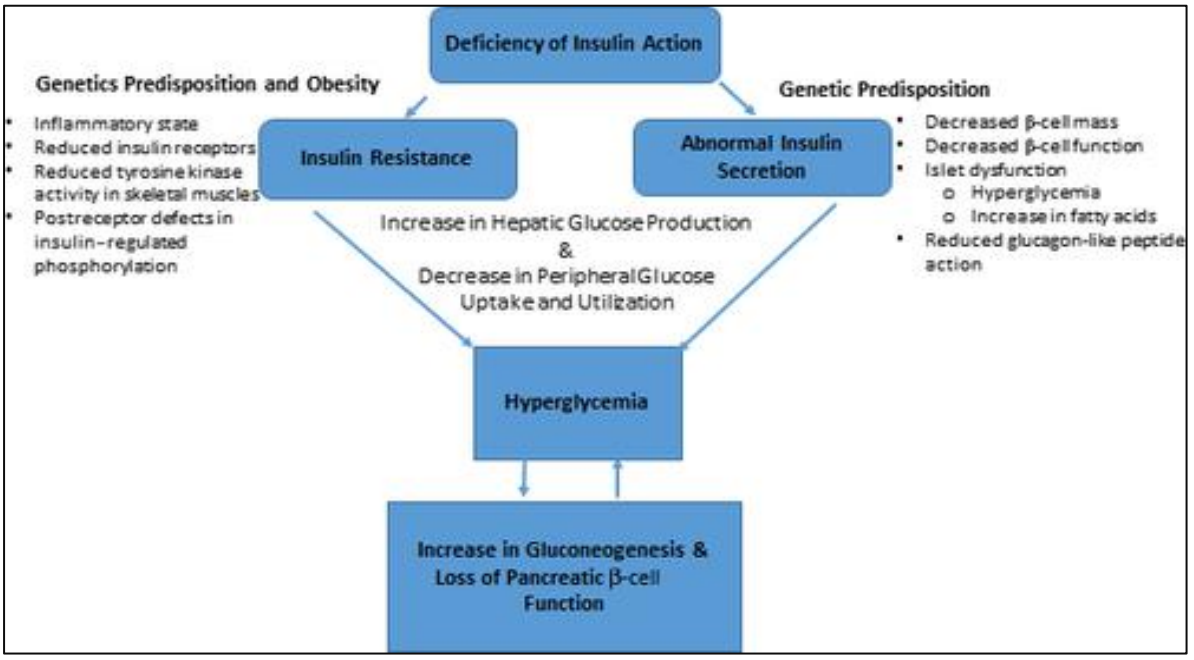

Figure 2: Schematic representation of DM type 2 pathophysiology

Candidate gene studies (CGS) target genes suspected to be involved in the disease based on prior knowledge of their roles in disease mechanisms. In T2DM, CGS primarily focused on genes associated with glucose homeostasis, including those involved in insulin production, secretion, and action, such as the insulin receptor (INSR), glycogen synthase 1 (GYS1), glucose transporter 4 (GLUT4), and insulin receptor substrate-1 (IRS-1) [11, 12]. However, the effectiveness of CGS in identifying robust genetic associations in T2DM has been limited. This is due to factors such as the disease's complex nature, small sample sizes, high costs of genotyping, and low genetic signal throughput. Despite these limitations, CGS have led to the identification of significant variants in susceptibility genes like peroxisome proliferator-activated receptor gamma (PPAR-γ) and KCNJ11, which encodes the inwardly rectifying Kir6.2 component of the β-cell ATP-sensitive potassium channel (KATP channel) [13].

Genome-wide association studies (GWAS) utilize an unbiased, hypothesis-free approach to explore the entire genome for associations between genetic variants and phenotypes [7]. By comparing genetic markers between individuals with T2DM and control subjects, GWAS have the potential to reveal novel genetic loci associated with disease susceptibility. Many of the limitations of CGS, such as small sample sizes and low throughput, are addressed by GWAS, resulting in the discovery and validation of numerous genetic loci [11, 14]. Initial GWAS on diabetes, published about a decade ago, identified several loci strongly associated with T2DM risk, with single nucleotide polymorphisms (SNPs) in the transcription factor 7-like 2 (TCF7L2) gene showing the most significant association. This locus, discovered through whole-genome microsatellite marker analysis in a cohort of approximately 1000 Icelandic subjects [16], was later validated in subsequent

T2DM GWAS [14, 17]. TCF7L2 encodes a high-mobility group box transcription factor potentially influencing diabetes risk through pancreatic β-cell dysfunction via the Wnt signaling pathway [16]. Other validated signals include SNPs in the KCNJ11, PPAR-γ, and Fat Mass and Obesity (FTO) genes [15]. The NHGRI-EBI Catalog of published GWAS currently lists over 157 diabetes studies with more than 1500 genome-wide significant associations ($p = 5 \times 10^{-8}$) [18]. One assumption of the GWAS approach is that disease susceptibility variants are common (frequency > 5%) in studied populations, which may not fully apply to T2DM. It has been suggested that only a small portion of heritability may be explained by common variants, with rare alleles of smaller effect sizes potentially accounting for a larger fraction of T2DM heritability. However, recent findings from large-scale sequencing studies have not supported the significant role of low-frequency rare variants in T2DM predisposition [17].

Selected Genes and Single Nucleotide Polymorphisms Associated with Insulin Action or β-Cell Function in T2DM Risk/Susceptibility GWAS

Numerous genetic variants have been identified in genome-wide association studies (GWAS) as being associated with the risk and susceptibility to type 2 diabetes mellitus (T2DM), particularly concerning insulin action and β-cell function. Key genes and single nucleotide polymorphisms (SNPs) linked to these processes include:

The ADAMTS9 gene, located on chromosomes 11 and 14, with the SNP rs4607103, has been associated with insulin action, showing an odds ratio of 1.09 [2008]. ADCY5, found on chromosome 14, is associated with insulin action through the SNP rs11708067, which has an odds ratio of 1.12 [2010]. BCAR1, which is found on chromosomes 14 and 17, involves a docking protein that regulates β-cell function, with the SNP rs7202877 showing an odds ratio of 1.12 [2012]. Another gene, BCL11A, located on chromosomes 14 and 17, encodes a zinc finger protein that also regulates β-cell function, with the SNP rs243021 presenting an odds ratio of 1.08 [2010].

The gene CCND2, located on chromosome 17, regulates the cell cycle and enhances insulin secretion. The SNP rs76895963 associated with CCND2 has an odds ratio of 0.53, indicating a protective effect [2014]. CDKAL1, present on chromosomes 9, 11, 14, and 17, encodes a methylthiotransferase involved in β-cell function regulation, with the SNP rs7754840 showing an odds ratio of 1.15 [2007]. Similarly, the CDKN2A/B gene, found on chromosomes 9, 11, 14, and 17, encodes a cyclin-dependent kinase inhibitor affecting β-cell function, with the SNP rs7754840 also showing an odds ratio of 1.20 [2007].

The FTO gene, located on chromosomes 9, 11, 14, and 17, is associated with insulin action through the SNP rs8050136 and has an odds ratio of 1.27. This gene is linked to fat mass and obesity and acts as a nucleic acid demethylase. The GCKR gene, present on chromosomes 11 and 17, is involved in insulin action, with the SNP rs780094 showing an odds ratio of 1.08 [2007]. HHEX/IDE, found on chromosomes 9, 11, 14, and 17, encodes a transcriptional repressor affecting intracellular insulin degradation, with the SNP rs1111875 showing an odds ratio of 1.15 [2007].

IGF2BP2, located on chromosomes 9, 11, 14, and 17, encodes an insulin-like growth factor II mRNA-binding protein that regulates β-cell function, with the SNP rs4402960 having an odds ratio of 1.17 [2007]. The IRS1 gene, found on chromosomes 11, 14, and 17, encodes a docking protein involved in insulin action, with the SNP rs2943640 showing an odds ratio of 1.12 [2009]. JAZF1, present on chromosomes 9, 11, 14, and 17, encodes a zinc finger protein regulating β-cell function, with the SNP rs864745 presenting an odds ratio of 1.10 [2008].

KCNJ11, located on chromosomes 11 and 17, encodes the inwardly rectifying potassium channel Kir6.2, which regulates insulin secretion. The SNP rs5219 is associated with an odds ratio of 1.14 [2003]. The KCNQ1 gene, found on chromosomes 9, 11, 14, and 17, encodes a potassium channel affecting β-cell function, with the SNP rs2237892 showing an odds ratio of 1.23 [2008]. The NOTCH2 gene, present on chromosomes 9, 11, 14, and 17, encodes a transmembrane receptor involved in pancreatic cell development, with the SNP rs10923931 showing an odds ratio of 1.13 [2008].

The PPAR-γ gene, located on chromosomes 9, 11, 14, 15, and 17, encodes a peroxisome proliferator-activated receptor involved in insulin action regulation. The SNP rs1801282 has an odds ratio of 1.11 [2000]. The SLC30A8 gene, found on chromosomes 9, 11, 14, and 17, encodes a β-cell zinc efflux transporter crucial for insulin storage and secretion, with the SNP rs13266634 showing an odds ratio of 1.15 [2007]. Finally, TCF7L2, located on chromosomes 14 and 15, encodes a T-cell transcription factor affecting β-cell function, with the SNP rs7903146 presenting an odds ratio of 1.40 [2006]. TSPAN8, found on chromosomes 9, 11, 14, and 17, encodes a cell surface glycoprotein involved in β-cell function, with the SNP rs7961581 showing an odds ratio of 1.09.

Monogenic Diabetes Syndrome

Monogenic diabetes syndrome encompasses a diverse group of single-gene, autosomally inherited diabetes types that do not fall under the classifications of type 1 or type 2 diabetes mellitus (DM). This syndrome is primarily divided into two major forms: maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM).

Maturity-Onset Diabetes of the Young (MODY)

Unlike polygenic type 2 diabetes mellitus (T2DM), MODY is caused by monogenic defects affecting pancreatic β-cell function, with minimal or no impairment in insulin action. Clinical features of MODY include autosomal dominant inheritance, early onset of the disease (before the age of 25), absence of obesity, and evidence of preserved β-cell function, as indicated by endogenous insulin secretion [20]. Currently, there are approximately 13 recognized types of MODY (types 1 through 14), each associated with abnormalities in various loci across different chromosomes and categorized based on the specific defective gene responsible for the observed phenotype [21]. MODY accounts for about 1–4% of pediatric diabetes cases. Due to its presentation, which can resemble either type 1 diabetes mellitus (T1DM) (early onset, lean body mass) or type 2 diabetes

mellitus (T2DM) (preserved β-cell function, familial aggregation), misdiagnosis is common [22, 23].

MODY types 1, 2, and 3 are among the most well-characterized subtypes. MODY 1, which constitutes approximately 10% of MODY cases in characterized cohorts, results from mutations in the HNF4α gene, which encodes the transcription factor hepatocyte nuclear factor 4-α [21, 22]. MODY 3, the most prevalent subtype, is caused by mutations in the HNF1α gene. Together with MODY 2, MODY 3 accounts for about 50% of all MODY cases. These hepatic transcription factors facilitate the transcription of numerous genes involved in glucose metabolism and insulin production and secretion. MODY 2 is attributed to mutations in the glucokinase (GCK) gene, leading to reduced functionality of glucokinase, an enzyme crucial for maintaining blood glucose homeostasis in pancreatic β cells. This mutation results in impaired glucose phosphorylation in hepatic cells, which is responsible for the mild hyperglycemia observed in patients with MODY 2 [20, 28].

Common MODY Subtypes, Phenotypes, and Select Associated Genetic Mutations

Maturity-Onset Diabetes of the Young (MODY) encompasses several subtypes, each associated with distinct genetic mutations and clinical features. Here is an overview of common MODY subtypes, their implicated genes, and related phenotypes:

MODY 1: *Gene and Mutations*: This subtype is linked to mutations in the HNF-4α gene (Hepatocyte Nuclear Factor 4α), including naturally occurring heterozygous mutations such as Q268X, R154X, and R127W [21-23]. *Chromosome and Frequency*: The gene is located on chromosome 20, with a frequency of approximately 5% among MODY patients [21-23]. *Age at Diagnosis and Pathophysiology*: MODY 1 typically manifests during adolescence or early adulthood and involves a transcription factor crucial for β-cell function in the pancreas [21-23]. *Phenotype*: The clinical presentation includes neonatal hyperinsulinism and diabetes [21-23].

MODY 2: *Gene and Mutations*: This form is associated with the GCK gene (Glucokinase), with heterozygous mutations such as A378T and E339K [8, 20-23]. *Chromosome and Frequency*: Located on chromosome 7, it constitutes 10–60% of MODY cases [8, 20-23]. *Age at Diagnosis and Pathophysiology*: MODY 2 typically presents from birth to early childhood. The glucokinase enzyme, acting as a glucose sensor in the pancreas and liver, is affected, leading to mild hyperglycemia [8, 20-23].

MODY 3: *Gene and Mutations*: Mutations in the TCF1 or HNF-1α gene (Hepatocyte Nuclear Factor 1α) are responsible for this subtype, with heterozygous mutations such as 291 + C [20-23]. *Chromosome and Frequency*: This gene is located on chromosome 12, affecting 30–60% of MODY patients [20-23]. *Age at Diagnosis and Pathophysiology*: MODY 3 generally appears during adolescence or early adulthood and involves a

transcription factor affecting β-cell function in both the pancreas and kidney [20-23]. *Phenotype*: Patients typically present with diabetes [20-23].

MODY 4: *Gene and Mutations*: The IPF1 or PDX1 gene (Insulin Promoter Factor 1) is associated with this subtype, particularly with heterozygous mutations such as Pro63fsdelC [20-23]. *Chromosome and Frequency*: Located on chromosome 13, it is found in less than 1% of MODY cases [20-23]. *Age at Diagnosis and Pathophysiology*: MODY 4 generally presents in early adulthood and involves a transcription factor essential for β-cell function in the pancreas [20-23]. *Phenotype*: The primary clinical outcome is diabetes [20-23].

MODY 5: *Gene and Mutations*: Mutations in the TCF1 or HNF-1β gene (Hepatocyte Nuclear Factor 1β), such as E101X and delT, are implicated [20]. *Chromosome and Frequency*: This gene is located on chromosome 17 and is found in 3–10% of MODY cases [20]. *Age at Diagnosis and Pathophysiology*: MODY 5 usually appears during adolescence or early adulthood, with the gene affecting β-cell function in the pancreas [20]. *Phenotype*: The condition is characterized by diabetes [20].

MODY 6: *Gene and Mutations*: The NEUROD1 gene (Neurogenic Differentiation factor 1) is associated with heterozygous mutations such as 206 + C [20]. *Chromosome and Frequency*: Located on chromosome 2, it is very rare among MODY patients [20]. *Age at Diagnosis and Pathophysiology*: MODY 6 manifests later in life and involves a transcription factor affecting β-cell function in both the pancreas and kidney [20]. *Phenotype*: The clinical presentation includes diabetes [20].

Transient Neonatal Diabetes Mellitus (TNDM): *Gene and Mutations*: Associated with several genes, including ZAC, ABCC8, KCNJ11, and HNF-1β, with heterozygous mutations [20-26]. *Frequency and Age at Diagnosis*: This form is rare, presenting from birth to 6 months of age [20-26]. *Phenotype*: TNDM is characterized by transient diabetes [20-26].

Permanent Neonatal Diabetes Mellitus (PNDM): *Gene and Mutations*: Linked to mutations in KCNJ11, ABCC8, GCK*, and IPF1*, with both heterozygous and homozygous mutations [20-26]. *Frequency and Age at Diagnosis*: Also rare, with onset from birth to 6 months of age [20-26]. *Phenotype*: PNDM results in permanent diabetes [20-26].

Neonatal Diabetes Mellitus Syndrome

Neonatal Diabetes Mellitus (NDM) is an uncommon form of diabetes that presents within the first six months of life. Infants with NDM experience inadequate insulin production, resulting in elevated blood glucose levels. The condition manifests in two main forms: permanent neonatal diabetes mellitus (PNDM), where the condition persists, and transient neonatal diabetes mellitus (TNDM), where the condition resolves during infancy. Genetic mutations are a significant cause of NDM, with variations found in genes such as KCNJ11, ABCC8, GCK, INS, and ZFP57 [23-26]. The most prevalent genetic causes are mutations in KCNJ11 and

ABCC8, which encode different subunits of the ATP-sensitive potassium channel in pancreatic islet β cells. These mutations impair insulin secretion by disrupting membrane depolarization.

Pharmacogenetic-Based Associations for Common Oral Glucose-Lowering Therapies

A variety of pharmacological agents are employed to manage diabetes mellitus (DM). These agents differ in their mechanisms of action, efficacy, and ability to achieve treatment goals, such as preventing macrovascular and microvascular complications. Additionally, antihyperglycemic agents are categorized based on their propensity to induce side effects that can negatively impact the management of DM [5, 27].

Classification of Oral Medications Used in Diabetes Mellitus Treatment [5, 27]

- **Biguanides**
  Drug: Metformin *Cellular Mechanism*: Activates AMP-activated protein kinase (AMPK), increasing intracellular AMP *Physiological Mechanism*: Reduces hepatic glucose production and intestinal glucose absorption; enhances insulin sensitivity *HbA1c % Decrease*: 1.0–1.5 *Hypoglycemia Risk*: Neutral *Weight Effect*: Slight loss
- **Sulfonylureas**
  Drugs: Glyburide, Glipizide, Glimepiride *Cellular Mechanism*: Closes KATP channels on pancreatic β-cell plasma membranes *Physiological Mechanism*: Stimulates insulin release from β cells; reduces glucose output from the liver; increases insulin sensitivity *HbA1c % Decrease*: 0.8 *Hypoglycemia Risk*: Moderate to severe *Weight Effect*: Gain
- **Meglitinides**
  Drugs: Repaglinide, Nateglinide *Cellular Mechanism*: Closes KATP channels on pancreatic β-cell plasma membranes. *Physiological Mechanism*: Stimulates insulin release from pancreatic β cells *HbA1c % Decrease*: 0.7 *Hypoglycemia Risk*: Mild to moderate *Weight Effect*: Gain
- **Thiazolidinediones**
  Drugs: Pioglitazone, Rosiglitazone. *Cellular Mechanism*: Activates the nuclear transcription factor PPAR-γ. *Physiological Mechanism*: Improves target cell response to insulin. *HbA1c % Decrease*: 0.8. *Hypoglycemia Risk*: Neutral. *Weight Effect*: Gain
- **α-Glucosidase Inhibitors**:
  Drugs: Acarbose, Miglitol. *Cellular Mechanism*: Inhibits intestinal alpha-glucosidase enzyme. *Physiological Mechanism*: Slows intestinal carbohydrate digestion and absorption. *HbA1c % Decrease*: 0.6. *Hypoglycemia Risk*: Neutral. *Weight Effect*: Neutral
- **DPP-4 Inhibitors**
  Drugs: Sitagliptin, Saxagliptin, Linagliptin, Alogliptin. *Cellular Mechanism*: Inhibits DPP-4 activity, increasing postprandial active incretin (GLP-1, GIP) concentrations *Physiological Mechanism*: Increases glucose-dependent insulin secretion and decreases glucose production. *HbA1c % Decrease*: 0.7. *Hypoglycemia Risk*: Neutral. *Weight Effect*: Neutral

- **SGLT2 Inhibitors**
  Drugs: Canagliflozin, Empagliflozin. *Cellular Mechanism*: Inhibits SGLT2 in the proximal nephron. *Physiological Mechanism*: Blocks glucose reabsorption in kidneys
  HbA1c % Decrease: 0.7–1.0. *Hypoglycemia Risk*: Neutral. *Weight Effect*: Loss
- **GLP-1 Receptor Agonists**
  Drugs: Exenatide, Liraglutide, Albiglutide, Dulaglutide. *Cellular Mechanism*: Activates GLP-1 receptors. *Physiological Mechanism*: Increases glucose-dependent insulin secretion, decreases glucagon secretion, slows gastric emptying, and increases satiety *HbA1c % Decrease*:. *Hypoglycemia Risk*: Neutral. *Weight Effect*: Loss
- **Amylin Mimetics**
  Drug: Pramlintide. *Cellular Mechanism*: Activates amylin receptors. *Physiological Mechanism*: Decreases glucagon secretion, slows gastric emptying, and increases satiety. *HbA1c % Decrease*: 0.3. *Hypoglycemia Risk*: Severe. *Weight Effect*: Loss

Metformin

Metformin is a widely used oral glucose-lowering therapy (OGLT) classified under biguanides. Despite various known mechanisms, the full extent of metformin's action is not entirely understood. It is believed to exert its glucose-lowering effects through multiple pleiotropic mechanisms [28]. A major hypothesis is that metformin activates AMP-activated protein kinase (AMPK) [29]. Additionally, it helps prevent hyperglycemia by decreasing intestinal glucose absorption and enhancing peripheral glucose uptake and utilization [30]. The drug's efficacy is highly variable; approximately 35% of patients do not achieve initial reductions in hemoglobin A1c (HbA1c), and many become less responsive to metformin over time [31][32]. The variability in response may be influenced by pharmacogenetic factors affecting metformin's pharmacokinetics (PK) and pharmacodynamics (PD).

Metformin: Pharmacokinetics/Pharmacodynamics

Metformin is not metabolized but is actively transported into tissues and excreted via the kidneys. It is absorbed into intestinal cells by plasma monoamine transporters (PMAT, SLC29A4), into the bloodstream by the organic cation transporter OCT1 (SLC22A1), and then into renal tubular cells by OCT2 (SLC22A2). Finally, metformin is excreted into urine via multidrug and toxin extrusion transporters MATE1 and MATE2 (SLC47A1 and SLC47A2) [28].

Metformin: Evidence of Pharmacogenetic Associations

Pharmacogenetic research into metformin has primarily utilized candidate gene studies (CGS) and genome-wide association studies (GWAS) [33]. A notable example is the Genetics of DARTS (GoDARTS) study, which involved 1024 type 2 diabetes mellitus (T2DM) patients on metformin. This study identified a strong association between metformin response and the intronic variant rs11212617 near the ATM gene, which encodes a serine/threonine kinase. The minor C allele of rs11212617 was associated with better treatment outcomes, including lower

HbA1c levels and achieving target HbA1c values of 7% or lower. It is hypothesized that mutations in the ATM gene may affect AMPK regulation, thereby influencing the glycemic response to metformin [39].

Pharmacogenomics of Diabetes Medications

Metformin

- **Genetic Variants:**
  - **rs11212617**: Positive association between the minor C allele and metformin response, supported by meta-analyses [37]. Discrepancies with the Diabetes Prevention Program (DPP) due to different phenotypes and study outcomes [40].
  - **OCT1, OCT2, MATE1**: Variations impact metformin efficacy and renal clearance [30, 33, 38, 54]. The GoDARTS study did not replicate associations for two SLC22A1 variants (rs12208357, rs72552763) but discovered a novel SLC22A1 variant (rs683369) linked to decreased diabetes incidence risk [33].

Sulfonylureas (SUs)

- **Mechanism of Action:**
  - Bind to sulfonylurea receptor type 1 (SUR1) on pancreatic β-cells, encoded by ABCC8 [56, 57]. This binding closes the KATP channel, leading to increased insulin secretion [57].
- **Pharmacokinetics (PK):**
  - Metabolized by CYP2C9. Variants such as CYP2C9*2 (rs1799853) and CYP2C9*3* (rs1057910) affect drug clearance [36].
- **Pharmacodynamics (PD):**
  - **ABCC8 and KCNJ11**: Variants E23K (KCNJ11) and S1369A (ABCC8) impact SU response but findings are mixed across studies [45, 46, 61, 62].
  - **TCF7L2**: Variants like rs12255732 and rs7903146 associated with SU response and treatment failure [48, 49].
- **Pharmacogenetic Associations:**
  - **GoDARTS Study**: Carriers of CYP2C9*2/*3 alleles had a better response to SU therapy but mixed results for hypoglycemia risk [41, 42, 43, 44]. TCF7L2 variants linked to SU response with inconsistent results across studies [48, 49, 65].

Thiazolidinediones (TZDs)

- **Mechanism of Action:**
  - Activate PPAR-γ, improving insulin sensitivity by affecting gene expression related to metabolic homeostasis [68, 69].
- **Pharmacokinetics (PK) and Pharmacodynamics (PD):**
  - TZDs are metabolized by CYP2C8 and transported by OATP1B (SLCO1B1) [71, 51]. Genetic variants in these genes can influence drug response [51, 72].
  - PPAR-γ gene variants, such as rs1801282 (Pro12Ala), have shown mixed results in response to TZD therapy [73, 74].

- ADIPOQ gene variants also affect TZD response, with conflicting results regarding their impact on fasting plasma glucose and HbA1c levels [52, 74].

Gliptins:

Gliptins, or dipeptidyl peptidase IV (DPP4) inhibitors, enhance incretin signaling by inhibiting the enzyme DPP4, which degrades glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1, secreted post-meal, promotes insulin secretion, suppresses glucagon release, inhibits gastric emptying, and reduces appetite. Inhibiting DPP4 prolongs GLP-1 activity, enhancing insulin secretion and reducing glucagon levels [79].

- **Pharmacogenetic Evidence:**
  - Gliptins are mainly cleared through renal excretion rather than cytochrome P450 enzymes, with saxagliptin being an exception [7]. Few pharmacogenetic studies are available [80].
  - SNP rs7202877 near CTRB1/CTRB2 affects response to DPP-4 inhibitors. The G allele of rs7202877, linked to increased risk for T1DM and decreased risk for T2DM, was associated with enhanced GLP-1 secretion but reduced response to DPP-4 inhibitors in T2DM patients [81].

Personalized Treatment Strategy for Diabetes Mellitus (DM)

- **Challenges:**
  - Managing DM involves balancing treatment efficacy, hypoglycemia risk, and medication selection based on disease pathogenesis. Precision medicine is increasingly recommended [55].
  - The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) is investigating personalized treatment strategies by comparing metformin with glimepiride, sitagliptin, liraglutide, or insulin glargine in patients with newly diagnosed DM [82]. Outcomes include efficacy, adverse events, complications, quality of life, and cost-effectiveness.
- **Genetic Risk Scores (GRS):**
  - GRS, which aggregate risk alleles from multiple SNPs, can predict diabetes risk. Studies like the Framingham Heart Study and Diabetes Prevention Program (DPP) show GRS can improve risk prediction, though challenges remain in identifying clinically relevant variants [83, 84].

Applications of Pharmacogenomics in Monogenic Diabetes Syndromes

- **Monogenic Diabetes:**
  - Identifying MODY subtypes (e.g., MODY 1 and 3) impacts treatment decisions. For example, patients with MODY due to KCNJ11 or ABCC8 mutations are typically treated with sulfonylureas (SUs), as these agents increase insulin secretion [23, 85]. MODY 2, often managed without pharmacotherapy, contrasts with MODY 1 and 3, where SU sensitivity is noted due to downregulation of HNF1-α and HNF4-α target genes [80, 85].

- **Testing and Guidelines:**
    - Genetic testing is recommended for diabetes onset before age 25 to avoid misdiagnosis and guide treatment [23, 5, 86, 87].

Pharmacogenomics in Predicting Response to Therapy

- **Metformin and SUs:**
    - Genetic variants affecting metformin pharmacokinetics (e.g., SLC transporters) and SU response (e.g., CYP2C9, KCNJ11, ABCC8) are under study. These variants could guide therapy selection and dosage adjustments [46, 36, 48, 54].
- **TZDs:**
    - While pharmacogenomic findings have been clinically significant, current guidelines still prioritize risk-benefit considerations [71].

Future Prospects

- **Genetic Risk Scores and Screening:**
    - GRS might predict diabetes risk better when combined with other risk factors and could aid in newborn screening and ethnically targeted treatments [83, 84, 17].
- **Pharmacogenetics for Side Effect Prediction:**
    - Identifying variants associated with intolerance or low response to medications like metformin and SUs could enhance personalized therapy and prevent severe side effects [80].

Conclusion

Managing Diabetes Mellitus (DM) has undergone significant transformation with the advent of personalized medicine, driven by advancements in genetic research and pharmacogenomics. The integration of genetic insights into DM management holds promise for more tailored and effective treatments. Type 1 and Type 2 diabetes, along with monogenic forms like Maturity-Onset Diabetes of the Young (MODY) and Neonatal Diabetes Mellitus (NDM), present distinct challenges and opportunities for personalized care. Recent research has identified various genetic variants associated with DM susceptibility and treatment responses. For Type 1 DM, genetic factors such as HLA gene variations play a critical role in disease pathogenesis, while Type 2 DM is influenced by multiple genetic factors affecting glucose homeostasis and insulin function. Monogenic forms of DM, though less common, also offer insights into the genetic basis of diabetes and necessitate specialized treatment strategies. Pharmacogenomics, the study of how genetic variations affect drug responses, has emerged as a crucial component of personalized medicine. Advances in this field have enabled the identification of genetic markers that predict patient responses to glucose-lowering medications, thereby allowing for more precise and effective treatment plans. However, the challenge lies in translating these genetic insights into routine clinical practice. Issues such as the high cost of genetic testing, limited access to personalized therapies, and the need for healthcare professionals to be well-versed in genetic information pose barriers to widespread implementation. In conclusion, while personalized medicine represents a significant step forward in managing DM, ongoing research and healthcare system adaptations are necessary to fully realize its potential. Continued exploration of genetic factors and their implications for

drug responses will be pivotal in enhancing the management of diabetes, ultimately leading to improved patient outcomes and reduced healthcare costs.

References

1. World Health Organization. Diabetes: Key Facts, November 2016. Available from **www.who.int/mediacentre/factsheets/fs312/en/**. Accessed February 13, 2017.
2. World Health Organization. Diabetes: Global report on diabetes. Available from **www.who.int/diabetes/global-report/en/**. Accessed February 13, 2017.
3. Centers for Disease Control and Prevention. Chronic Disease Prevention and Health Promotion: Diabetes, July 2016. Available from **www.cdc.gov/chronicdisease/resources/publications/aag/diabetes.htm**. Accessed February 13 2017.
4. **American Diabetes Association**. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013; **36**: 1033–46.
5. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2016; **39**: S1–106.
6. Barroso I. Genetics of type 2 diabetes. *Diabet Med* 2005; **22**: 517–35.
7. Hupfeld CJ, Courtney H, Olefsky JM. Type 2 diabetes mellitus: etiology, pathogenesis, and natural history. In: JL Jameson, LJ De Groot, eds. *Endocrinology: adult and pediatric*. Philadelphia, PA: Elsevier Health Sciences, 2010: 765–87.
8. Carmody D, Naylor RN, Bell CD, et al. GCK-MODY in the US National Monogenic Diabetes Registry: frequently misdiagnosed and unnecessarily treated. *Acta Diabetol* 2016; **53**: 703–8.
9. Tan JT, Chia KS, Ku CS. The molecular genetics of type 2 diabetes: past, present and future. In: *Encyclopedia of life sciences*. Chichester, UK: John Wiley & Sons, 2009. doi: **10.1002/9780470015902.a0021994**.
10. Denny JC, Ritchie MD, Basford MA, et al. PheWAS: demonstrating the feasibility of a phenome-wide scan to discover gene-disease associations. *Bioinformatics* 2010; **26**: 1205–10.
11. Brunetti A, Chiefari E, FTI D. Recent advances in the molecular genetics of type 2 diabetes mellitus. *World J Diabetes* 2014; **5**: 128–40.
12. Owen KR, McCarthy MI. Genetics of type 2 diabetes. *Curr Opin Genet Dev* 2007; **17**: 239–44.
13. Doria A, Patti M-E, Kahn CR. The emerging genetic architecture of type 2 diabetes. *Cell Metab* 2008; **8**: 186–200.
14. Morris AP, Voight BF, Teslovich TM, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. *Nat Genet* 2012; **44**: 981–90.
15. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661–78.
16. Grant SF, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 2006; **38**: 320–3.
17. Fuchsberger C, Flannick J, Teslovich TM, et al. The genetic architecture of type 2 diabetes. *Nature* 2016; **536**: 41–7.

18. GWAS Catalog. The NHGRI-EBI catalog of published genome-wide association studies, February 2017. Available from **www.ebi.ac.uk/gwas/**. Accessed February 13, 2017.
19. Bonnefond A, Froguel P. Rare and common genetic events in type 2 diabetes: what should biologists know? *Cell Metab* 2015; **21**: 357–68.
20. Vaxillaire M, Froguel P. Genetic basis of maturity-onset diabetes of the young. *Endocrinol Metab Clin North Am* 2006; **35**: 371–84.
21. Chambers C, Fouts A, Dong F, et al. Characteristics of maturity onset diabetes of the young in a large diabetes center. *Pediatr Diabetes* 2016; **17**: 360–7.
22. Pihoker C, Gilliam LK, Ellard S, et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J Clin Endocrinol Metab* 2013; **98**: 4055–62.
23. Rubio-Cabezas O, Hattersley AT, Njølstad PR, et al. ISPAD Clinical Practice Consensus Guidelines 2014. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2014; **15**(Suppl 20): 47–64.
24. Babenko AP, Polak M, Cave H, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med* 2006; **355**: 456–66.
25. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* 2004; **350**: 1838–49.
26. Colombo C, Delvecchio M, Zecchins C, et al. Transient neonatal diabetes mellitus is associated with a recurrent (R201H) KCNJ11 (KIR6.2) mutation. *Diabetologia* 2005; **48**: 2439–41.
27. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic management of type 2 diabetes: 2016 interim update. *Can J Diabetes* 2016; **40**: 193–5.
28. Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics* 2012; **22**: 820–7.
29. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. *J Clin Invest* 2001; **108**: 1167–74.
30. Pawlyk AC, Giacomini KM, McKeon C, Shuldiner AR, Florez JC. Metformin pharmacogenomics: current status and future directions. *Diabetes* 2014; **63**: 2590–9.
31. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006; **355**: 2427–43.
32. Riedel AA, Heien H, Wogen J, Plauschinat CA. Loss of glycemic control in patients with type 2 diabetes mellitus who were receiving initial metformin, sulfonylurea, or thiazolidinedione monotherapy. *Pharmacotherapy* 2007; **27**: 1102–10.
33. Jablonski KA, McAteer JB, De Bakker PIW, et al. Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. *Diabetes* 2010; **59**: 2672–81.
34. Shu Y, Sheardown SA, Brown C, et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *J Clin Invest* 2007; **117**: 1422–31.

35. Zhou K, Donnelly LA, Kimber CH, et al. Reduced-function SLC22A1 polymorphisms encoding organic cation transporter 1 and glycemic response to metformin: a GoDARTS study. *Diabetes* 2009; **58**: 1434–9.
36. Becker ML, Pearson ER, Tkáč I. Pharmacogenetics of oral antidiabetic drugs. *Int J Endocrinol* 2013; **2013**: Article ID 686315. doi: **10.1155/2013/686315**.
37. van Leeuwen N, Nijpels G, Becker ML, et al. A gene variant near ATM is significantly associated with metformin treatment response in type 2 diabetes: a replication and meta-analysis of five cohorts. *Diabetologia* 2012; **55**: 1971–7.
38. Chen Y, Li S, Brown C, et al. Effect of genetic variation in the organic cation transporter 2 on the renal elimination of metformin. *Pharmacogenet Genomics* 2009; **19**: 497–504.
39. Zhou K, Bellenguez C, Spencer CC, et al. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. *Nat Genet* 2011; **43**: 117–20.
40. Florez JC, Barrett-Connor E, Jablonski KA, et al. The C allele of ATM rs11212617 does not associate with metformin response in the diabetes prevention program. *Diabetes Care* 2012; **35**: 1864–7.
41. Zhou K, Donnelly L, Burch L, et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. *Clin Pharmacol Ther* 2010; **87**: 52–6.
42. 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; **10**: 1781–7.
43. Holstein A, Plaschke A, Ptak M, et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. *Br J Clin Pharmacol* 2005; **60**: 103–6.
44. Holstein A, Hahn M, Patzer O, Seeringer A, Kovacs P, Stingl J. Impact of clinical factors and CYP2C9 variants for the risk of severe sulfonylurea-induced hypoglycemia. *Eur J Clin Pharmacol* 2011; **67**: 471–6.
45. Feng Y, Mao G, Ren X, et al. Ser 1369Ala variant in sulfonylurea receptor gene ABCC8 Is associated with antidiabetic efficacy of gliclazide in Chinese type 2 diabetic patients. *Diabetes Care* 2008; **31**: 1939–44.
46. Florez JC, Jablonski KA, Kahn SE, 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; **56**: 531–6.
47. Holstein JD, Kovacs P, Patzer O, Stumvoll M, Holstein A. The Ser1369Ala variant of ABCC8 and the risk for severe sulfonylurea-induced hypoglycemia in German patients with type 2 diabetes. *Pharmacogenomics* 2012; **13**: 5–10.
48. Pearson ER, Donnelly LA, Kimber C, et al. Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study. *Diabetes* 2007; **56**: 2178–82.
49. Holstein A, Hahn M, Korner A, Stumvoll M, Kovacs P. TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes. *BMC Med Genet* 2011; **12**: 30.
50. Kang ES, Park SY, Kim HJ, et al. Effects of Pro12Ala polymorphism of peroxisome proliferator-activated receptor gamma2 gene on rosiglitazone response in type 2 diabetes. *Clin Pharmacol Ther* 2005; **78**: 202–8.

51. Dawed AY, Donnelly L, Tavendale R, et al. CYP2C8 and SLCO1B1 variants and therapeutic response to thiazolidinediones in patients with type 2 diabetes. *Diabetes Care* 2016; **39**: 1902–8.
52. Kang ES, Park SY, Kim HJ, et al. The influence of adiponectin gene polymorphism on the rosiglitazone response in patients with type 2 diabetes. *Diabetes Care* 2005; **28**: 1139–44.
53. Morris AD, Boyle DI, MacAlpine R, et al. The diabetes audit and research in Tayside Scotland (DARTS) study: electronic record linkage to create a diabetes register. DARTS/MEMO Collaboration. *BMJ* 1997; **315**: 524–8.
54. Shu Y, Brown C, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1, OCT1, on metformin pharmacokinetics. *Clin Pharmacol Ther* 2008; **83**: 273–80.
55. American Diabetes Association. 7. Approaches to glycemic treatment. *Diabetes Care* 2016; **39**(Suppl 1): S52–9.
56. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; **131**: 281–303.
57. Aquilante CL. Sulfonylurea pharmacogenomics in type 2 diabetes: the influence of drug target and diabetes risk polymorphisms. *Expert Rev Cardiovasc Ther* 2010; **8**: 359–72.
58. Kirchheiner J, Roots I, Goldammer M, Rosenkranz B, Brockmoller J. Effect of genetic polymorphisms in cytochrome p450 (CYP) 2C9 and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance. *Clin Pharmacokinet* 2005; **44**: 1209–25.
59. Group UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 1998; **352**: 837–53.
60. Schopman J, Simon A, Hoefnagel S, Hoekstra J, Scholten R, Holleman F. The incidence of mild and severe hypoglycaemia in patients with type 2 diabetes mellitus treated with sulfonylureas: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2014; **30**: 11–22.
61. Li Q, Chen M, Zhang R, et al. KCNJ11 E23K variant is associated with the therapeutic effect of sulphonylureas in Chinese type 2 diabetic patients. *Clin Exp Pharmacol Physiol* 2014; **41**: 748–54.
62. Hamming KSC, Soliman D, Matemisz LC, et al. Coexpression of the type 2 diabetes susceptibility gene variants KCNJ11 E23K and ABCC8 S1369A alter the ATP and sulfonylurea sensitivities of the ATP-sensitive K+ channel. *Diabetes* 2009; **58**: 2419–24.
63. Javorsky M, Klimcakova L, Schroner Z, et al. KCNJ11 gene E23K variant and therapeutic response to sulfonylureas. *Eur J Intern Med* 2012; **23**: 245–9.
64. Sesti G, Laratta E, Cardellini M, et al. The E23K Variant of KCNJ11 encoding the pancreatic β-cell adenosine 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; **91**: 2334–9.
65. Kimber CH, Doney AS, Pearson ER, et al. TCF7L2 in the Go-DARTS study: evidence for a gene dose effect on both diabetes susceptibility and control of glucose levels. *Diabetologia* 2007; **50**: 1186–91.
66. Sesti G, Marini MA, Cardellini M, 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; **27**: 1394–8.
67. Prudente S, Morini E, Lucchesi D, et al. IRS1 G972R missense polymorphism is associated with failure to oral antidiabetes drugs in white patients with type 2 diabetes from Italy. *Diabetes* 2014; **63**: 3135–40.
68. van Leeuwen N, Swen JJ, Guchelaar HJ, 't Hart LM. The role of pharmacogenetics in drug disposition and response of oral glucose-lowering drugs. *Clin Pharmacokinet* 2013; **52**: 833–54.
69. Della-Morte D, Palmirotta R, Rehni AK, et al. Pharmacogenomics and pharmacogenetics of thiazolidinediones: role in diabetes and cardiovascular risk factors. *Pharmacogenomics* 2014; **15**: 2063–82.
70. Aquilante CL, Zhang W, McCollum M. Race, ethnicity, and use of thiazolidinediones among US adults with diabetes. *Curr Med Res Opin* 2007; **23**: 489–94.
71. 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; **3**: 7–16.
72. Kirchheiner J, Thomas S, Bauer S, et al. Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. *Clin Pharmacol Ther* 2006; **80**: 657–67.
73. Gouda HN, Sagoo GS, Harding A-H, Yates J, Sandhu MS, Higgins JPT. The association between the peroxisome proliferator-activated receptor-gamma2 (PPARG2) Pro12Ala gene variant and type 2 diabetes mellitus: a HuGE review and meta-analysis. *Am J Epidemiol* 2010; **171**: 645–55.
74. Aquilante CL. Pharmacogenetics of thiazolidinedione therapy. *Pharmacogenomics* 2007; **8**: 917–31.
75. Bluher M, Lubben G, Paschke R. Analysis of the relationship between the Pro12Ala variant in the PPAR-gamma2 gene and the response rate to therapy with pioglitazone in patients with type 2 diabetes. *Diabetes Care* 2003; **26**: 825–31.
76. Hsieh MC, Lin KD, Tien KJ, 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; **59**: 1139–44.
77. Kang ES, Cha BS, Kim HJ, et al. The 11482G>A polymorphism in the perilipin gene is associated with weight gain with rosiglitazone treatment in type 2 diabetes. *Diabetes Care* 2006; **29**: 1320–4.
78. Bailey SD, Xie C, Do R, et al. Variation at the NFATC2 locus increases the risk of thiazolidinedione-induced edema in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study. *Diabetes Care* 2010; **33**: 2250–3.
79. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; **368**: 1696–705.
80. Kleinberger JW, Pollin TI. Personalized medicine in diabetes mellitus: current opportunities and future prospects. *Ann N Y Acad Sci* 2015; **1346**: 45–56.
81. 't Hart LM, Fritsche A, Nijpels G, et al. The CTRB1/2 locus affects diabetes susceptibility and treatment via the incretin pathway. *Diabetes* 2013; **62**: 3275–81.

82. Nathan DM, Buse JB, Kahn SE, et al. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (GRADE). *Diabetes Care* 2013; **36**: 2254–61.
83. Hivert M-F, Jablonski KA, Perreault L, et al. Updated genetic score based on 34 confirmed type 2 diabetes loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. *Diabetes* 2011; **60**: 1340–8.
84. Meigs JB, Shrader P, Sullivan LM, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008; **359**: 2208–19.

اتجاهات وتحديات إدارة مرض السكري - الطب الشخصي

الملخص:

الخلفية :يعتبر مرض السكري (DM) قضية صحية عالمية كبيرة، حيث يساهم في معدلات مرضية ووفاة مرتفعة وأعباء اقتصادية كبيرة. أفادت منظمة الصحة العالمية بزيادة في تشخيص حالات السكري، حيث تأثر به 422 مليون بالغ عالميًا حتى عام 2014. على الرغم من انخفاض الحالات الجديدة المُشخصة في الولايات المتحدة، لا يزال مرض السكري منتشرًا، ويؤثر بشكل كبير على صحة القلب والأوعية الدموية ويتسبب في تكاليف صحية كبيرة.

الهدف :يهدف هذا المقال إلى استكشاف الاتجاهات والتحديات في إدارة مرض السكري من خلال الطب الشخصي، مع التركيز على الرؤى الجينية والفارماكوجينوميات لتحسين استراتيجيات العلاج.

الطرق :يشمل الاستعراض التقدمات الأخيرة في البحث الجيني والفارماكوجينوميات المتعلقة بمرض السكري. يناقش الأسس الجينية لمرض السكري من النوع الأول والنوع الثاني، بما في ذلك الأشكال أحادية الجين مثل MODY و .NDMيتم تقييم منهجيات مختلفة، مثل دراسات الارتباط على مستوى الجينوم (GWAS) ودراسات الجينات المرشحة، لمدى إسهامها في فهم عرضة مرض السكري واستجابات العلاج.

النتائج :تسلط النتائج الضوء على التقدم الكبير في تحديد المتغيرات الجينية المرتبطة بخطر مرض السكري واستجابة العلاج. تم التعرف على جينات رئيسية مثل TCF7L2 و KCNJ11و PPAR-γالتي لها علاقة بالعرضة واستجابة الأدوية. الأشكال أحادية الجين مثل MODY و NDMتقدم ملفات جينية مميزة تتطلب استراتيجيات علاجية مخصصة. تقدم الفارماكوجينوميات إمكانيات للعلاج الشخصي استنادًا إلى الاستعدادات الجينية.

الاستنتاج :تطور الطب الشخصي في إدارة مرض السكري مع تحسين الرؤى الجينية والفارماكوجينوميات. يمكن أن يعزز تخصيص العلاج استنادًا إلى الملفات الجينية من الفعالية ويقلل من الآثار الجانبية، على الرغم من أن التحديات ما زالت قائمة في دمج هذه التقدمات في الممارسة السريرية.

الكلمات المفتاحية :مرض السكري، الطب الشخصي، الفارماكوجينوميات، البحث الجيني، مرض السكري من النوع الأول، مرض السكري من النوع الثاني، MODY، NDM، GWAS.