



Precision Medicine in Type 2 Diabetes Mellitus: Utility and Limitations

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Abstract: Type 2 diabetes mellitus (T2DM) is one of the most widespread diseases in Western countries, and its incidence is constantly increasing. Epidemiological studies have shown that in the next 20 years. The number of subjects affected by T2DM will double. In recent years, owing to the development and improvement in methods for studying the genome, several authors have evaluated the association between monogenic or polygenic genetic alterations and the development of metabolic diseases and complications. In addition, sedentary lifestyle and socio-economic and pandemic factors have a great impact on the habits of the population and have significantly contributed to the increase in the incidence of metabolic disorders, obesity, T2DM, metabolic syndrome, and liver steatosis. Moreover, patients with type 2 diabetes appear to respond to antihyperglycemic drugs. Only a minority of patients could be considered true non-responders. Thus, it appears clear that the main aim of precision medicine in T2DM is to identify patients who can benefit most from a specific drug class more than from the others. Precision medicine is a discipline that evaluates the applicability of genetic, lifestyle, and environmental factors to disease development. In particular, it evaluated whether these factors could affect the development of diseases and their complications, response to diet, lifestyle, and use of drugs. Thus, the objective is to find prevention models aimed at reducing the incidence of pathology and mortality and therapeutic personalized approaches, to obtain a greater probability of response and efficacy. This review aims to evaluate the applicability of precision medicine for T2DM, a healthcare burden in many countries.

Keywords: type 2 diabetes mellitus, precision medicine, risk factors, genomic, environmental factors, drugs

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most widespread diseases in Western countries, and its incidence is constantly increasing. Epidemiological studies have shown that in the next 20 years, the number of subjects affected by T2DM will double. This expected increase in incidence is likely associated with several causes. Among them, a sedentary lifestyle, an unbalanced diet due to an increase in the percentage of daily carbohydrate intake, the absence of robust screening and public health information programs, and the lack of simple access to specialized healthcare could represent some of these reasons. Thus, a great challenge for the healthcare system is to reduce the incidence of the disease and its complications to improve the prognosis and quality of life of the patients.

Precision medicine is a discipline that evaluates the applicability of genetic, lifestyle, and environmental factors to disease development. In particular, it evaluated whether these factors could affect the development of diseases and their complications, response to diet, lifestyle, and use of drugs (Table 1). Consequently, the clinician could identify groups of subjects at higher risk for the development of some diseases or groups of individual responders or non-responders to lifestyle modifications and use of drug classes. Thus, the goal is to find prevention models aimed at reducing the

Table 1 Main Genetic Variants Influencing Glycaemic Response

Treatment	Genetic Variants	Polymorphisms	Therapeutic Effect	Population	Reference
Metformin	SLC22A1	rs622342	Increased	South Indian	[1]
		rs594709	Increased	Chinese	[2]
	SLC22A2	rs201919874	Increased	Pakistani	[3]
		rs316019	Increased	South Indian	[4]
			No effect	Mexican and Caucasian	[5]
		rs10755577	No effect	Jordanian	[6]
Sulfonylurea	SLC47A1	rs2289669	Increased	Chinese	[7]
	SLC47A2	rs12943590	Reduced	USA	[8]
	ABCC8	S1369A	Increased	Cells	[9]
	CYP2C9	rs1057910	Increased	Danish	[10]
		rs1799853	Increased	Danish	[10]
	TCF7L2	rs12255372	Reduced	Scottish	[11]
Thiazolidinedione	SLCO1B1	rs4149056	Increased	Scottish	[12]
	CYP2C8	rs10509681	Reduced	Scottish	[12]
	PPARγ	rs1801282	Increased	Han Chinese	[13]
	PTPRD	rs17584499	Increased	Han Chinese	[13]
DPP-4	CTRB1/2	rs7202877	Reduced	Caucasian Netherlands and Germans	[14]
GLP-1 RA	TCF7L2	rs7903146	Reduced	Mixed	[15]
	CNRI A	rs1049353	Increased	Spanish	[16]
SGLT2i	TCF7L2	rs7903146	Increased	Brazilian	[17]
	SORCS1	rs1416406	Increased	Chinese	[18]
	SLC5A2	rs9934336	No effect	German	[19]
		rs9924771	No effect	German	[19]
		rs3813008	No effect	German	[19]
		rs3116150	No effect	German	[19]
	UGT1A9*3 allele		No effect	Mixed	[20]
	UGT2B4*2 allele		No effect	Mixed	[20]

incidence of pathology and mortality and therapeutic personalized approaches to obtain a greater probability of response and efficacy.

This review aims to evaluate the applicability of precision medicine for T2DM, a healthcare burden in many countries.

Role of Genomic

In recent years, owing to the development and improvement in methods for studying the genome, several authors have evaluated the association between monogenic or polygenic genetic alterations and the development of metabolic diseases and complications. Furthermore, these studies investigated the association between diabetes, development of complications and response to treatments.

Monogenic Diabetes

Monogenic diabetes accounts for almost 3% of all diabetes cases and mainly involves a mutation in the transcription factor gene HNF1A or GCK.^{21,22} Subjects with these mutations develop diabetes at an age lower than 25 years, are negative for autoimmunity, and have phenotypic characteristics similar to those of individuals with type 1 diabetes (T1DM). Individuals with mutations in the GCK gene do not usually need any treatment, whilst HNF1A mutated patients are particularly responsive to sulfonylureas, probably through a mechanism that involves an increase in insulin secretion compared to normal responders. The authors observed an association between the pharmacodynamic effects of sulfonylureas and the Kir6.2 mutation.²³ A similar mechanism of drug sensitivity has been observed in neonatal diabetes caused by mutations in the KCNJ11 and ABCC8 genes.^{23–25}

For what concerns T2DM, still today there are little data on the association between monogenic mutations and the development of the disease.^{26,27}

Polygenic Diabetes

Research on multiple genes or variants, together with increasing the risk of developing diabetes or its complications, is object of precision medicine studies.²⁸ Genome-wide association studies (GWAS) have identified about a hundred loci associated with the development of T2DM. In a cohort study on French subjects with T2DM, approximately 300,000 single-nucleotide polymorphisms were evaluated. By comparing the results of both study populations with the development of high-density arrays, four loci containing variants associated with an increased risk of T2DM were identified.²⁹

Accordingly, another study evaluated 386,731 common single-nucleotide polymorphisms (SNPs) in a population of approximately 3000 subjects equally distributed between diabetic and healthy control individuals. At the end of the study, three loci were identified as associated with T2DM in non-coding regions, specifically in introns of IGF2BP2, CDKAL1, and SLC30A8.³⁰ Results of similar studies on northern European and Chinese populations described new diabetes susceptibility loci and variants, and confirmed those previously identified, for a total of about 10 genomic loci associated with the development of T2DM.^{31–33} More recently, the results of DIAGRAM and MAGIC meta-analyses, through the evaluation of genetic studies on European populations, have led to the identification of new loci (99), for a total of about 200 loci associated with insulin resistance, rise in HbA1c, fasting 2-hr glucose, and fasting insulin.^{34–36}

Another study on the gene polymorphisms of approximately 800 subjects from North India with and without T2DM evaluated the role of the mitochondrial uncoupling protein 2 (UCP2) gene polymorphism –866 G/A. UCP2 is a mitochondrial protein that plays a modulatory role in oxidative stress reactions, insulin sensitivity, and fatty acid metabolism.^{37–39} As previously highlighted, this study confirmed that UCP2 locus is associated with the development of obesity and T2DM.^{40,41} In particular, it has been highlighted that the 866 G/A SNP of UCP2 may be associated with the development of T2DM, both in homozygosis and heterozygosis. Furthermore, this association was more evident in subjects aged >50 years and in those with BMI > 25.⁴²

Recently, based on genetic discoveries and improved computational algorithms, some authors have evaluated whether novel clusters of genetic loci allow to identify subsets of individuals with T2DM.⁴³ In particular, Udler et al, through data from GWAS, have identified five clusters of T2DM loci and traits associated with beta cell function and insulin resistance.⁴³ At the end of the study, the authors identified cluster genetic risk scores associated with distinct clinical outcomes (eg stroke, hypertension, and myocardial infarction).

Similar results have been reported for other datasets in genomic, transcriptomic, and epigenetic categories.^{44,45} Some authors have identified 10 key drivers associated with T2DM. Of these, COL5A1, IRF7, CD74, and HLA-DRB1 may play diagnostic roles, whereas others (PSMB9, COL1A1, and COL4A1) were presented at high levels in subjects with T2DM.⁴⁶ These key drivers (hub genes) are the immune system and inflammatory response modulators, particularly associated with the activity of factors such as chemokines and cytokines, growth factor 19/21, TNF- α , Interleukin-1 beta (IL-1 β), Interleukin-6 (IL-6), Interleukin-18 (IL-18), adiponectin and C-reactive protein.⁴⁶ The authors refer to the thesis through which T2DM appears due to the action of these factors, thereby hypothesizing a diagnostic and potentially useful role for susceptibility to some drugs on these key drivers.

In conclusion, discovery of those loci could allow identifying potential causal and tissue-specific regulatory mechanisms associated with pathways associated with insulin resistance and insulin deficiency. Moreover, by clustering the population of T2DM subjects, it will be possible to obtain precision surveillance and clinical response to different treatment regimens.

Epigenetic Changes

Epigenetics is a discipline that studies the role of environmental and non-environmental factors (eg, diet, chemical agents, physical activity, and age) in modulating gene expression, without modifying DNA sequences. The main mechanisms of epigenetic regulation are DNA methylation, histone tails, and chromatin structure modifications.⁴⁷

DNA methylation involves the addition of a methyl group to DNA molecules, often occurring at cytosine residues in a CpG dinucleotide context. Usually, the result of methylation is to silence some promoters, thus inhibiting the

transcription. This process can influence gene expression and has been linked to various metabolic disorders, including obesity and T2DM^{48–50} In particular, DNA methylation and gene expression analyses have been performed in the adipose tissue of subjects with T2DM and obesity. The authors observed many methylations associated with these pathologies, 11120 differentially methylated CpG sites (DMCs) and 96 differentially methylated regions (DMRs). Furthermore, the correlation between differences in DNA methylation and changes in gene expression profiles was evaluated. Sixteen genes encoding DMCs, including ATP11A, LPL, and EHD2, were also significantly correlated with fasting glucose and HbA1c levels. These observations led authors to hypothesize that these loci with methylated DNA could be considered markers of disease.⁵¹ In this regard, the association between methylated DNA sequences obtained from the white blood cells of Indian subjects with diabetes was evaluated. In almost 1300 patients enrolled in the study, methylated positions (DMPs) associated with T2DM were 49. The observed genes with these methylations were associated with insulin sensitivity (SREBF1), cholesterol, and phospholipid transport (ABCG1), as indicated for the development of complications (HDAC). However, these results were not confirmed by multiple comparisons correction.⁵²

Further studies are needed to better define the roles of genomic, epigenomic, and transcriptomic analyses, in terms of their diagnostic and prognostic roles. The variability in response to environmental factors, object of study of precision medicine and epigenetics, will be discussed in the subsequent sections.

Role of Metabolomics

Metabolomics is a comprehensive analysis of metabolites in a biological specimen and is an emerging discipline that could be strictly associated with precision medicine.⁵³ Through new methods for detecting biomarkers in body fluids (eg, serum and urine), it is possible to identify and define the role of multiple metabolomics. Liquid chromatography mass spectrometry (LC-MS), the most common profiling technology used for detecting biomarkers, could show changes in the metabolic profile and particular metabolic abnormalities, by quantifying and specifying the number of modified biomarkers.⁵³ More recently, some authors have evaluated whether known metabolomics or new metabolomics could have not only a role in describing metabolic status of subjects but also in predicting the development of T2DM. In this regard, a study on a population of about 2500 subjects without diabetes followed for about 12 years, showed that some amino acids (isoleucine, leucine, valine, tyrosine, phenylalanine, and 2-amino adipic acid) were significantly associated with the development of T2DM.^{54,55} Results from a retrospective cohort study on 100 subjects showed other biomarkers associated with the development of T2DM. At the end of the study, about 10 new metabolites were significantly associated with the development of the disease.⁵⁶

Some investigators then evaluated whether the intake of food and probiotics could be associated with a modification of the metabolomics and alterations of the intestinal microbiome. Furthermore, it was evaluated whether these changes could have a role in the development or progress of diabetic disease. For example, *Bifidobacterium longum*, which is normally part of the intestinal microbiota, showed positive effects after the assumption for 5 weeks on the progression of T2DM and obesity in diabetes model mice.⁵⁷ In another population of hypercholesterolemia hamsters, a diet with addition of hawthorn seed oil decreased plasma cholesterol and favorably modulated gut microbiota composition and gut-derived metabolites associated with cholesterol regulation.⁵⁸ More recently, some authors have demonstrated that lipid extract of foxtail millet (LEFM) feeding in diabetic mice could modify gut microbiota composition, reduce harmful bacteria, and induce a bloom of probiotics. In particular, they observe a reduction in *Escherichia-Shigella*, *Peptococcus*, and *norank_f_Oscillospiraceae*, an increase of short-chain fatty acid producing bacteria (*Adlercreutzia*, *Faecalibaculum*, and *Bifidobacterium*). Moreover, LEFM treatment altered serum concentration of some metabolites by increasing the levels of L-carnitine and L-glutamine and reducing S-acetyl dihydrolipoamide-E and sphingosine.⁵⁹ Briefly, it seems that some modifications of the intestinal microbiome could not only modify the amount of serum metabolites but also have a positive impact on the progression of the diabetic disease.

Other studies on adults with T2DM then evaluated whether some biomarkers could be predictive of T2DM complications. In particular, it seems that phosphocreatine and cyclic guanosine monophosphate could be associated with coronary heart disease.⁶⁰ Moreover, propionic acid, oxoadipic acid, leucine, isovaleric acid, isobutyric acid, and indole-3-carboxylic acid seem markedly and independently associated with diabetic kidney disease, while fatty acid

desaturase 2 (FADS2) seems an important potential contributor to the pathogenesis of proliferative diabetic retinopathy.^{61,62}

Lifestyle and Environmental Factors

Over the last 20 years, the incidence of both diabetes and obesity has significantly increased. Some authors describe a real pandemic, especially in Western countries, and agree that unbalanced lifestyles and environmental factors are responsible. There has been a spread of a predominantly energy-rich diet with an increased consumption of refined carbohydrates at the expense of a more varied diet. Moreover, a sedentary lifestyle, which is widespread due to various environmental, socio-economic, and pandemic factors, has a great impact on the habits of the populations and, first of all, on their food lifestyle.^{63,64} These factors have significantly contributed to an increase in the incidence of metabolic disorders, such as obesity, T2DM, metabolic syndrome, liver steatosis.^{65–71}

In this context, for the clinician, it is crucial to identify the “tailored” diet for each subject. Among hundreds of genes associated with T2DM, the main genomic, lifestyle, and environmental factors linked to this disease are summarized in Figure 1.

Diet

The influence of diet is fundamental, not only to the development of the disease but also to the development of cardiovascular complications. In this regard, the most recent European Society of Cardiology (ESC) guidelines demonstrate, with an I B level of evidence, that a healthy diet is essential for the prevention of cardiovascular risk in all individuals.⁷²

It is suitable to follow a Mediterranean diet and consume plants, including whole grains, fruits, vegetables, pulses, and nuts. In addition, subjects should prefer unsaturated fats to saturated fats, fish a couple of times a week rather than meat, to minimize alcohol and free sugar consumption.^{73–76}

Many trials have demonstrated the effectiveness of the Mediterranean diet in reducing the risk of developing metabolic, cardiovascular, and other diseases (relative risk (RR) for comparing extreme quantiles: 0.87; 95% confidence interval (CI):0.82, 0.93). Diet patterns characterized by legumes, vegetables, poultry, fruits, and fish (“mainly healthy”) were inversely associated with T2DM (RR:0.84; 95% CI:0.77, 0.91). On the other hand, a diet with high consumption of

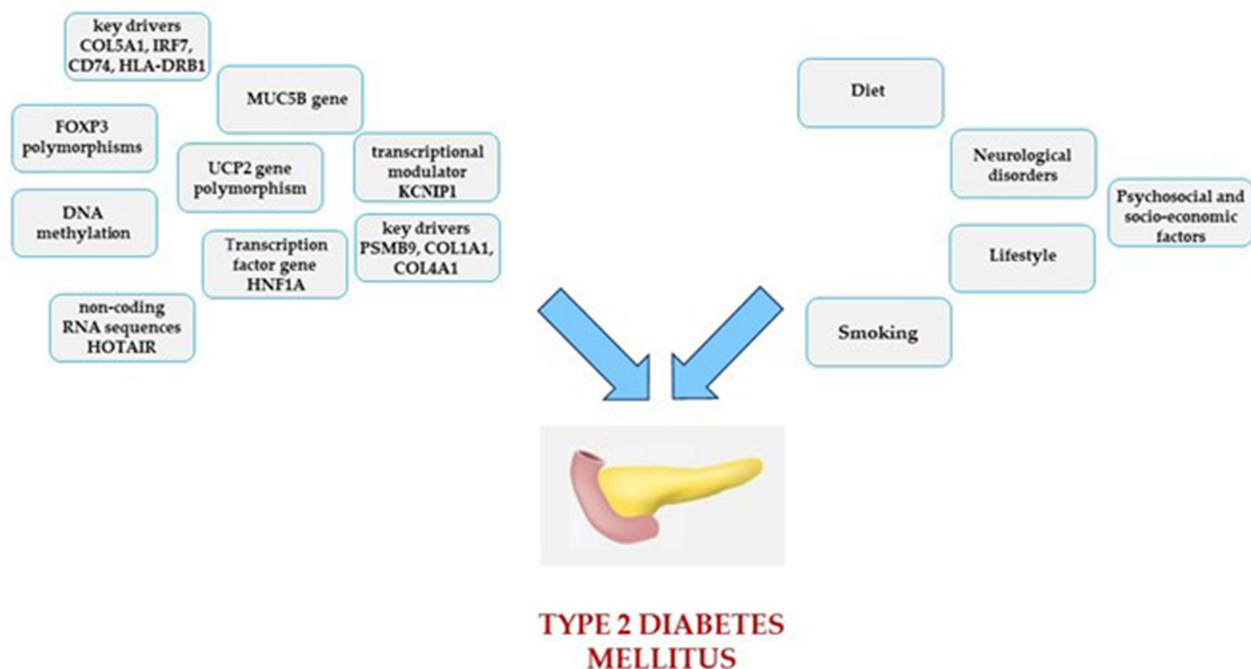


Figure 1 An example of main genomic, lifestyle and environmental factors linked to type 2 Diabetes Mellitus.

processed meat, high-fat dairy, refined grains, fried products, and eggs (“mainly unhealthy”), seems positively associated with the development of T2DM (RR:1.44; 95% CI:1.27, 1.62).^{77–83}

More recently, the ketogenic diet has stimulated the interest of many authors and nutritionists, also in subjects affected by T2DM. This diet has already been used in the past and even nowadays for the treatment of epilepsy. Ketogenic diet is based on the principle of reducing the consumption of a certain amount of carbohydrates, to a maximum of 50 g daily, and high fat content, moderate protein content, with the formation of ketone bodies as a source of energy.^{84–91}

Some authors therefore suggest that a personalized approach could be useful, especially in those with visceral obesity, dyslipidemia, and high levels of transaminases.⁹²

Intermittent Fasting is another type of diet characterized by two different phases. In one, the subject practices a low-calorie diet and, during the second, the subject eats without specific limitations. There are several types, mainly differentiated according to the duration of each phase.⁹³ Some studies demonstrate that intermittent fasting can improve glycemic control in individuals with T2DM, while others fail to demonstrate such efficacy.^{94–98}

In addition, many people around the world observe a month of Ramadan fasting during their life, according to their religious custom. For this reason, some authors have evaluated the impact of this kind of Intermittent Fasting on glycemic control in patients with T2DM. As a result, it has been observed that people observing a period of pre-Ramadan assessment with clinicians, as a personalized approach, could improve metabolic balance and also prevent acute complications during and after Ramadan period.^{99,100}

Nutrigenetics studies the role of genetic variants in the modulation of response to diet and the implications in the development, or prevention, of diseases. In particular, some genetic variants seem associated with diet response for what concerns the development of cardiovascular diseases, mainly obesity and diabetes.¹⁰¹ A study described a gene–diet interaction with the Mediterranean diet for both the FTO rs9939609 and for the MC4R rs17782313. People with these variant alleles showed a higher T2DM risk, as compared to wild-type subjects, when the Mediterranean diet was not followed. However, the association does not seem to be observed when subjects support a Mediterranean diet.¹⁰² Other studies have also described the interactions between different alleles and diet in modulating T2DM risk. In particular, for what concerns TCF7L2 rs7903146, wholegrain intake seems inversely associated with T2DM risk among CC carriers, whereas this protective effect comes lost in presence of the T-allele.¹⁰³

Nutrition also seems to influence epigenetic modulation, especially through DNA methylation. In particular, early life nutritional experience, both during pre- and post-natal life, could seriously induce metabolic and physiological changes through altered offspring epigenetic profile. Maternal malnutrition can lead to different susceptibilities to various chronic diseases in subsequent years.¹⁰⁴

Lifestyle

As recommended by the most recent guidelines, physical activity is one of the main therapeutic measures for both the general population and particularly for subjects with T2DM.^{72,105} It is recommended to practice 150–300 min of moderate-intensity aerobic activity per week. In elderly patients and those with chronic diseases, it is advisable to practice physical activity, as allowed by the underlying pathology.⁷² These measures can determine an improvement in metabolic parameters, HbA1c, and weight, and a reduction in the risk of micro and macrovascular complications.¹⁰⁶ Some trials enrolling individuals at high cardiovascular risk have demonstrated that the risk of coronary heart disease can be reduced by 14–20%, as well as the risk of developing diabetes by 6% after approximately 10 years of follow-up.^{107–109} Exercise may also be favorable for pregnant women to preventing excessive weight and reduce the risk of developing gestational diabetes (6.8% vs 2.6%; odds ratio, 0.363; 95% confidence interval, 0.138–0.953; $p=0.033$).¹¹⁰

In presence of complications, it seems that personalized physical exercise can determine beneficial effects. Individuals with peripheral neuropathy can benefit from an exercise program with both aerobic and strengthening components showing, after 10 weeks of personalized training, reductions in pain, neuropathic symptoms, and increased intraepidermal nerve fiber branching (-18.1 ± 35.5 mm on a 100 mm scale, $P=0.05$; -1.24 ± 1.8 on MNSI, $P=0.01$; $+0.11\pm0.15$ branch nodes/fiber, $P=0.008$).¹¹¹ Even individuals with diabetic nephropathy seem to benefit from physical exercises, both aerobic and anaerobic, as well as from aerobic exercises only. Although few trials are dedicated to this

topic, those available have shown how home training can determine decreased urinary albumin-to-creatinine ratio, serum urea nitrogen, urinary protein-to-creatinine ratio, and urinary protein excretion.¹¹² However, diet and lifestyle seem ineffective on other renal function outcomes (eg eGFR) and the sample size across randomized controlled trials is quite small. As a consequence and as limitations of studies, it is hard to identify subjects with different responses to the same interventions, thus the authors argue that in the future, new trials with large sample sizes will be required to better define the role of lifestyle in populations with diabetic nephropathy.

More recently, a study on subjects with non-proliferative diabetic retinopathy showed that after 12 weeks of a 45-min aerobic exercise program, 3 times a week, a lower fasting glycemia and central macular thickness could be observed.¹¹³ However, also here, it is not possible to identify different subgroups of diabetic subjects with different responses to the intervention, due to the small sample size and the endpoint of the study.

As above described, some literatures have identified different genetic clusters of T2DM subjects and associated genetic risk scores for developing cardiovascular diseases.⁴³ Based on previous literature, other authors have thus evaluated the effects of lifestyle associated with genetic risk scores on a population of almost 35,000 individuals naïve for cardiovascular diseases.¹¹⁴ At the end of almost 20 years follow-up, 4,433 participants were diagnosed with type 2 diabetes. Subsequently, the authors identified a global polygenic score and different pathway associated scores (particularly describing insulin impaired secretion and insulin impaired sensitivity). The observed relative risk of T2DM for global polygenic score was 1.29 (95% confidence interval [CI] 1.25, 1.32; $P < 0.001$), while different risks were associated with pathway-specific polygenic scores (ranging from 1.26 [95% CI 1.22, 1.30; $I^2 = 55.5\%$; $P < 0.001$] for the beta-cell dysfunction polygenic score to 1.09 [95% CI 1.05, 1.12; $I^2 = 49.1\%$; $P < 0.001$] for the obesity-mediated insulin resistance polygenic score). Moreover, the population was also subdivided according to the genetic risk (low, intermediate, and high) and the quality of diet and lifestyle (low, intermediate, and high). At the end of the study, low-quality diet was associated with higher T2DM risk, independently from genetic risk. Moreover, high-quality diet and lifestyle was associated with lower T2DM risk across all classes of genetic risk.¹¹⁴ However, the efficacy of high-quality diet and lifestyle comes progressively lost proceeding from the low genetic risk subgroup to the high. The authors argue that this observation underlines the potential of genetic risk assessment for future risk stratification and surveillance.¹¹⁴

Neurological Disorders

T2DM is a chronic disease that affects patients from the time of diagnosis to exitus.^{115–119} In addition, T2DM can contribute to the development of anxious depressive conditions and is often associated with chronic neurological diseases.^{30,120}

T2DM is associated with a 73% higher risk of developing all types of dementia, 56% of developing Alzheimer's disease, and more than double the risk of developing vascular dementia compared to the general population.^{121,122} Moreover, women with diabetes seem to have a higher risk to develop vascular dementia than men. Accordingly, other authors showed a greater risk of cognitive decline of approximately 1.2-fold (95% CI 1.05–1.4) and 1.7-fold (95% CI 1.3–2.3) in the T2DM population compared to the healthy subjects. In addition, the same authors observed an almost doubled risk of developing future dementia (95% CI 1.4–1.8).¹²³

Owing to the development of complications, T2DM is often a cause of disability, which greatly influences the patient's quality of life.¹²⁴ Furthermore, subjects with T2DM and disabilities are not able to maintain physical activity; therefore, their sedentary lifestyle does not allow them to obtain adequate glycemic control.¹²⁴ Consistently, in a study of approximately 7000 elderly people with overweight/obesity and metabolic syndrome, executive functions were directly and negatively associated with T2DM, high BMI, and depressive symptoms. In addition, participants with good glycemic control ($HbA1c < 53$ mmol/mol) showed better cognitive performance, treatment adherence, and quality of life.^{121,125}

Insulin resistance, oxidative stress, inflammation, glycated end-products, and autophagy seem to be pathophysiological common mechanisms underlying the association between mental/neurological disorders and diabetes.¹²⁶ This evidence has led several authors to evaluate whether antidiabetic drugs could have a positive role in the progression of cognitive impairment.^{127,128} It seems that some of them, especially metformin and glucagon-like peptide-1 receptor agonists (GLP-1 RA), could have a beneficial effect, not only on HbA1c and other metabolic factors but also on neurological functions.^{127,128} In particular, these drugs play neurotrophic and neuroprotective roles in central nervous system, by exerting anti-inflammatory effect and reducing A β aggregation/deposition and hyperphosphorylation of tau

protein.^{127–129} Clinical consequences seem to be a reduction in cognitive impairment, improvement of cognitive subdomains of delayed memory, attention, and executive function in subjects who have assumed those drugs vs placebo. Consistently, literature provides evidence that treating some mental disorders could improve diabetes outcomes and contribute to the prevention of diabetes.¹³⁰ However, a number of studies in this field are lacking, and sample size is often very small, with sometimes evidence inconsistent. For this reason, it is difficult to generalize those results and identify subgroups of subjects with different prognoses or different responses to anti-diabetic treatments, in order to stratify treatment recommendations based on mental disorders.¹³⁰

More recently, some devices can support subjects affected by complicated T2DM and affected by disabilities and mental disorders. For example, role of telemedicine has spread in recent years, especially during the COVID-19 Pandemic.¹³¹ Thanks to the use of digital smart ophthalmoscope devices, it was possible to carry out remote retinal evaluation, also in subjects who could not refer to specialist centres, both for physical disabilities and long distances from the hospital care unit domicilio.¹³² Other recent examples of a technological device, which has allowed a personalized and therapeutic approach through telemedicine include the insulin pump and the blood sugar sensor.^{133,134} In subjects with T2DM, educational programs through optimal diabetes self-management education via telemedicine, have demonstrated good compliance and good glyco-metabolic compensation in enrolled populations.^{135,136} In this context, some authors have proposed a web-mediated approach to perform cognitive-behavioral therapy in patients with diabetes and depression. In the experimental arm, a significant reduction of depressive symptoms (41% vs 24%; $p < 0.001$) but no effect on glyco-metabolic compensation was found.¹³⁷ Therefore, the use of technological devices could favor a personalized approach in people who present neurological disorders and diabetes. However, to date, no such studies have enrolled subjects with T2DM and diagnosed mental disorders, in order to better confirm this hypothesis.¹³⁰

Psychosocial and Socio-Economic Factors

Socioeconomic status (SES) describes the social condition of the participants based on their income, education, and occupation.¹³⁸ Several studies have evaluated the association between SES, the prevalence of T2DM, and the prognosis of these patients. It can be argued that low SES is associated with a greater risk of developing diabetes [relative risk (RR) = 1.41, 95% confidence interval (CI): 1.28–1.51], (RR = 1.31, 95% CI: 1.09–1.57) and (RR = 1.40, 95% CI: 1.04–1.88)].^{64,139} Moreover, subjects with low SES had worse glycol-metabolic control than those with high SES. Some results demonstrated that the pooled mean difference in HbA_{1c} levels among the groups was 0.26% (95% CI, 0.09–0.43) or 3.12 mmol/mol (95% CI, 1.21–5.04) for education and 0.20% (95% CI, 0.05 to 0.46) or 2.36 mmol/mol (95% CI, 0.61 to 5.33) for income. A recent trial of almost 2000 subjects demonstrated a greater risk of developing T2DM (OR: 1.48) and its complications (OR: 0.71 and 0.88) in individuals with low SES, while higher education was associated with a 53–69% decreased risk of diabetic retinopathy.^{140,141}

Precision Medicine to Address a Tailored Drug Intervention

Treatment Selection Approach in Diabetes

Treatment tailoring dates to the time of Hippocrates. In fact, Hippocrates' hypothesis was "It is more important to know what sort of person has a disease than to know what sort of disease a person has".¹⁴² However, the role of precision medicine has only increased in recent years owing to the growth of both new diagnostic and informatics tools, which has widened our understanding of the molecular basis (Figure 2).¹⁴²

Most patients with T2DM respond to antihyperglycemic drugs. Only a minority of patients could be considered true non-responders. Thus, it appears clear that the main aim of precision medicine in T2DM is to identify patients who can benefit most from a specific drug class more than from the others.²⁶ To achieve this, it is crucial to detect markers that can robustly predict a greater or lesser response to each drug class. However, among the single markers, none has emerged, presenting a huge effect. Thus, the use of a combination of these markers for personalized treatment has been proposed.

Metformin is widely acknowledged as the primary treatment choice for T2DM.¹⁴³ However, there is growing evidence supporting the potential of Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) and GLP-1 RA as first-line therapies for type 2 diabetes, given their ability to enhance treatment outcomes. Despite the promising effects of SGLT2i

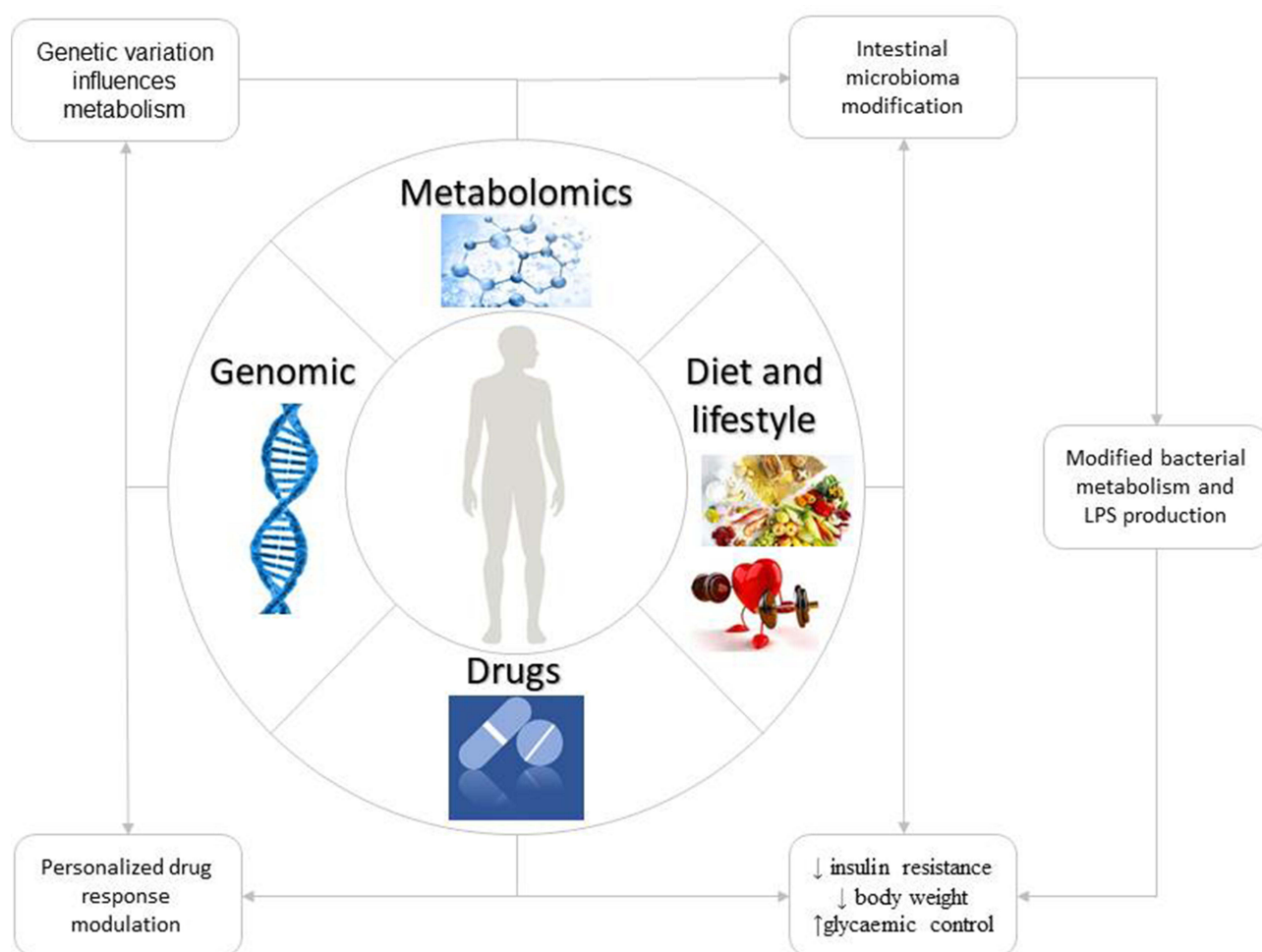


Figure 2 Potential applications of Precision Medicine.

and GLP-1 RA, the issue of cost-effectiveness remains a significant consideration. To achieve cost-effectiveness, a substantial reduction in the current costs of these treatments, amounting to at least 70%, would be necessary. Indeed, it would be worth exploring the possibility that in patients with genetically determined low responsiveness to metformin, the cost-effectiveness landscape might change. The main genetic variants influencing glycaemic response are summarized in Table 1. Nevertheless, further research and studies are required to better understand this aspect.¹⁴⁴

Metformin

Metformin primary actions include increasing glucose uptake by muscles, liver, and adipose tissues, as well as reducing hepatic glucose output, which results in improved insulin resistance. Moreover, metformin may influence the gut by promoting the release of incretins, enhancing insulin secretion, and improving glucose homeostasis.¹⁴⁵ In addition, the insulin sensitizer effect seems to be beneficial for weight loss in obese patients (-0.62 [-1.00 to -0.25] kg vs placebo).¹⁴⁶

As metformin is cleared through renal filtration, one of the primary concerns regarding its prescription is kidney insufficiency. In such cases, metformin blood levels may rise due to reduced excretion, leading to the risk of lactic acidosis. However, it is noteworthy that this complication is rare and has shown a decreasing trend over time.^{145–147} Moreover, the FDA has revised the metformin label to reflect its safety use in patients with an estimated glomerular filtration rate (eGFR) of $30 \text{ mL/min/1.73 m}^2$.¹⁴³

Studies on metformin have also made considerable progress in understanding the genetic basis underlying its therapeutic response. In a Genome-Wide Association Study (GWAS) analysis, researchers estimated the heritability of glucose response to metformin to be up to 34% (for the absolute reduction in HbA1c adjusted for pretreatment HbA1c) in

patients with type 2 diabetes.¹⁴⁸ Metformin is transported across cellular membranes via different isoforms of organic cation transporters (OCTs). These transporters are involved in the uptake of metformin into cells. The primary transporter involved in hepatic uptake is OCT1, which is encoded by the solute carrier family 22-member 1 (SLC22A1) gene. On the other hand, OCT2, encoded by SLC22A2, is primarily responsible for metformin's tubular secretion.^{149,150}

Genetic variants in these transporter molecules, as well as in multidrug and toxin extrusion (MATE) transporters responsible for metformin excretion through bile and urine, have been associated with both metformin efficacy and intolerance.¹⁵¹ For example, certain genetic variants in the SLC22A1 gene (OCT1), such as SNP rs622342 AA and rs594709, have been linked to increased response to metformin among South Indian and Chinese patients with T2DM, respectively.^{1,2} In another study of Chinese patients with T2DM, the SLC22A2 808G>T (rs316019) variant was associated with a greater reduction in HbA1c levels, along with reduced renal clearance of metformin.¹⁵² Likewise, several variants within the SLC22A2 gene (OCT2), namely rs201919874 and rs316019, were identified as being linked to decreased renal clearance of metformin and a consequent improvement in HbA1c levels.^{3,4} However, the latter association was observed in certain populations but not in others.^{5,153} Conversely, the variant rs10755577 did not exhibit any significant impact on glycemic control.⁶ Furthermore, carriers of the SLC47A1 rs2289669 variant in Chinese patients demonstrated an increased response to metformin.⁷ Conversely, the SLC47A2 (solute carrier family 47 member 2, encoding MATE2) variant rs12943590 was associated with a poor treatment response to metformin in a US population.⁸ However, the predictive insights have been modest.^{145,154}

Sulfonylurea and Thiazolidinedione

With the spread of new drug therapies, the use of both Sulfonylurea and Thiazolidinedione is decreasing because of an increased risk of side effects as well as little effect on cardiovascular outcomes.¹⁴³ Observational data from the UK Clinical Practice Research Datalink (CPRD), which enrolled approximately 22,000 patients starting sulfonylurea or thiazolidinedione therapy, reported that males without obesity benefit most from sulfonylurea treatment on glucose-lowering response rather than thiazolidinedione. Conversely, women with obesity showed a greater response to thiazolidinedione than sulfonylurea treatment.¹⁵⁵ Notably, pioglitazone has proven to be effective in patients with non-alcoholic steatohepatitis (NASH) and T2DM, in reducing hepatic steatosis, inflammation, aspartate aminotransferase and alanine aminotransferase serum levels, and in improving liver fibrosis.¹⁵⁶ However, further studies are needed to better assess this relationship and to include this treatment option in non-alcoholic fatty liver disease (NAFLD) treatment guidelines.

Information on sulfonylureas comes from decades of research and clinical experience. The best study example testing treatment response to genetic variation is the GoDARTS study, which reported reduced glycemic control achieved through sulfonylurea treatment in carriers of the TCF7L2 T2DM risk allele.¹¹ In addition, various pharmacogenetic determinants have been investigated, encompassing genetic variations in genes associated with sulfonylurea metabolism, sulfonylurea receptors, insulin action, and β -cell function. These genes include CYP2C9, ABCC8, KCNJ11, IRS1, CDKAL1, CDKN2A, CDKN2B, KCNQ1, and NOS1AP.^{145,157} Among these, the sulfonylurea receptor-1 (SUR1) coding variant ABCC8 S1369A has been associated in functional studies with an enhanced treatment response to a particular subclass of sulfonylureas (gliclazide, an A-site sulfonylurea).^{9,158} Moreover, the metabolism of sulfonylureas is primarily mediated by cytochrome P450 2C9 (CYP2C9), and variants of this enzyme (rs1057910, rs1799853) result in reduced clearance of sulfonylureas and increased sensitivity to sulfonylureas therapy.¹⁰ Consequently, individuals carrying these CYP2C9 variants are recommended to take lower doses to minimize the risk of hypoglycemia.¹⁵¹ In addition, carriers of TCF7L2 gene variants, particularly the T/T genotype at rs12255372, which is well-known for its association with type 2 diabetes, have been found to exhibit reduced responsiveness to sulfonylureas.¹¹ Besides pharmacogenetic responses, these varied genotype-treatment interactions may also reflect the extent of β -cell dysfunction influenced by these genetic variants, ultimately impacting the individual's response to sulfonylureas therapy.

In contrast, thiazolidinediones' understanding of the genetic determinants underlying beneficial or adverse therapeutic responses has been less investigated. In carriers of rs4149056 variants within SLC01B1, which encodes the organic anion transporting polypeptide 1B1 (OATP1B1), the use of rosiglitazone enhanced glycemic response, and in carriers of variations within CYP2C8, encoding cytochrome P450 2C8 metabolizing enzyme (rs10509681), rosiglitazone was

associated with reduced glycemic response and reduced weight gain. Moreover, these results did not appear to be applicable to pioglitazone therapy.¹² Limited data from a small Asian sample size have highlighted that genetic variation in PPAR γ rs1801282 and protein tyrosine phosphatase receptor type D (PTPRD) gene polymorphism rs17584499 are associated with increased responsivity to thiazolidinediones. However, this result was not confirmed by a previous study. Therefore, its clinical relevance remains uncertain.^{13,145}

Acarbose

Acarbose is an α -glucosidase inhibitor with limited use in Western countries; however, it is widely used in some parts of Asia, particularly in China. Major benefits of acarbose treatment have been reported in the management of postprandial hyperglycemia as it delays carbohydrate digestion from the brush border of the small intestine. An old meta-analysis of seven randomized, double-blind, placebo-controlled acarbose studies (MeRIA7) found an association between the reduced incidence of cardiovascular events in T2DM and acarbose treatment (HR 0.65, 95% CI 0.48–0.88).¹⁵⁹ However, none of the included trials were explicitly conducted to test this hypothesis, and the number of myocardial infarction was extremely low in both arms (19 in placebo vs 9 in acarbose treatment).¹⁶⁰ The Acarbose Cardiovascular Evaluation (ACE) large-scale cardiovascular outcome trial reported that acarbose failed to reduce the risk of Major Adverse Cardiovascular Events but reduced the risk of new-onset diabetes by 18% for a median of 5.0 years follow-up.¹⁶¹

The STOP-NIDDM trial found associations between genetic variations in PPAR α , HNF4A, LIPC, PPARG2, PPARGC1A, and acarbose treatment response in prediabetic patients.¹⁶² However, these associations are modest and have not been tested in patients with overt diabetes.

Dipeptidyl Peptidase 4 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonist

A prospective predicting response to incretin-based agents (PRIBA) study reported that in patients with higher levels of insulin resistance (fasting C-peptide, HOMA2 insulin resistance, and triglycerides), treatment with Dipeptidyl Peptidase-4 Inhibitors (DPP-4is) is associated with a reduced glycaemic response.¹⁶³ The same study highlighted an increased treatment response in patients with obesity and high triglyceride levels, compared to non-obese, low triglyceride subgroup, at 6-months evaluation (25.3 mmol/mol [20.5%] and 211.3 mmol/mol [21.0%], respectively). However, no evidence has been reported on the association between markers of insulin resistance and treatment response in patients initiating GLP-1RA.¹⁶³ Similar findings were reported in non-insulin-treated diabetic patients from the UK National Health Service starting with GLP-1RA treatment. However, in the same study, a reduced glycemic response to GLP-1RAs was associated with a longer duration of diabetes, lower C-peptide levels, and positive glutamic acid decarboxylase (GAD) or Islet Antigen 2 (IA-2) autoantibodies.¹⁶⁴ A recent systematic review showed that a higher baseline HbA1c level was associated with a greater treatment response to both DPP-4i and GLP-1RA therapies.¹⁶⁵ In addition, DPP-4i treatment response seems to be increased in Asian ethnicity.¹⁶⁶ There have been limited pharmacogenetic investigations concerning DPP-4i treatment efficacy to date. In one association study, researchers observed a correlation between rs7202877, located near CTRB1/2 (chymotrypsinogen B1/2), and a reduced HbA1c response to dipeptidyl peptidase-4 inhibitors.¹⁴ In addition, in an association study, researchers reported that the diabetes risk-related variant TCF7L2 rs7903146 was associated with a smaller reduction in HbA1c after linagliptin treatment in homozygous T-allele carriers, representing 10% of the patients.¹⁵ However, the role of other potential predictors remains unclear and requires further investigation. In a recent meta-analysis of 764 trials enrolling more than 400,000 diabetic patients, GLP-1RA have been proven to reduce the overall risk of all-cause cardiovascular mortality (OR 0.88, 95% CI 0.80–0.96), non-fatal myocardial infarction (OR 0.92, 95% CI 0.85–0.99), non-fatal stroke (OR 0.84, 95% CI 0.76–0.93), and kidney failure (OR 0.91, 95% CI 0.69–1.20), with an increasing benefit according to the risk profile. Moreover, GLP-1RA treatment may also lower body weight, with a mean difference of –1.45 kg (95% CI –1.72 to –1.18), which may be beneficial in obese patients.¹⁶⁷

Genetic variants of the glucagon-like peptide 1 (GLP-1) receptor gene have been implicated in a reduced glycemic lowering response to DPP-4i treatment. Moreover, other gene variants (KCNQ1, KCNJ11, CTRB1/2, PRKD1, CDKAL1, IL6 promoter region, TCF7L2, DPP4, and PNPLA3) have been suggested to induce similar or minimal responses to DPP-4i treatment, although replication studies are lacking.¹⁶⁸ Several studies investigating GLP1R variant allele carriers

found a greater weight reduction benefit with GLP-1RA treatment.^{16,169} Other variants related to GLP-1RA response were cannabinoid receptor 1 (CNR1), TCF7L2, and SORCS1. The CNR1 A polymorphism (rs1049353) improved insulin resistance after liraglutide treatment owing to weight loss and glycaemic control improvement, whereas non-carriers of the A allele showed an improvement in cholesterol levels after weight loss.¹⁷⁰ Carrier of TCF7L2 rs7903146 T allele showed a significant reduction in postprandial plasma insulin peak levels compared to non-carriers after exenatide treatment.¹⁷ Finally, it was highlighted that newly diagnosed type 2 diabetic patients carrying the SORCS1 gene rs1416406 with the GG genotype might benefit the most from early exenatide treatment.¹⁸

Sodium-Glucose Cotransporter 2 Inhibitors

Trial data analysis has shown an incremental reduction in HbA_{1c} with increasing baseline HbA_{1c} with SGLT2i treatment compared to DPP-4i or sulfonylureas.^{171,172} In a retrospective study enrolling more than 10,000 patients initiating Sodium-glucose co-transporter-2 inhibitors (SGLT2is), a greater response to SGLT2is treatment was reported in subjects with a higher estimated glomerular filtration rate (eGFR) and alanine transaminase.¹⁷³ Several studies have reported a different response to SGLT2i treatment according to baseline renal function, with increasing efficacy with higher eGFR levels (90 vs 60–90 mL/min/1.73 m²).^{174–177} A recent prospective meta-analysis reported that SGLT2Is effectively improve liver function parameters in patients with diabetes and ameliorate alanine transaminase levels and liver steatosis in a prospective study.^{178,179} In a recent large-scale metanalysis, SGLT2i have been proven to reduce the overall risk of all-cause cardiovascular mortality (OR 0.85, 95% CI 0.79–0.92), non-fatal myocardial infarction (OR 0.87, 95% CI 0.79–0.97), admission for heart failure (OR 0.70, 95% CI 0.63–0.77), and kidney failure (OR 0.71, 95% CI 0.57–0.89), with an increasing benefit based on the risk profile. Moreover, SGLT2is treatment might also impact on body weight lowering, with a mean difference of 1.92 kg (95% CI –2.23 to –1.62).¹⁶⁷

SGLT2 is encoded by the *SLC5A2* gene, which is located on chromosome 16. It has been suggested that four intronic nucleotide polymorphisms within *SLC5A2* could affect the SGLT2is response to treatment. However, a cross-sectional study enrolling 2600 diabetic patients showed that the *SLC5A2* common genetic variants (rs9934336, rs9924771, rs3813008, and rs3116150) did not affect diabetes-related metabolic traits nor had a clinically relevant impact on SGLT2 treatment response.¹⁹

SGLT2 inhibitors are primarily eliminated through O-glucuronidation, a process facilitated by uridine diphosphate glucuronosyl-transferases (UGTs). A study involving 134 participants, comprising both healthy individuals and those with T2DM, revealed that individuals carrying the reduced-function variants *UGT1A9*3* and *UGT2B4*2* exhibited higher plasma concentrations of canagliflozin when compared to individuals with the wild-type alleles.¹⁸⁰ However, a large population study including 9061 pharmacokinetic samples from 1616 volunteers (both healthy volunteers and type 2 diabetic patients) failed to prove that polymorphisms of genes encoding uridine 5'-diphosphoglucuronosyltransferase affected canagliflozin pharmacokinetics.²⁰ Further studies are needed to assess the role of genetic variant's role in SGLT2is treatment response.

Classification of Diabetes According to Multiple Subtypes

Evidence regarding the treatment response continues to increase over time, also for what concerns other diseases and systems.^{181–183} However, how this can be easily translated into current clinical practice remains debated. Currently, researchers are looking for methods to detect subtypes of diabetes in several phenotypes, which could help predict drug therapy responses. In 2018, Ahlqvist et al aimed to identify discrete subtypes of diabetes that could provide a powerful tool for personalized treatment regimen.¹⁸⁴ By performing a cluster analysis of 8980 newly diagnosed diabetic patients from the Swedish All New Diabetics in Scania cohort, Ahlqvist et al identified five different diabetes subtypes. This distinction was made based on the following clinical variables: age at diagnosis, autoantibodies, BMI, HbA_{1c} level, and estimates of β -cell function and insulin resistance. This clustering was further supported by similar results obtained in newly diagnosed patients and in longer-term diabetes by the C-peptide levels, which were relatively constant over time, and the clustering of established genetic associations differed between these subtypes. Moreover, the risk of complications differs across the subtypes. In particular, researchers reported that diabetic retinopathy was detected earlier in subjects presenting with relative insulin deficiency, whereas the risk of diabetic kidney disease increased in insulin-

resistant patients.¹⁸⁴ Several other researchers have attempted to validate and/or add new diabetes subtypes to improve targeted prevention and treatment, thus enabling a more accurate model for precision medicine applicability in diabetes and its complications.^{185–189} However, further studies are needed to assess the treatment response to different drug classes among the subtypes of diabetes, as well as to refine and improve this classification.

Limitations

Currently, there is an increase in medical demand owing to a growing life expectancy, which is accompanied by an increased number of comorbidities. The potential for treating a patient with a disease at best represents the optimal target. By estimating the different treatment responses to a specific treatment, we can implement clinical outcomes and reduce the onset of micro- and macrovascular complications. However, to do so, a better understanding of the underlying disease mechanisms, as well as of the pharmacogenetics is mandatory.²⁶ Moreover, numerous challenges still exist in the future of precision medicine, including cost, ethics, Big Data security, and trained researchers being able to deal with these data and create new algorithms.¹⁹⁰ However, one of the main questions is whether we truly need this complexity in diabetes management. In fact, several reports and studies have reported that making small improvements in any healthcare setting care delivery would have a bigger impact on our patient's wellness than precision medicine.¹⁹¹ In fact, it has been reported in the STENO-2 trial that small changes in the intensity of multifactorial interventions were associated with a 50% reduction in the incidence of cardiovascular events, which was recently confirmed in the NID-2 study.^{192–195} This highlights the need to implement effective approaches beyond the development of new strategies. Another main issue is represented by increased health-care costs, which, of course, will lead to inequalities as, at least at the beginning, will be available within high-income countries and rich individuals.

Our study presents several limitations. We did not address some important aspects of precision medicine, described elsewhere by other authors. First of all, it lacks a section describing adverse drug reactions that can be evaluated through a pre-emptive genotyping strategy. Some authors have recently observed the importance of this approach in reducing the incidence of adverse drug reactions.¹⁹⁶ Secondly, an evaluation of the pathways involved through the cardiovascular response to intensive glycaemic control obtained from specific drugs (eg GLP-1 agonists and fibrates) has not been described.^{197–199}

Conclusions

In summary, our perspective underscores the evolving potential of precision medicine in revolutionizing the landscape of diabetes management. While the existing evidence does not robustly support its widespread use based on genetic variants, algorithms, and drug responses, the future holds immense promise. To fully harness this potential, it is imperative to enhance the availability of novel clinical markers. Lowering the cost of genetic variant analysis can enable specialists to categorize patients effectively, predicting prognosis and treatment responses with higher precision. Additionally, the integration of genetic markers and clinical data from electronic records into advanced algorithms stands as a beacon of progress. These innovative algorithms can pave the way for tailored clinical approaches in treating patients with T2DM. Moreover, the application of data-driven machine learning and artificial intelligence offers exciting possibilities. These approaches can decipher complex genetic and clinical data, leading to the creation of new predictive models. This, in turn, facilitates a more comprehensive and customized therapeutic approach for patients with T2DM. In light of these advancements, it is crucial to focus on refining precision medicine applications. Conducting rigorous and insightful future trials will be instrumental. These trials should explore the full spectrum of possibilities that precision medicine offers. Through ongoing research and continuous improvement, we can unlock the true potential of precision medicine, ensuring its transformative impact on diabetes care and paving the way for a future where personalized and effective treatments are the norm.

Abbreviations

DPP-4is, Dipeptidyl Peptidase-4 Inhibitors; DMCs, differentially methylated CpGs; DMRs, differentially methylated regions; ESC, European Society of Cardiology; GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonist; HR, hazard ratio;

KCNIP, 1 Kv channel-interacting protein 1; RR, risk ratio; socioeconomic status; SGLT2i, Sodium-Glucose cotransporter 2 inhibitors; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes; UCP2, uncoupling protein 2; SES.

Disclosure

The authors report no conflicts of interest in this work.

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