

Review

Cite this article: Xia M and Li X (2023). Updates of precision medicine in type 2 diabetes. *Cambridge Prisms: Precision Medicine*, **1**, e24, 1–7
<https://doi.org/10.1017/pcm.2023.12>

Received: 07 October 2022

Revised: 02 February 2023

Accepted: 26 March 2023

Keywords:

Precision medicine; diabetes; genetics; epigenetics; artificial intelligence

Corresponding author:

Xiaoying Li;

Email: li.xiaoying@zs-hospital.sh.cn

© The Author(s), 2023. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted re-use, distribution and reproduction, provided the original article is properly cited.



Updates of precision medicine in type 2 diabetes

Mingfeng Xia¹  and Xiaoying Li^{1,2}

¹Ministry of Education Key Laboratory of Metabolism and Molecular Medicine, Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai, China and ²Shanghai Key Laboratory of Metabolic Remodeling and Health, Institute of Metabolism and Integrative Biology, Fudan University, Shanghai, China

Abstract

Diabetes mellitus is prevalent worldwide and affects 1 in 10 adults. Despite the successful development of glucose-lowering drugs, such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 inhibitors recently, the proportion of patients achieving satisfactory glucose control has not risen as expected. The heterogeneity of diabetes determines that a one-size-fits-all strategy is not suitable for people with diabetes. Diabetes is undoubtedly more heterogeneous than the conventional subclassification, such as type 1, type 2, monogenic and gestational diabetes. The recent progress in genetics and epigenetics of diabetes has gradually unveiled the mechanisms underlying the heterogeneity of diabetes, and cluster analysis has shown promising results in the substratification of type 2 diabetes, which accounts for 95% of diabetic patients. More recently, the rapid development of sophisticated glucose monitoring and artificial intelligence technologies further enabled comprehensive consideration of the complex individual genetic and clinical information and might ultimately realize a precision diagnosis and treatment in diabetics.

Impact statement

Diabetes mellitus has become a global public health crisis that affects 537 million people worldwide. Despite the great success in the development of novel glucose-lowering drugs, the proportion of patients achieving satisfactory glucose control has not risen as expected during the last decade. The heterogeneity of diabetes determines that a one-size-fits-all strategy is not suitable for people with diabetes. Our review article summarized the current progress in heterogeneity of diabetes from the perspective of genetics and epigenetics, and introduced a promising clinical substratification of type 2 diabetes. Thanks to the recent rapid development of sophisticated glucose monitoring and artificial intelligence technologies in the management of diabetes, we are able to process a large number of individual multi-dimensional genetic, anthropometric, clinical, biochemical and imaging information and make objective and correct judgment to improve the long-term outcome of diabetic patients. The emergence of new technologies might provide solutions for precision diagnosis and treatment of diabetes.

Introduction

Diabetes mellitus is diagnosed if blood glucose concentration exceeds a threshold, which predisposes to microvascular and microvascular end-organ complications. Diabetes continues to increase in prevalence worldwide (Ingelfinger and Jarcho, 2017). Currently, diabetes affects 537 million people worldwide (IDF, 2021). Diabetes is also the leading cause of disability globally (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018), as well as causing an increase in the risk of death from cardiovascular disease, renal disease, and cancer, and reducing life expectancy by 4–10 years on average (Rao Kondapally Seshasai et al., 2011). Early and intensive management of diabetes to achieve the recommended glycemic and metabolic targets can reduce long-term diabetes complications (Khunti and Millar-Jones, 2017).

In recent decades, great success has been achieved in the development of novel glucose-lowering drugs, such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 inhibitors. At present, pharmacological therapies, comprising 10 classes of medicines approved by the FDA, could be utilized to control blood glucose. However, the proportion of patients achieving satisfactory glucose control has not risen as expected (Bhat et al., 2021). The inadequate understanding of the diverse pathophysiological mechanisms and personalized treatment of diabetes partly limits our ability to treat diabetes.

The aim of our current review is to provide an overview of precision medicine in diabetes, focusing on the genetics and epigenetics, clinical stratification and personalized prevention, treatment of this disease and its related complications (Figure 1).

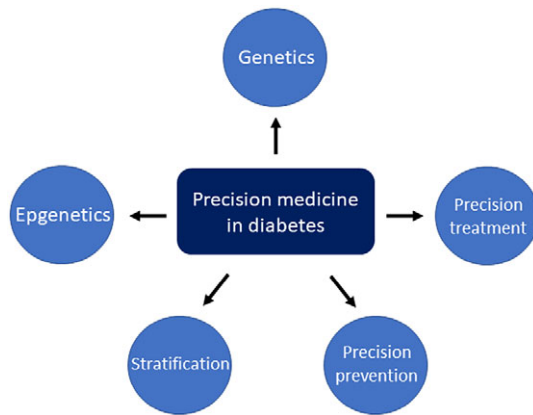


Figure 1. The precision medicine in diabetes management.

Heterogeneity of diabetes

The heterogeneity of diabetes was recognized several decades ago, when diabetic patients were divided into insulin-sensitive and insulin-insensitive subgroups based on the oral glucose tolerance test (OGTT) (Himsworth and Kerr, 1939). In 1979, the classification of type 1 and type 2 diabetes was first proposed by the American Diabetes Association (National Diabetes Data Group, 1979). Meanwhile, Fajans and Tattersall described a subgroup of diabetes with inheritance across many generations called “maturity onset diabetes in the young” (MODY) (Tattersall and Fajans, 1975). However, it was not until the introduction of genomic medicine in the recent 20 years, that the molecular mechanisms of the monogenic diabetes were uncovered.

Patients with diabetes do not equally respond to glucose-lowering therapies. Thus, pharmacologic intervention should be individualized based on factors such as duration of diabetes, presence of existing comorbidities, expected duration of life, weight, age, family history of diabetes-related complications and funding for prescribed medications and technology. Previous studies indicated that approximately 30% of individuals with type 2 diabetes do not respond well to metformin, and 5% have intolerable side effects (Kahn et al., 2006; Cook et al., 2007). Clinical diabetic patients with different etiological processes, such as obesity, metabolic syndrome, beta cell dysfunction or lipodystrophy, respond differently to glucose-lowering drugs with different mechanisms (Udler and Kim, 2018). Patients from different ethnicities respond differently to glucose-lowering drugs, including dipeptidyl peptidase-4 inhibitors (Kim et al., 2013), metformin (Williams et al., 2014) and glucagon-like peptide 1 agonist (Velásquez-Mieyer et al., 2008). Thus, stratification of diabetic patients based on their genetic backgrounds and pathophysiological mechanisms could be considered for implementation of precision medicine in diabetes.

Genetics of diabetes

Precision medication in monogenic diabetes has successfully guided clinical treatment. For example, individuals with rare mutation in *HNFI1A* (MODY3), *HNFI4A* (MODY1) and *ABCC8* (MODY12) are incredibly sensitive to the effects of sulfonylureas (Pearson et al., 2003). While individuals with loss-of-function mutations in the *GCK* gene are unlikely to develop diabetic complications, and have no need for unnecessary treatment (Steele et al., 2014). However, identification of monogenic diabetes still has not

solved discrepancy in the individual response to glucose-lowering medications in a large number of patients with type 2 diabetes.

In 2007, the first genome-wide association study (GWAS) in type 2 diabetes was reported (Sladek et al., 2007). There was much hope that genetics would also represent a breakthrough in understanding of the heterogeneity of type 2 diabetes at that time, however, it turned out that more than 400 genetic variants associated with type 2 diabetes to date could only explain 18% of the risk of diabetes (Mahajan et al., 2018). Moreover, every individual variant is very modestly associated with the risk of type 2 diabetes, except for the variant in the *TCF7L2* gene (Lyssenko et al., 2007). Therefore, the genomic information alone has limited value in guiding precision medicine in type 2 diabetes.

Recently, GWAS has also been performed to investigate the genetic risk alleles of type 1 diabetes (Sharp et al., 2019). Fortunately, recent studies have shown that the identified genetic variants could account for the majority of the risk of type 1 diabetes in certain populations, and type 1 diabetes genetic risk scores could well predict the risk of type 1 diabetes with both sensitivity and specificity exceeding 80% in neonatal and African-ancestry populations (Onengut-Gumuscu et al., 2019; Sharp et al., 2019). The genetics of diabetes mellitus and diabetes complications is well summarized in the literature (Cole and Florez, 2020; Riddle et al., 2020; Deutsch et al., 2022).

Epigenetics of diabetes

Obesity and metabolic syndrome is the main risk factor for type 2 diabetes which is caused by a complex inheritance-environment interaction (Wu et al., 2014). Epigenetics represents the heritable reversible modifications to the genome associated with environmental factors and clinical phenotypes (BLUEPRINT Consortium, 2016). Epigenetics explores the mechanism in which phenotypes are changed by non-DNA sequence variation, including DNA methylation, histone modifications, non-coding RNAs regulations. Previous studies have shown that blood methylation markers in the *TXNIP*, *ABCG1*, *PHOSPHO1*, *SOCS3* and *SREBF1* genes were associated with the risk of incident type 2 diabetes (Chambers et al., 2015). Since epigenetic patterns have vast plasticity, the epigenetic alteration in type 2 diabetes could be targeted for personalized treatment. The non-coding RNAs, especially the short noncoding RNAs (microRNAs), can regulate the expression of protein-coding genes or epigenetic regulators including DNA methyltransferases, histone deacetylases and polycomb protein coding gene (Bushati and Cohen, 2007). MicroRNA changes in vivo were associated with the insulin resistance level in type 2 diabetes (Gallagher et al., 2010), and its value as biomarkers for type 2 diabetes has been investigated (de Candia et al., 2017). Integrating both genetic and epigenetic risk factors might reflect the inheritance-environment interaction, and provide a promising solution for subclassification of type 2 diabetes.

Recently, the complex association between SARS-CoV-2 Infection (COVID-19) and diabetes has emphasized the environmental factors in promoting diabetes (Shin et al., 2021; Cao et al., 2023). Studies showed that critical COVID-19 and hospitalized COVID-19 subjects had an increased risk of type 2 diabetes, and genetic liability to COVID-19 had a causal effect on type 2 diabetes (Cao et al., 2023). Mechanistically, the COVID-19 spike protein physically interacted with GRP78 protein in cell surface of adipose tissue, promoting hyperinsulinemia in adipocytes via XBPI, which may be

attributed to the development and progress of diabetes (Shin et al., 2021).

Stratification of diabetes

Various pathogenic mechanisms and outcomes of disease have been observed in the large range of type 2 diabetes (Philipson, 2020). Thus, the stratification of type 2 diabetes may be relevant in the field of precision medicine for diabetes diagnosis. Cluster analysis based on high-dimensional data, such as electronic medical records or omics data (genomics, proteomics, metabolomics, transcriptomics, lipidomics, etc.), has been utilized to identify subtypes of type 2 diabetes (Li et al., 2015; Udler et al., 2018; Wagner et al., 2021). In 2018, a study of the Swedish population with newly diagnosed diabetes used both hierarchical and *k*-means clustering to identify five subtypes of adult-onset diabetes, named severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD) and mild age-related diabetes (MARD), based on six clinical variables (autoantibodies, age at diagnosis, BMI, HbA1c, C peptide together with glucose for estimation of insulin secretion, HOMA-B and insulin-sensitivity, HOMA-IS) (Ahlqvist et al., 2018). SAID was characterized by the presence of GAD autoantibodies, low insulin secretion and poor metabolic control, SIDD was characterized by low insulin secretion, poor metabolic control and increased risk of retinopathy, SIRD was characterized by severe insulin resistance, obesity, late onset and markedly increased risk of nephropathy, MOD was characterized by obesity, early onset and good metabolic control, and MARD was characterized by late onset and good metabolic control. This classification of adult-onset diabetes has been most frequently replicated in three independent cohorts from different ethnicities (Philipson, 2020). These subgroups differ in genetic predisposition to diabetes, with increased frequency of *HLA* rs2854275 variant in SAID and *TCF7L2* rs7903146 variant in SIDD, MOD and MARD (Lyssenko et al., 2007). Both SIRD and MOD patients were obese, but SIRD represented the unhealthy obesity with insulin resistance and non-alcoholic fatty liver disease and MOD represented healthy obesity without insulin resistance (Cohen et al., 2011). More importantly, the new subclassification of diabetes might guide the personalized treatment. The MOD and MARD patients usually had good metabolic control and disease prognosis, thus, it may be that these cases require less frequent glucose monitoring and could be easily managed with metformin and lifestyle intervention. Several medications with confirmed protective effects on specific vital organs, such as sodium-glucose cotransporter 2 (SGLT2) on cardiovascular and renal outcomes, might be especially suitable for SIRD (Wanner et al., 2016). Thus, the attempts on stratification of diabetes by cluster analysis might be promising for precision diagnosis of diabetes.

More recently, the application of artificial intelligence (AI) technology was able to comprehensively ingest all required parameters in supplied formats (text, image/video, biometric data) for analysis, leading to the prediction of incident diabetes (AUROCs: 0.71–0.87) (Ellahham, 2020) and risk stratification of diabetic populations (Zou et al., 2018). Recently, a study using genomic and tabular data to predict type 2 diabetes based on Recurrent Neural Networks has been reported (Srinivasu et al., 2022). The results showed that the proposed model could predict future diabetes with fair accuracy, which may be used in real-world scenarios (Srinivasu et al., 2022). The use of AI in diabetes management could

establish a more accurate and objective stratification of type 2 diabetes based on a broad range of candidate parameters.

Precision prevention

Comprehensive management of diabetes includes diet and exercise interventions, patient education, glucose monitoring and drug treatment. By the time the diabetes is diagnosed, diabetes-related tissue damage has occurred in nearly half of the patients (Ambady and Chamukuttan, 2008). An early intervention in patients with prediabetes, either with lifestyle interventions or pharmacologic interventions, reduces the risk of incident diabetes and improves long-term outcomes (Haw et al., 2017). However, there has been a big variation among the patients diagnosed with prediabetes in their response to lifestyle or drug intervention (Knowler et al., 2002; Knowler et al., 2009). Those who lost the least weight in the early stages of intervention showed the highest risk of incident diabetes (Delahanty et al., 2014). The reduction of body weight in patients with prediabetes after lifestyle or drug intervention was related to genetic variants (Papandonatos et al., 2015). For instance, the protective effect of metformin in reducing incidence of diabetes was associated with variation in the *SLC47A1* gene in the Diabetes Prevention Program (Jablonski et al., 2010). Therefore, the patients diagnosed with prediabetes who are unlikely to respond well to lifestyle modification might be better served by other therapeutic treatments, but more studies were required to properly identify this subgroup of prediabetes. Meanwhile, efforts have also been made to prevent the incidence of type 1 diabetes in high-risk children with at least two islet autoantibodies using dietary interventions and/or immune-targeting approaches (Skyler et al., 2018). Unfortunately, most previous intervention studies were unable to slow, halt or reverse the destruction of beta cells or delay the progression of type 1 diabetes (Hummel et al., 2011; Knip et al., 2018).

Precision treatment

Drug treatment was recommended to achieve good glucose control and lower the risk of cardiovascular disease and specific diabetic complications in diabetic patients. Although FDA has approved 10 classes of diabetes medications, each of these medications showed great heterogeneity in therapeutic efficacy, being effective for some patients, but less effective for others, with some even experiencing adverse effects (Dennis et al., 2018). Trials of medications on diabetes have recognized that different etiologic processes of diabetes would influence the therapeutic effect of antidiabetic medications recently (Dennis et al., 2019). Reanalysis of the data from the ADOPT and RECORD studies found that the subtype of diabetic patients with insulin resistance responded better to treatment with thiazolidinediones and that older patients responded better to sulfonylureas (Dennis et al., 2019). Similar studies using prospective and primary care data in the UK found that the subgroup of diabetics with insulin resistance, obesity or high triglycerides had reduced initial response to DDP4 inhibitor and more rapid failure of therapy (Dennis et al., 2018).

There is also an ethnic difference in the individual response to a specific antidiabetic medication. Previous studies indicated that the therapeutic effect of DDP4 inhibitors is greater in Asians than in other demographic groups. Consistently, a subgroup analysis of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) showed a greater reduction in blood glucose in East Asians

(Davis et al., 2018), and a recent REWIND study found the protective effect of Dulaglutide on cardiovascular disease is significantly stronger in the Asian Pacific area than other regions of the world (Gerstein et al., 2019). Moreover, the effect of metformin also differed among different ethnic groups, with African Americans having a greater response to metformin than was observed for European Americans (Williams et al., 2014).

The use of genetics in guiding the pharmaceutical treatment of diabetes is an important step toward the precision treatment of diabetes. A typical successful example is the application of genetics in treatment of monogenic diabetes. In that case, a specific single gene mutation is causal for the development of diabetes and targeted treatment can well bypass the etiological defect, such as the use of sulfonylurea in MODY3 caused by the mutation of *HNFI1A* gene (Pearson et al., 2003). However, type 2 diabetes is much more complex than MODY, which is influenced by the complex interaction of hundreds of etiological gene variants and environmental risk factors. Traditionally, genetic studies of drug response in type 2 diabetes have focused on candidate genes known to relate to etiological processes or drug transport or metabolism. Studies have shown that a variant in the *SLC22A1* gene encoding the organic cation transporter 1 (OCT1) is involved in the cellular transport of metformin and influenced the individual response to metformin (Shu et al., 2007). Similarly, a variant in *MATE1* (Becker et al., 2009) was also associated with metformin response. Studies also found that *KCNJ11/ABCC8* risk variant increases, but *TCF7L2* risk variant reduces glycemic response to sulfonylureas (Pearson et al., 2007; Feng et al., 2008). The *PPARG* risk variant was associated with reduced glycemic response to thiazolidinediones (Kang et al., 2005). GWAS in the pharmacogenetics of diabetes made no assumptions about the drug mechanism and metabolism, and have therefore provided novel insights into genetic factors related with response to antidiabetic medication, and successfully identified variants at the *ATM* and *SLC2A2* genes as modulators of individual response to metformin (GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group et al., 2011; Zhou et al., 2016). GWAS of response to other antidiabetic drugs was still necessary to establish the drug response prediction system based on genetics to guide clinical treatment.

The management of diabetes is a comprehensive approach, and glucose monitoring, patient education and lifestyle intervention also played essential roles in diabetes treatment in addition to diabetes medications. Currently, the use of remote continuous glucose monitoring (CGM) enables monitoring of a complete view of glucose control over 24 h (Battelino and Danne, 2019), and the in-depth insights of glucose and direct feedback provided by CGM system have efficaciously controlled the blood glucose and reduced the incidence of hypoglycemia (Beck et al., 2017). The accurate CGM also enabled the personalized lifestyle intervention prescription tailored to each diabetic patient. An AI-based decision support system named the Advisor Pro was recently developed. This system sends the data from CGM to a cloud server and uses AI to determine required insulin doses remotely. Studies showed that insulin doses recommended by the Advisor Pro had no significant difference compared with that given by physicians, suggesting this to be a convenient approach in managing diabetes (Nimri et al., 2018; Nimri et al., 2022). With the rapid development in the AI field, it is highly possible that AI will introduce a revolutionary shift in management of diabetes from conventional therapeutic strategies to data-driven precision treatment, based on the combination of individual genetic and glucose monitoring information and decision-making systems based on machine learning.

Lifestyle modifications and first-line medication treatment do not prevent the progressive decline of β -cell mass and function in some patients. Therefore, advanced strategies need to be developed to address this issue. Stem cell therapy for the treatment of diabetes has made great progress in recent years (Furuyama et al., 2019; Siehler et al., 2021). Both type 1 diabetes and type 2 diabetes can benefit from stem cell therapy. Studies showed that stem cell therapy increased serum C-peptide and reduced glycosylated hemoglobin (HbA1c) in subjects with type 1 diabetes or type 2 diabetes, but had no significant effect on fasting glucose (Zhang et al., 2020). Additionally, stem cell therapy improved insulin requirements in subjects with type 2 diabetes (Zhang et al., 2020). Different types of stem cells affect the clinical efficacy of therapy for diabetes. Bone marrow mononuclear cells were more effective than mesenchymal stem cells in the treatment of type 1 diabetes, whereas both bone marrow mononuclear cells and mesenchymal stem cells had favorable effects on type 2 diabetes (Zhang et al., 2020). This all suggests that stem cell therapy for the treatment of diabetes is an attractive and potential strategy, but is still facing enormous challenges, for instance, the need for greater diversity in the source of stem cells, and also inconsistency in stem cell preparation, evaluation systems and safety.

Future outlook

The heterogeneity of diabetes creates challenges for the wider applicability of precision medicine in successful treatment of this disease. Although the implementation of precision medicine in diabetes is progressing well, more recent developments within precision medicine may benefit both newly diagnosed patients with diabetes, as well as those exposed to glycemic toxicity for years. Multidisciplinary cooperation will be conducive to further in-depth analysis and understanding of diabetes. Currently, our knowledge on the association of individual genetic background with the pathogenesis and drug response of diabetes is increasing rapidly. The application of AI in the management of diabetes enables the objective and comprehensive analysis and process of a large number of individual multi-dimensional genetic, anthropometric, clinical, biochemical and imaging information, and might provide a solution for precision diagnosis and treatment of diabetes. The concept and tools of precision medicine help to accurately predict, diagnose and treat diabetes and its complications. Although there is still a long way to go, precision medicine will become the driving force for early intervention, early prevention and accurate management of diabetes in the future.

Open peer review. To view the open peer review materials for this article, please visit <http://doi.org/10.1017/pcm.2023.12>.

Acknowledgement. We have obtained financial supports from National Key Research and Development Program of China (2021YFC27 00403), Shanghai Municipal Science and Technology Commission Foundation (23XD1423300).

Competing interest. All authors declare that there is no duality of interest.

References

- Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spégel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark Å, Lahti K, Forsén T, Tuomi T, Rosengren AH and Groop L (2018) Novel subgroups of adult-onset diabetes and their association with outcomes: A

- data-driven cluster analysis of six variables. *The Lancet Diabetes and Endocrinology* 6, 361–369.
- Ambaby R and Chamukuttan S** (2008) Early diagnosis and prevention of diabetes in developing countries. *Reviews in Endocrine & Metabolic Disorders* 9(3), 193–201.
- Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, Cobelli C, Dassau E, DeVries JH, Donaghue KC, Dovc K, Doyle III FJ, Garg S, Grunberger G, Heller S, Heinemann L, Hirsch IB, Hovorka R, Jia W, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Levine B, Mayorov A, Mathieu C, Murphy HR, Nimri R, Nørgaard K, Parkin CG, Renard E, Rodbard D, Saboo B, Schatz D, Stoner K, Urakami T, Weinzimer SA and Phillip M** (2019) Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. *Diabetes Care* 42(8), 1593–1603
- Beck RW, Riddlesworth TD, Ruedy KJ, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D and for the DIAMOND Study Group** (2017) Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: The DIAMOND randomized clinical trial. *JAMA* 317(4), 371–378.
- Becker ML, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG and Stricker BH** (2009) Genetic variation in the multidrug and toxin extrusion 1 transporter protein influences the glucose-lowering effect of metformin in patients with diabetes: A preliminary study. *Diabetes* 58, 745–749.
- Bhat S, Chowta M, Chowta N, Shastry R and Kamath P** (2021) The proportion of type 2 diabetic patients achieving treatment goals and the survey of Patients' attitude towards insulin initiation in patients with inadequate glycaemic control with oral anti-diabetic drugs. *Current Diabetes Reviews* 17(5), e110620182719.
- The BLUEPRINT consortium** (2016) Quantitative comparison of DNA methylation assays for biomarker development and clinical applications. *Nature Biotechnology* 34, 726–737.
- Bushati N and Cohen SM** (2007) microRNA functions. *Annual Review of Cell and Developmental Biology* 23, 175–205.
- Cao H, Baranova A, Wei X, Wang C and Zhang F** (2023) Bidirectional causal associations between type 2 diabetes and COVID-19. *Journal of Medical Virology* 95(1), e28100.
- Chambers JC, Loh M, Lehne B, Drong A, Kriebel J, Motta V, Wahl S, Elliott HR, Rota F, Scott WR, Zhang W, Tan ST, Campanella G, Chadeau-Hyam M, Yengo L, Richmond RC, Adamowicz-Brice M, Afzal U, Bozaoglu K, Mok ZY, Ng HK, Pattou F, Prokisch H, Rozario MA, Tarantini L, Abbott J, Ala-Korpela M, Albeti B, Ammerpohl O, Bertazzi PA, Blancher C, Caiazzo R, Danesh J, Gaunt TR, de Lusignan S, Gieger C, Illig T, Jha S, Jones S, Jowett J, Kangas AJ, Kasturiratne A, Kato N, Kotea N, Kowlessur S, Pitkaniemi J, Punjabi P, Saleheen D, Schafmayer C, Soininen P, Tai ES, Thorand B, Tuomilehto J, Wickremasinghe AR, Kyrtopoulos SA, Aitman TJ, Herder C, Hampe J, Cauchi S, Relton CL, Froguel P, Soong R, Vineis P, Jarvelin MR, Scott J, Grallert H, Bollati V, Elliott P, McCarthy MI and Kooper JS** (2015) Epigenome-wide association of DNA methylation markers in peripheral blood from Indian Asians and Europeans with incident type 2 diabetes: A nested case-control study. *The Lancet Diabetes and Endocrinology* 3, 526–534.
- Cohen JC, Horton JD and Hobbs HH** (2011) Human fatty liver disease: Old questions and new insights. *Science* 332, 1519–1523.
- Cole JB and Florez JC** (2020) Genetics of diabetes mellitus and diabetes complications. *Nature Reviews. Nephrology* 16(7): 377–390.
- Cook MN, Gorman CJ, Stein PP and Alexander CM** (2007) Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care. *Diabetic Medicine* 24(4), 350–358.
- Davis TME, Mulder H, Lokhnygina Y, Aschner P, Chuang LM, Raffo Grado CA, Standl E, Peterson ED, Holman RR and for the TECOS Study Group** (2018) TECOS study group. Effect of race on the glycaemic response to sitagliptin: Insights from the trial evaluating cardiovascular outcomes with Sitagliptin (TECOS). *Diabetes, Obesity & Metabolism* 20, 1427–1434.
- de Candia P, Spinetti G, Specchia C et al.** (2017) A unique plasma microRNA profile defines type 2 diabetes progression. *PLoS One* 12, e0188980.
- Delahanty LM, Pan Q, Jablonski KA, Aroda VR, Watson KE, Bray GA, Kahn SE, Florez JC, Perreault L, Franks PW and for the Diabetes Prevention Program Research Group** (2014) Diabetes prevention program research group. Effects of weight loss, weight cycling, and weight loss maintenance on diabetes incidence and change in cardiometabolic traits in the diabetes prevention program. *Diabetes Care* 37, 2738–2745.
- Dennis JM, Shields BM, Henley WE, Jones AG and Hattersley AT** (2019) Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: An analysis using clinical trial data. *The Lancet Diabetes and Endocrinology* 7, 442–451.
- Dennis JM, Shields BM, Hill AV, McDonald T, Knight BA, Rodgers LR, Weedon MN, Henley WE, Sattar N, Holman RR, Pearson ER, Hattersley AT, Jones AG and MASTERMIND Consortium** (2018) Precision medicine in type 2 diabetes: Clinical markers of insulin resistance are associated with altered short- and long-term glycaemic response to DPP-4 inhibitor therapy. *Diabetes Care* 41, 705–712.
- Dennis JM, Shields BM, Jones AG, Pearson ER, Hattersley AT, Henley WE and MASTERMIND Consortium** (2018) Evaluating associations between the benefits and risks of drug therapy in type 2 diabetes: A joint modeling approach. *Clinical Epidemiology* 10, 1869–1877.
- Deutsch AJ, Ahlqvist E and Udler MS** (2022) Phenotypic and genetic classification of diabetes. *Diabetologia* 65(11), 1758–1769.
- Ellahham S** (2020) Artificial intelligence: The future for diabetes care. *The American Journal of Medicine* 133(8), 895–900.
- Feng Y, Mao G, Ren X, Xing H, Tang G, Li Q, Li X, Sun L, Yang J, Ma W, Wang X and Xu X** (2008) Ser1369Ala variant in sulfonylurea receptor gene ABCC8 is associated with antidiabetic efficacy of gliclazide in Chinese type 2 diabetic patients. *Diabetes Care* 31, 1939–1944.
- Furuyama K, Chera S, van Gorp L, Oropeza D, Ghila L, Diamond N, Vethe H, Paulo JA, Joosten AM, Berney T, Bosco D, Dorrell C, Grompe M, Ræder H, Roep BO, Thorel F and Herrera PL** (2019) Diabetes relief in mice by glucose-sensing insulin-secreting human alpha-cells. *Nature* 567(7746), 43–48.
- Gallagher IJ, Scheele C, Keller P, Nielsen AR, Remenyi J, Fischer CP, Roder K, Babraj J, Wahlestedt C, Hutvagner G, Pedersen BK and Timmons JA** (2010) Integration of microRNA changes in vivo identifies novel molecular features of muscle insulin resistance in type 2 diabetes. *Genome Medicine* 2 (2), 9.
- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators** (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392(10159), 1789–1858.
- Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, et al.** (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. *Lancet* 394(10193), 121–130.
- The GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group, The Wellcome Trust Case Control Consortium 2, Zhou K, Bellenguez C et al.** (2011) Common variants near ATM are associated with glycaemic response to metformin in type 2 diabetes. *Nature Genetics* 43, 117–120.
- Haw JS, Galaviz KI, Straus AN, Kowalski AJ, Magee MJ, Weber MB, Wei J, Narayan KMV and Ali MK** (2017) Longterm sustainability of diabetes prevention approaches: A systematic review and meta-analysis of randomized clinical trials. *JAMA Internal Medicine* 177, 1808–1817.
- Himsworth HP and Kerr RB** (1939) Insulin-sensitive and insulininsensitive types of diabetes mellitus. *Clinical Science* 4, 119–152.
- Hummel S, Pfluger M, Hummel M, Bonifacio E and Ziegler AG** (2011) Primary dietary intervention study to reduce the risk of islet autoimmunity in children at increased risk for type 1 diabetes: The BABYDIET study. *Diabetes Care* 34:1301–1305.
- IDF** (2021) *IDF Diabetes Atlas*, 10th Edn.
- Ingelfinger JR and Jarcho JA** (2017) Increase in the incidence of diabetes and its implications. *The New England Journal of Medicine* 376(15), 1473–1474.
- Jablonski KA, McAteer JB, de Bakker PI, Franks PW, Pollin TI, Hanson RL, Saxena R, Fowler S, Shuldiner AR, Knowler WC, Altshuler D, Florez JC**

- and for the Diabetes Prevention Program Research Group (2010) Common variants in 40 genes assessed for diabetes incidence and response to metformin and lifestyle intervention in the diabetes prevention program. *Diabetes* 59, 2672–2681.
- Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B and Viberti G (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *The New England Journal of Medicine* 355(23), 2427–2443.
- Kang E, Park S, Kim H, Kim C, Ahn C, Cha B, Lim S, Nam C and Lee H (2005) Effects of Pro12Ala polymorphism of peroxisome proliferator-activated receptor gamma2 gene on rosiglitazone response in type 2 diabetes. *Clinical Pharmacology and Therapeutics* 78, 202–208.
- Khunti K and Millar-Jones D (2017) Clinical inertia to insulin initiation and intensification in the UK: A focused literature review. *Primary Care Diabetes* 11(1), 3–12
- Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS and Cho YM (2013) Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: A systematic review and meta-analysis. *Diabetologia* 56, 696–708.
- Knip M, Åkerblom HK, al Taji E, Becker D, Bruining J, Castano L, Danne T, de Beaufort C, Dosch HM, Dupre J, Fraser WD, Howard N, Ilonen J, Konrad D, Kordonouri O, Krischer JP, Lawson ML, Ludvigsson J, Madacsy L, Mahon JL, Ormiston A, Palmer JP, Pozzilli P, Savilahti E, Serrano-Rios M, Songini M, Taback S, Vaarala O, White NH, Virtanen SM, Wasikowa R and Writing Group for the TRIGR Study Group (2018) Effect of hydrolyzed infant formula vs conventional formula on risk of type 1 diabetes: The TRIGR randomized clinical trial. *JAMA* 319, 38–48.
- Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM and Diabetes Prevention Program Research Group (2002) Diabetes prevention program research group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine* 346, 393–403.
- Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM and Diabetes Prevention Program Research Group (2009) Diabetes prevention program research group. 10-year follow-up of diabetes incidence and weight loss in the diabetes prevention program outcomes study. *Lancet* 374, 1677–1686.
- Li L, Cheng WY, Glicksberg BS, Gottesman O, Tamler R, Chen R, Bottinger EP and Dudley JT (2015) Identification of type 2 diabetes subgroups through topological analysis of patient similarity. *Science Translational Medicine* 7(311), 311ra174.
- Lysenko V, Lupi R, Marchetti P, del Guerra S, Orho-Melander M, Almgren P, Sjögren M, Ling C, Eriksson KF, Lethagen L, Mancarella R, Berglund G, Tuomi T, Nilsson P, del Prato S and Groop L (2007) Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *The Journal of Clinical Investigation* 117, 2155–2163.
- Lysenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjögren M, Ling C, Eriksson K-F, Lethagen A-S, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S and Groop L (2007) Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *The Journal of Clinical Investigation* 117, 2155–2163.
- Mahajan A, Wessel J, Willems SM, et al. (2018) Refining the accuracy of validated target identification through coding variant finemapping in type 2 diabetes. *Nature Genetics* 50, 559–571.
- National Diabetes Data Group (1979) Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28, 1039–1057.
- Nimri R, Dassau E, Segall T, Muller I, Bratina N, Kordonouri O, Bello R, Biester T, Dovc K, Tenenbaum A, Brener A, Šimunović M, Sakka SD, Nevo Shenker M, Passone CGB, Rutigliano I, Tinti D, Bonura C, Caiulo S, Ruzsala A, Piccini B, Giri D, Stein R, Rabbone I, Bruzzi P, Omladić JŠ, Steele C, Beccuti G, Yackobovitch-Gavan M, Battelino T, Danne T, Atlas E and Phillip M (2018) Adjusting insulin doses in patients with type 1 diabetes who use insulin pump and continuous glucose monitoring: Variations among countries and physicians. *Diabetes, Obesity & Metabolism* 20(10), 2458–2466.
- Nimri R, Oron T, Muller I, Kraljevic I, Alonso MM, Keskinen P, Milicic T, Oren A, Christoforidis A, den Brinker M, Bozzetto L, Bolla AM, Krcma M, Rabini RA, Tabba S, Smith L, Vazeou A, Maltoni G, Giani E, Atlas E and Phillip M (2022) Adjustment of insulin pump settings in type 1 diabetes management: Advisor pro device compared to Physicians' recommendations. *Journal of Diabetes Science and Technology* 16(2), 364–372.
- Onengut-Gumuscu S, Chen WM, Robertson CC, Bonnie JK, Farber E, Zhu Z, Oksenberg JR, Brant SR, Bridges Jr SL, Edberg JC, Kimberly RP, Gregersen PK, Rewers MJ, Steck AK, Black MH, Dabelea D, Pihoker C, Atkinson MA, Wagenknecht LE, Diver J, Bell RA, SEARCH for Diabetes in Youth, Type 1 Diabetes Genetics Consortium, Erlich HA, Concannon P and Rich SS (2019) Type 1 diabetes risk in African-ancestry participants and utility of an ancestry-specific genetic risk score. *Diabetes Care* 42, 406–415.
- Papandonatos GD, Pan Q, Pajewski NM, Delahanty LM, Peter I, Erar B, Ahmad S, Harden M, Chen L, Fontanillas P, GIANT Consortium, Wagenknecht LE, Kahn SE, Wing RR, Jablonski KA, Huggins GS, Knowler WC, Florez JC, McCaffery JM, Franks PW and for the Diabetes Prevention Program and the Look AHEAD Research Groups (2015) GIANT consortium; diabetes prevention program and the look AHEAD research groups. Genetic predisposition to weight loss and regain with lifestyle intervention: Analyses from the diabetes prevention program and the look AHEAD randomized controlled trials. *Diabetes* 64, 4312–4321.
- Pearson ER, Donnelly LA, Kimber C, Whitley A, Doney ASF, McCarthy MI, Hattersley AT, Morris AD and Palmer CNA (2007) Variation in TCF7L2 influences therapeutic response to sulfonylureas: A GoDARTs study. *Diabetes* 56, 2178–2182
- Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT (2003) Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* 362, 1275–1281.
- Philips LH (2020) Harnessing heterogeneity in type 2 diabetes mellitus. *Nature Reviews. Endocrinology* 16(2), 79–80.
- Rao Kondapally Seshasai S, Kaptoge S, Thompson A, di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njolstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J and Emerging Risk Factors Collaboration (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. *The New England Journal of Medicine* 364, 829–841.
- Riddle MC, Phillips LH, Rich SS, Carlsson A, Franks PW, Greeley SAW, Nolan JJ, Pearson ER, Zeitler PS and Hattersley AT (2020) Monogenic diabetes: From genetic insights to population-based precision in care. Reflections from a diabetes care editors' expert forum. *Diabetes reviews (Alexandria, Va)* 43(12), 3117–3128.
- Sharp SA, Rich SS, Wood AR, Jones SE, Beaumont RN, Harrison JW, Schneider DA, Locke JM, Tyrrell J, Weedon MN, Hagopian WA and Oram RA (2019) Development and standardization of an improved type 1 diabetes genetic risk score for use in newborn screening and incident diagnosis. *Diabetes Care* 42(2), 200–207.
- Shin J, Toyoda S, Nishitani S, Fukuhara A, Kita S, Otsuki M and Shimomura I Possible involvement of adipose tissue in patients with older age, obesity, and diabetes with SARS-CoV-2 infection (COVID-19) via GRP78 (BIP/HSPA5): Significance of hyperinsulinemia management in COVID-19. *Diabetes* 70(12), 2745–2755.
- Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, Ianculescu AG, Yue L, Lo JC, Burchard EG, Brett CM and Giacomini KM (2007) Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. *The Journal of Clinical Investigation* 117, 1422–1431.
- Stehler J, Blochinger AK, Meier M and Lickert H (2021) Engineering islets from stem cells for advanced therapies of diabetes. *Nature Reviews. Drug Discovery* 20(12), 920–940.
- Skylar JS, Kirchner JP, Becker D, Rewers M (2018) Chapter 37: Prevention of Type 1 Diabetes in America, 3rd Edn., Cowie CC, Casagrande SS, et al., Eds. Bethesda, MD: National Institutes of Health.
- Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, Balkau B, Heude B, Charpentier G, Hudson TJ, Montpetit A, Pshezhetsky AV, Prentki M, Posner BI, Balding DJ, Meyre D, Polychronakos C and Froguel P (2007) A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* 445, 881–885.
- Srinivasu PN, Shafi J, Krishna TB, Sujatha CN, Praveen SP and Ijaz MF (2022) Using recurrent neural networks for predicting Type-2 diabetes from genomic and tabular data. *Diagnostics (Basel)* 12(12).

- Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S and Hattersley AT (2014) Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *JAMA* **311**: 279–86.
- Tattersall RB and Fajans SS (1975) A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes* **24**, 44–53.
- Udler MS, Kim J, von Grotthuss M, Bonàs-Guarch S, Cole JB, Chiou J, Christopher D. Anderson on behalf of METASTROKE and the ISGC, Boehnke M, Laakso M, Atzmon G, Glaser B, Mercader JM, Gaulton K, Flannick J, Getz G and Florez JC (2018) Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. *PLoS Medicine* **15**, e1002654.
- Udler MS, Kim J, von Grotthuss M, Bonàs-Guarch S, Cole JB, Chiou J, Christopher D. Anderson on behalf of METASTROKE and the ISGC, Boehnke M, Laakso M, Atzmon G, Glaser B, Mercader JM, Gaulton K, Flannick J, Getz G and Florez JC (2018) Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. *PLoS Medicine* **15**(9), e1002654.
- Velásquez-Mieyer PA, Cowan PA, Pérez-Faustinelli S, Nieto-Martínez R, Villegas-Barreto C, Tolley EA, Lustig RH and Alpert BS (2008) Racial disparity in glucagon-like peptide 1 and inflammation markers among severely obese adolescents. *Diabetes Care* **31**(4), 770–775.
- Wagner R, Heni M, Tabák AG, Machann J, Schick F, Randrianarisoa E, Hrabě de Angelis M, Birkenfeld AL, Stefan N, Peter A, Häring HU and Fritsche A (2021) Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. *Nature Medicine* **27**(1), 49–57.
- Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, Johansen OE, Woerle HJ, Broedl UC and Zinman B (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. *The New England Journal of Medicine* **375**, 323–334.
- Williams LK, Padhukasahasram B, Ahmedani BK, Peterson EL, Wells KE, González Burchard E and Lanfear DE (2014) Differing effects of metformin on glycemic control by race-ethnicity. *The Journal of Clinical Endocrinology and Metabolism* **99**, 3160–3168.
- Wu Y, Ding Y, Tanaka Y and Zhang W. (2014) Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *International Journal of Medical Sciences* **11**(11), 1185–1200.
- Zhang Y, Chen W, Feng B and Cao H (2020) The clinical efficacy and safety of stem cell therapy for diabetes mellitus: A systematic review and meta-analysis. *Aging and Disease* **11**(1), 141–153.
- MetGen Investigators, DPP Investigators, ACCORD Investigators, Zhou K, Yee SW, Seiser EL, van Leeuwen N, Tavendale R, Bennett AJ, Groves CJ, Coleman RL, van der Heijden AA, Beulens JW, de Keyser CE, Zaharenko L, Rotroff DM, Out M, Jablonski KA, Chen L, Javorský M, Židzik J, Levin AM, Williams LK, Dujic T, Semiz S, Kubo M, Chien HC, Maeda S, Witte JS, Wu L, Tkáč I, Kooy A, van Schaik RHN, Stehouwer CDA, Logie L, Sutherland C, Klovin J, Pirags V, Hofman A, Stricker BH, Motsinger-Reif AA, Wagner MJ, Innocenti F, Hart LM, Holman RR, McCarthy MI, Hedderston MM, Palmer CNA, Florez JC, Giacomini KM and Pearson ER (2016) Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin. *Nature Genetics* **48**, 1055–1059.
- Zou Q, Qu K, Luo Y, Yin D, Ju Y and Tang H (2018) Predicting diabetes mellitus with machine learning techniques. *Frontiers in Genetics* **9**, 515.