

Perspective

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Multifaceted nature of young-onset diabetes - can genomic medicine improve the precision of diagnosis and management?

Juliana C. N. Chan^{1,2,3} , Elaine Chow^{1,2,3,4} , Alice Kong^{1,2,3} , Elaine Cheung^{1,2}, Tony O¹, Cadmon Lim^{1,2,3}, Baoqi Fan^{1,3}, Sandra Tsoi^{1,3}, Yingnan Fan^{1,3}, Mai Shi^{1,3}, Risa Ozaki^{1,2,3}, Ronald Ma^{1,2,3} , Andrea Luk^{1,2,3,4}

¹Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China.

²Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China.

³Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China.

⁴Phase 1 Clinical Trial Centre, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China.

Correspondence to: Prof. Juliana C. N. Chan, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, China. E-mail: jchan@cuhk.edu.hk

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Abstract

Young-onset type 2 diabetes (YOD), defined as diabetes diagnosis before age 40, has an aggressive clinical course with premature mortality, in part due to long disease duration and lack of evidence to guide diagnosis and management. Autoimmune type 1 diabetes, maturity-onset diabetes of the young (MODY), and latent autoimmune diabetes in adults (LADA) are subtypes of diabetes in young people, which, however, cannot fully explain their complex clinical course. Similarly, family members carrying the same rare genetic variant of monogenic diabetes can have different presentations and outcomes. Ancestral heterogeneity, ecological transition, inter-ethnic differences in genomic architecture, and variations in living environment, lifestyles, access to care, and timeliness of diagnosis and treatment can influence the age of diagnosis and exposure to these cardiometabolic-renal risk factors. Despite the wealth of literature on genetic associations with diabetes, the familial cosegregation of rare variants and their relevance to YOD remains uncertain. This perspective was motivated by decades of clinical observations and learnings from an ongoing randomized controlled trial that uses biogenetic markers to classify patients with YOD for improving outcomes. Apart from highlighting the need to use family-based studies to improve the precision of diagnosis, we discussed atypical causes for diabetic ketoacidosis and the importance of



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lifecourse and psychosocial-behavioral factors in patients with YOD. Apart from detailed clinical evaluation, we propose using plasma C peptide, homeostasis model of assessment (HOMA) indexes, autoantibodies, and polygenic risk scores to stratify risk, classify diabetes subtypes, and personalize treatment in YOD. To achieve these goals, we advocate changing the practice environment and team structure to enable physicians to use the insights they learn from patients and their family members to implement precision medicine and improve the outlook of these high-risk individuals.

Keywords: Young-onset type 2 diabetes, YOD, genomic medicine, precision medicine, autoimmunity, type 1 diabetes, monogenic diabetes, MODY, LADA, PRISM, randomized controlled trial

INTRODUCTION

In 2021, diabetes affected 537 million people, with 80% coming from low- and middle-income countries^[1]. Age, obesity, and family history of diabetes are major risk factors for diabetes^[2]. Thus, people who develop diabetes at a young age, especially if lean, require comprehensive investigations to explain their early metabolic decompensation. In part due to childhood obesity, there is a growing prevalence of young-onset type 2 diabetes (YOD), defined as diabetes diagnosis before the age of 40^[3], which affects one in five adults with type 2 diabetes in Asia^[4].

Patients with YOD may be exposed to decades of glycemic burden with rapid deterioration of glycemic control^[5] and shortened lifespan by 10 years or more^[6]. Compared to their peers with late-onset diabetes, patients with YOD had a 2-6 times higher risk of cardiovascular-renal events, recurrent hospitalizations, and premature death, with mental illness and kidney dysfunction being prominent clinical features^[7-9].

While there are ongoing large-scale epidemiological, genetic^[10], and interventional studies^[11] in people with youth-onset diabetes (less than 18 years old), there are research gaps in YOD diagnosed during adulthood to guide diagnosis and management^[12]. In high-income jurisdictions with well-developed healthcare systems, such as Hong Kong, despite overall falling trends of diabetes and related death^[13,14], the incidence of YOD continued to rise^[15]. Individuals with YOD have experienced mortality rates that are 5-8 times higher than those with late-onset diabetes^[16].

MOTIVATION, FRAMEWORK AND OBJECTIVES

During the last three decades, the Chinese University of Hong Kong Diabetes Care and Research Team has combined practice and research to gather data and use data to inform practice and policies^[3,17]. In the ongoing Precision Medicine to Redefine Insulin Secretion and Monogenic Diabetes Randomized Controlled Trial (PRISM-RCT) in Chinese Patients with Young-Onset Diabetes, we performed comprehensive clinical assessment and used biogenetic information to increase the precision of diagnosis and management of these high-risk patients (<https://clinicaltrials.gov/ct2/show/NCT04049149>)^[18].

In part motivated by learnings from the PRISM-RCT, in this invited perspective not intended to be a review article, we shared our three decades of insights learned from diagnosing, classifying, and managing patients with YOD while pursuing active research in the field of genetics/genomics of diabetes focusing on translation. We first highlighted the minute amount of islets endowment at birth and the many lifecourse factors that may damage their structure and function, ultimately leading to diabetes. We briefly discussed Latent Autoimmune Diabetes in Adults (LADA) and monogenic diabetes as well-recognized subtypes of YOD. In our discussion on autoimmune type 1 diabetes, we highlighted the caveat that atypical diabetes due to acute destruction of islets related to viral infections and immunomodulating therapies may also present

with diabetic ketoacidosis. In our discussion on monogenic diabetes, including Maturity-Onset Diabetes of the Young (MODY), we highlighted the pitfalls of sole reliance on bioinformatics and few reported cases to classify the pathogenic nature of variants, which can lead to missed opportunities for early diagnosis and intervention, especially in populations where common genetic variants may contribute to trajectories of YOD different from that reported in European populations. With the availability of genome sequencing and preconception counseling services, we used clinical examples, albeit rare, to highlight how the detection of mutations with autosomal recessive inheritance in patients with YOD may alert the possibility of syndromic diabetes in homozygous carriers, which calls for genetic and preconception counseling.

We then discussed the clinical application of polygenetic risk scores, now widely accepted by the scientific community to have potential utilities for improving the precision of prediction, prevention, diagnosis, and therapies in complex diseases such as diabetes, and their relevance to YOD. We concluded by summarizing the design of the PRISM-RCT aimed at closing these knowledge gaps but at the same time advocating the need to create an environment conducive to reducing genomic medicine to practice, taking into consideration the unmet psychosocial-behavioral needs in YOD.

Against this background, the motivation underlying this perspective is to encourage more physicians who stand between patients (and their families) and technologies, to gather data systematically to improve our understanding of the nature of this complex syndrome and implement person-centered solutions with ongoing evaluation to inform practice and policies. To non-physicians involved in creating these genomic/genetic data, we emphasize to them the myriad of factors that need to be considered when interpreting these data and translating them into a technology or service aimed at benefiting the patients and those at risk.

DIABETES AND PANCREATIC ISLETS

Blood glucose is maintained within a narrow range of 4-8 mmol/L most of the time, irrespective of energy intake or expenditure, due to efficient glucose sensing and insulin release by the pancreatic beta-cells^[19-21]. Stress hormones, including catecholamines, glucagon, growth hormone, and cortisol, can increase blood glucose, while insulin is the only hormone that lowers blood glucose^[19,20]. Other mechanisms of type 2 diabetes include non-suppression of glucagon and hepatic glucose production, excessive lipolysis, insulin resistance in peripheral tissues, dysregulation of appetite control, and abnormal incretin physiology^[22]. Recent meta-analyses of multi-ethnic genome-wide association studies (GWAS) discovered hundreds of loci implicated in pancreas, adipose, and muscle tissue biology in type 2 diabetes^[23-25].

In an autopsy series of 100 deceased subjects, the weight of pancreatic islets increased from approximately 0.2 grams at birth to a plateau of 1.0 gram at the age of 21 with marked inter-individual variations [Figure 1]^[26]. Other autopsy series revealed close correlations between body mass index (BMI) and pancreatic islet mass, with diabetes cases having lower beta-cell mass and larger alpha-cell mass than cases without diabetes^[27]. Oxidized proteins, fat infiltration, amyloid deposits, and atherosclerosis were common features in diabetes pancreas^[28]. Insufficient islet mass may lead to diabetes and early insulin requirement, so-called type 3c diabetes, due to chronic pancreatitis, pancreatic ductal adenocarcinoma, hemochromatosis, cystic fibrosis, and previous pancreatic surgery^[29].

Islet autoimmunity and type 1 diabetes

Autoimmune destruction of islets can lead to progressive and severe insulin deficiency with rising blood glucose. This is accompanied by lipolysis as an alternative fuel with weight loss and ketone formation, culminating in diabetic ketoacidosis and coma^[30]. In 2021, 8 million people had type 1 diabetes. Amongst them, 1.5 million were children and adolescents, with the majority diagnosed after the age of 18^[31]. There

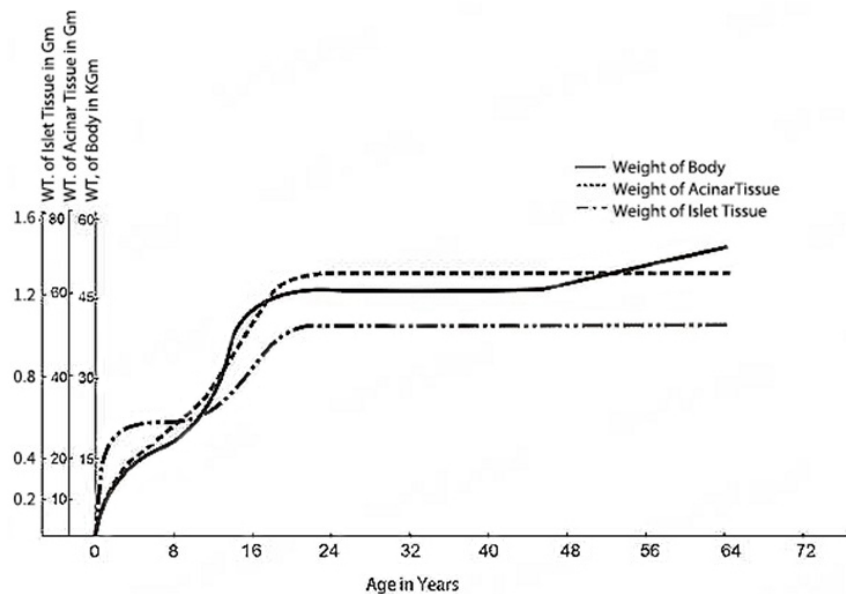


Figure 1. A quantitative analysis of 100 pancreases obtained from individuals in the United Kingdom in the mid-1930s, including newly-born infants and adults up to the age of 64 years, all of whom apparently had normal nutrition and died from different causes including pneumonia, cerebral hemorrhage, perforated gastric ulcer burns, showing the proportional weight of islets and their increase in size over time, reaching a plateau in early adulthood. The small islet mass and its plateau in early adulthood might contribute to the marked increase in diabetes prevalence given the average adult body weight of 60-70 kg today compared to 50 kg nearly 100 years ago (reproduced with permission)^[26].

was familial clustering of type 1 diabetes with 50% concordance amongst monozygotic twins^[32]. Human leukocyte antigen (HLA) haplotypes were associated with increased (e.g., HLA DQ2/DQ8) and decreased (e.g., HLA DQ6/x) risk of islet autoimmunity^[33,34]. Genetic risk score incorporating HLA haplotypes and non-HLA genetic variants predicted the onset of type 1 diabetes in European populations^[35-37].

In a proof-of-concept RCT conducted in the 1980s, researchers reported that 1-year treatment with cyclosporine, an immuno-modulating therapy, was more effective than placebo in causing remission in patients with type 1 diabetes (10-35 years old)^[38]. In 2022, teplizumab, a modified mono-antibody against C3 component on cytotoxic T cells, with a considerably safer profile, was approved by the regulatory agency for delaying the onset of type 1 diabetes^[39,40]. In the latest publication, teplizumab was also found to improve beta-cell function in children newly diagnosed with type 1 diabetes^[41]. These therapeutic advancements have opened up avenues for using biogenetic markers, such as polygenetic risk scores, to identify high-risk individuals for early prevention and intervention^[33,42]. From a treatment perspective, severe insulin deficiency and dysregulation of glucagon secretion put patients with type 1 diabetes at high risk of hyperglycemia and severe hypoglycemia. Advanced insulin formulation and delivery systems^[43], supplemented by continuous glucose monitoring devices^[44], had improved the safety and effectiveness of intensive insulin therapy, making early diagnosis of type 1 diabetes imperative to improve their prognosis^[45,46].

Atypical forms of type 1 diabetes

There are rare forms of type 1 diabetes due to islet destruction. One example is fulminant type 1 diabetes, which occurs within a few days after a viral illness presenting with diabetic ketoacidosis, often accompanied by increased biomarkers of exocrine dysfunction. These patients usually require life-long insulin treatment^[47]. These rare examples inspire new insights into alternative pathogenesis for acute diabetic

ketoacidosis other than autoimmunity. Acute infections such as the coronavirus infectious disease of 2019 (COVID-19) have been shown to increase the risk of type 2 diabetes^[48]. It remains to be proven whether these viral infections might precipitate acute or subacute forms of type 1 diabetes^[49-51].

Our immune system is tightly regulated to control viral infections and suppress cancer growth while avoiding host damage. In developing areas with endemic viral infections, chronic activation of the immune system may lead to immunological tolerance. The latter can contribute to the low prevalence of autoimmune disease but a high prevalence of chronic viral infection and cancer in these areas. Immune checkpoint inhibitor (ICI) increases the activity of cytotoxic T cells of the host to kill cancer cells, but may activate the autoimmune process and cause type 1 diabetes and other endocrine dysfunction^[52,53]. Given the increasing trend of young-onset cancer^[54] and the use of immune-modulating treatment, physicians should be aware of these atypical forms of ICI-associated type 1 diabetes^[55].

Latent autoimmune diabetes in adults

A subacute form of type 1 diabetes, often referred to as LADA, can be missed or undiagnosed, especially in adult patients with obesity or slow disease progression. The availability of many oral glucose-lowering drugs can inadvertently delay insulin treatment. Given the legacy effect of early glycemic control on increasing glycemic durability^[56,57] and reducing long-term complications^[58-60] in both type 1 and type 2 diabetes, misdiagnosis of LADA should be avoided.

In patients with type 2 diabetes, the presence of one anti-islet autoantibody, for example, glutamic acid decarboxylase antibodies (GADA), and that against IA2 and ZnT8 can be used to diagnose LADA. There is no agreed cut-off age for diagnosing LADA, although some experts proposed an age below 35. There is a need to standardize the assays of these autoantibodies. The suboptimal quality of these assays hinders the interpretation of low titers with uncertain significance. Additionally, many reports related to the diagnosis and treatment of LADA were of low quality in terms of study design, definitions, and methodologies. That said, the prevalence of LADA appeared to range from 3% to 12% in patients with type 2 diabetes, in whom high titers of antibodies predicted early insulin requirement^[61]. Although titers of these autoantibodies tend to decline after diagnosis, GADA could be detected up to 8 years after initial diagnosis. Patients with LADA tended to have an earlier age of diagnosis and lower BMI and were highly responsive to insulin treatment compared to their counterparts without LADA. In patients with LADA and residual beta-cell function, the use of sulphonylureas (SU) might hasten, while that of dipeptidyl peptidase 4 inhibitor (DPP4i) might slow the decline in beta-cell function^[62]. These findings underlie the need to assess beta-cell function and autoimmunity, especially in lean patients with type 2 diabetes, to avoid misclassification and inappropriate treatment.

MATURITY ONSET DIABETES OF THE YOUNG AND MONOGENIC DIABETES

The 90% concordance rates for type 2 diabetes amongst monozygotic twins^[63] and the 3- to 9-fold increased lifetime risk of diabetes amongst family members of affected individuals supported its strong genetic component^[64-66]. Monogenic diabetes is caused by a single gene mutation and maturity onset diabetes of the young (MODY) is the most common form of monogenic diabetes. Traditionally, MODY is characterized by absence of obesity, presentation before the age of 25 years, strong family history suggestive of autosomal dominant inheritance, absence of β -cell autoimmunity, and sustained pancreatic β -cell function. However, many patients with MODY had older age of diagnosis with considerable phenotypic heterogeneity. This complexity calls for more phenotypic and multiomic analysis in family-based cohorts to test for cosegregation of genetic variants amongst affected family members^[67].

In 1975, Tattersall first reported a MODY family affecting three generations. The affected members had a young age of diagnosis with non-ketotic presentation and mild clinical course^[68]. The use of family-based linkage analysis and sequencing technology has uncovered the cosegregation of mutations of multiple genes amongst affected family members. The “loss-of-function” and “gain-of-function” of these mutations supported the causal roles of these genes in pancreatic islets and other insulin-sensitive tissues. These genes often encode proteins implicated in neogenesis, differentiation, and maturation of islets, transcription factors, enzymes, ion channels, and mitochondria. Collectively, they coordinate the complex processes of glucose entry and sensing as well as synthesis, processing, and secretion of insulin to maintain glucose metabolism^[69-71]. Amongst the 40 subtypes of monogenic diabetes, MODY due to mutations in genes encoding glucokinase (*GCK*) and transcription factors including hepatocyte nuclear factor 4 α (*HNF4 α*), HNF1 homeobox A (*HNF1 α*), and HNF1 homeobox B (*HNF1 β*) were best described and most frequently reported. These mutations may be *de-novo* or transmitted from one generation to another with varying ages of diagnosis depending on the presence of other risk factors. Other rare mutations with Mendelian recessive mode of inheritance were associated with neonatal diabetes, severe insulin resistance, lipodystrophy, and syndromic features (e.g., deafness, visual impairment, liver/renal cysts, developmental abnormality)^[67] [Figure 2 and Table 1].

There are considerable overlaps in the phenotypes amongst individuals with MODY, LADA, type 1 diabetes, or type 2 diabetes in whom autoimmunity, common and rare variants may coexist. In a recent review article, the authors summarized the epidemiology, pathophysiology, diagnosis, and management of monogenic diabetes. As many as 90% of patients with monogenic diabetes were not diagnosed or misclassified in part due to the prohibitive cost of incorporating sequencing in routine service. Depending on the selection criteria, amongst young patients with type 2 diabetes without autoantibodies, the frequency of MODY ranged from less than 10% to more than 50%, with the majority having mutations in *HNF1 α* , *GCK*, and *HNF1 β* ^[67].

In a multi-ethnic cohort of 3,333 young patients under the age of 20 with a presumptive diagnosis of type 2 diabetes, whole exome sequencing indicated that 93 (2.8%) patients carried a pathogenic/likely pathogenic (P/LP) variant in genes encoding *HNF4 α* ($n = 16$), *GCK* ($n = 23$), *HNF1 α* ($n = 44$), pancreatic and duodenal homeobox 1 (*PDX1*) ($n = 5$), insulin (*INS*) ($n = 4$) and carboxyl ester lipase (*CEL*) ($n = 1$). Compared to those without P/LP variants, patients with MODY had a younger age of diagnosis and lower fasting plasma C-peptide (CP) levels. They were less likely to have hypertension and had higher HDL-C levels, although there were no distinct features that reliably distinguished MODY from other forms of diabetes. Importantly, the diagnosis of MODY would have changed clinical management in 89% of them^[72]. Although MODY risk calculators using age, age of diagnosis, family history of diabetes, HbA1c, fasting plasma glucose and CP, high sensitivity C-reactive protein, autoantibodies, and syndromic features had been developed in Europeans, their sensitivity and specificity remained suboptimal, especially in non-European populations^[73].

Clinical implications of identifying families with MODY or monogenic diabetes

There is good evidence that patients with *HNF1 α* and *HNF4 α* -MODY, as well as K-ATP channel mutations, respond particularly well to SU agents, while adding DPP4i may have incremental benefits^[74]. The use of these oral glucose-lowering drugs enabled insulin discontinuation in some patients misdiagnosed with type 1 diabetes. However, in many patients with MODY, notably those with transcription factor MODY, different background genetic profiles might contribute to progressive β -cell failure. Within a MODY family, carriers of the same rare variant might have different presentations and outcomes depending on the presence and control of other risk factors^[75,76].

Table 1. List of genes implicated in monogenic diabetes. Adapted from^[67]

Maturity-onset diabetes of the young	
ABCC8	ATP binding cassette subfamily C member 8
APPL1	Adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1
CEL	Carboxyl ester lipase
GCK	Glucokinase
HNF1A	HNF1 homeobox A
HNF1B	HNF1 homeobox B
HNF4A	Hepatocyte nuclear factor 4 alpha
INS	Insulin
KCNJ11	Potassium inwardly rectifying channel subfamily J member 11
NEUROD1	Neuronal differentiation 1
PAX4	Paired box 4
PDX1	Pancreatic and duodenal homeobox 1
RFX6	Regulatory factor X6
ZFP57	ZFP57 zinc finger protein
Syndromic diabetes	
CEL	Carboxyl ester lipase
CISD2	CDGSH iron sulfur domain 2
DCAF17	DDB1 and CUL4 associated factor 17
DNAJC3	DnaJ heat shock protein family (Hsp40) member C3
DYRK1B	Dual-specificity tyrosine-phosphorylation-regulated kinase 1B
GATA4	GATA binding protein 4
GATA6	GATA binding protein 6
HNF1B	HNF1 homeobox B
PAX6	Paired box 6
PCBD1	Pterin-4 alpha-carbinolamine dehydratase 1
PIK3R1	Phosphoinositide-3-kinase regulatory subunit 1
PPP1R15B	Protein phosphatase 1 regulatory subunit 15B
SLC29A3	Solute carrier family 29 member 3
TRMT10A	tRNA methyltransferase 10A
WFS1	Wolframin ER transmembrane glycoprotein
ZBTB20	Zinc finger and BTB domain containing 20
Neonatal diabetes	
ABCC8	ATP binding cassette subfamily C member 8
CISD2	CDGSH iron sulfur domain 2
GATA4	GATA binding protein 4
GATA6	GATA binding protein 6
GCK	Glucokinase
HNF1B	HNF1 homeobox B
INS	Insulin
INSR	Insulin receptor
KCNJ11	Potassium inwardly rectifying channel subfamily J member 11
NEUROD1	Neuronal differentiation 1
PDX1	Pancreatic and duodenal homeobox 1
RFX6	Regulatory factor X6
SLC29A3	Solute carrier family 29 member 3
WFS1	Wolframin ER transmembrane glycoprotein

Mitochondrial diabetes**Insulin resistance**

AKT2	AKT serine/threonine kinase 2
INSR	Insulin receptor
LMNA	Lamin A/C
PLIN1	Perilipin 1
POLD1	DNA polymerase delta 1, catalytic subunit
PPARG	Peroxisome proliferator-activated receptor gamma

Lipodystrophy

AGPAT2	1-acylglycerol-3-phosphate O-acyltransferase 2
BSCL2	BSCL2 lipid droplet biogenesis associated, seipin
CAV1	Caveolin 1
CIDEA	Cell death-inducing DFFA-like effector c
AKT2	AKT serine/threonine kinase 2
LMNA	Lamin A/C
PLIN1	Perilipin 1
PPARG	Peroxisome proliferator-activated receptor gamma
CAVIN1 (PTRF)	Caveolae-associated protein 1
ZMPSTE24	Zinc metalloproteinase STE24

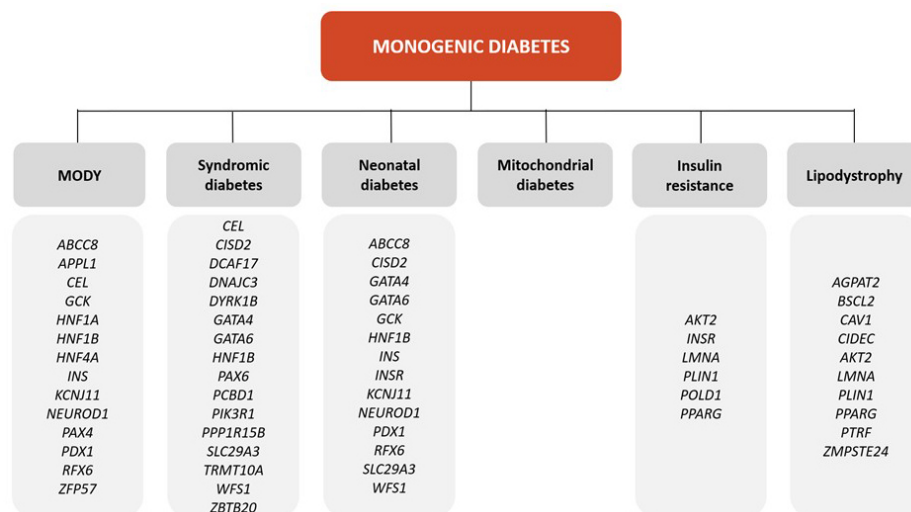


Figure 2. A schematic diagram showing the different types of monogenic diabetes often due to a mutation in a single gene with different clinical presentation, phenotypes, and mode of inheritance.

Hepatic nuclear factor 1 alpha

In the early 1990s, our group reported the first Chinese MODY family. The index patient was a young woman who presented with polyuria and polydipsia in her early 20s. Clinical examination showed severe retinopathy and proteinuria. An inquiry of family history revealed that her mother died of combined heart and kidney failure in her 50s and her grandmother died in her early 60s. Her elder sister presented with blindness due to severe retinopathy in her late 20s. One younger sister was detected to have diabetes during a minor operation at the age of 12 and has been on insulin ever since. The remaining two siblings

underwent oral glucose tolerance tests and the younger brother had a high 2-h plasma glucose level of 17 mmol/L at the age of 17. All siblings were lean. The two younger siblings detected by screening and put on insulin remained complications-free in their late 40s, while the index case died of end-stage kidney disease (ESKD) in her 50s. We later confirmed the cosegregation of a splice site mutation of *HNF1α* amongst all affected members despite their different outcomes depending on the timing of diagnosis and intervention^[77].

Glucokinase MODY

Distinct from transcription factor MODY, GCK-MODY is characterized by isolated fasting hyperglycemia due to suboptimal glucose sensing with normal post-prandial insulin secretion once glucose sensing is triggered^[78]. In European patients, carriers of *GCK* mutations usually have mild disease and do not require treatment^[79]. In Asia, patients with GCK-MODY share features similar to those of their European counterparts, with multiple generations being affected, suggestive of autosomal dominant inheritance. However, the high prevalence of common variants for type 2 diabetes genes and beta-cell dysfunction in young Asian patients, along with other lifecourse factors, may lead to considerable variations in terms of age of diagnosis and subphenotypes both within and across GCK-MODY families^[4,80,81].

Additionally, maternal-offspring *GCK* genotype concordance or discordance can affect the pregnancy outcome, which is highly relevant to young women with diabetes. Intensive insulin treatment in a GCK-MODY non-carrier may cause low birth weight in an offspring carrier who requires a high fasting plasma glucose to trigger insulin secretion. On the other hand, high fasting plasma glucose in an affected mother may lead to high birthweight in an offspring non-carrier due to fetal hyperinsulinemia^[82,83]. The newly developed *GCK* activator^[84] improved glucose sensing and triggered early insulin secretion. This new class of drug may provide precision therapy in patients with GCK-MODY, although more RCTs are needed to confirm this hypothesis^[85].

The discovery of these MODY families due to “gain-of-function” or “loss-of-function” of genetic mutations supports the biological importance of proteins encoded by these genes. Some of their common variants may cause qualitative or quantitative changes in gene expression to increase the risk of type 2 diabetes and its complications. Indeed, some of the loci associated with type 2 diabetes lie within the coding or non-coding regions of MODY genes^[24,25,86]. One example is the common variants of *GCK* and *GCK*-regulating proteins associated with glucose/lipid traits and ESKD^[87]. Mendelian randomization analysis suggested that genetic proxies of *GCK* were causally linked to cardiovascular disease^[88].

Thus, using multiomic analysis including whole exome sequencing focusing on coding regions and whole genome SNP arrays is complementary in identifying high-risk individuals with abnormal biology. Multiomic analysis in prospective cohorts with risk factors, interventions, and outcomes can provide valuable information in our pursuit of genomic medicine. However, the under-presentation of non-European populations, along with differences in ancestry, genomic architecture, and lifecourse factors, means major knowledge gaps in the heritability of YOD remain. Here, supported by other scientists, physicians with knowledge in human biology, pathophysiology, clinical medicine, drug mechanisms, technologies, and care delivery are in a good position to use these technologies and analytical tools to formulate hypotheses for translational purposes.

Wolfram syndrome/DIDMOAD

Currently, there are no guidelines on cascade family screening for heterozygous carriers of MODY genes with recessive mode of inheritance. While the homozygous carriers may suffer from severe disease with

multiple organ damage, the heterozygous carriers may only have "mild" diabetes as a feature. One such example is Wolfram Syndrome, also known as DIDMOAD, the acronym for Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness^[89,90]. The latter is a rare, autosomal recessive neurodegenerative disease due to mutations in the gene encoding Wolframin ER transmembrane glycoprotein (*WFS1* and *WFS2*) located in the Chromosome 4p16.1 region. These genes encode a transmembrane protein causing abnormal calcium metabolism and protein misfolding in the endoplasmic reticulum. These patients might also have mitochondrial dysfunction with marked heterogeneity in phenotypes^[89,91].

In the 1990s, we reported a Chinese man diagnosed with diabetes at the age of 12 with progressive loss of vision due to optic atrophy. At the age of 17, he presented with severe hyperglycemia and polyuria which was due to diabetes insipidus. Ultrasound imaging revealed severe hydronephrosis associated with autonomic dysfunction. With the loss of vision, the patient learned to tune the piano but later developed high-tone deafness. Both his parents had mild diabetes. Although genetic diagnosis was not available at the time, his clinical presentation suggested Wolfram Syndrome/DIDMOAD^[91]. Given the severe disabilities and premature mortality in these homozygous carriers, preconceptual counseling would have prevented these tragic stories while there are ongoing efforts to discover druggable pathways or use gene editing to correct these genetic abnormalities and their consequences^[89,90].

Clinical diagnosis versus prediction by bioinformatics and algorithms

Most of the recommendations on diagnosis and treatment of MODY were based on experiences in Europeans^[79]. The current classification of P/LP variants is largely determined by the rarity of variants, functional annotations, experimental studies, and/or reported cases. Many of these variants were predicted to cause amino acid change, protein truncation, premature initiation, or termination of gene transcription. Due to their high frequency and incomplete penetration, they were often classified as variants of uncertain significance (VUS). Although heterozygous carriers of variants with recessive mode of inheritance or carriers of compound heterozygous mutations are not considered to have monogenic diabetes^[92], these carriers may develop diabetes in the presence of additional risk factors^[51]. The significance of these VUS requires evaluation through detailed phenotyping, systematic family screening, and testing for cosegregation, especially in populations with a high prevalence of familial YOD^[71].

Discounting the significance of these VUS may lead to missed opportunities for early diagnosis and intervention. As an analogy, 7% of Asians have thalassemia minor due to a single copy of mutation affecting one of the oxygen-carrying globin proteins in the erythrocytes^[93]. The high prevalence of these mutations may have selection advantages. Heterozygous carriers have mild anemia and an increased risk of diabetes^[94] due to the close link between glucose and iron metabolism^[95]. Given the recessive mode of inheritance, one in four offsprings of parents who are both carriers may suffer from thalassemia major, requiring lifelong blood transfusion, iron overload, multi-organ failure, and premature death^[96]. In some countries, preconception counseling for couples who are both carriers has prevented the birth of these homozygous carriers^[97,98].

POLYGENIC RISK SCORES, RISK STRATIFICATION AND PRECISION THERAPY

Since the launching of the Human Genome Project in 1993^[99], a wealth of knowledge has been amassed confirming the inter-ethnic differences in genomic architecture with hundreds of loci scattered throughout the genome associated with complex diseases including diabetes, cardiovascular-renal disease, and cancer^[24,86]. In keeping with their frequent, albeit not invariable clustering, these diseases share common variants, which are mainly non-coding with small effect size, suggesting perturbation of common pathways in these disease clusters^[86,100-102]. While some of these genetic loci are potential drug targets^[103,104], other

researchers advocate the use of polygenic risk scores to increase the cost-effectiveness of screening for high-risk subjects for intervention and individualized treatment^[105-107].

In people with youth-onset diabetes (less than 18 years old), there are ongoing large-scale epidemiological, genetic^[10], and interventional studies^[11] to discover the causes and evaluate interventions. By contrast, there are major research gaps in adults with YOD often diagnosed by physicians who are less familiar with rare diseases^[12]. Amongst patients diagnosed before the age of 40 years, there is heterogeneity in etiologies and phenotypes depending on whether they present during infancy, childhood, adolescence, or early adulthood. Large-scale GWAS have identified different genetic variants associated with the age of diagnosis, with many of them being associated with common forms of type 2 diabetes^[108]. These variants can be used to generate polygenic risk scores to stratify risk for prevention and early intervention. Structured lifestyle modification and medications including metformin and alpha-glucosidase inhibitors prevent or delay the onset of type 2 diabetes in people with impaired glucose tolerance^[3]. In the United States^[109] and China Diabetes Prevention Program^[110], metformin was most effective in people under the age of 45. Thus, by combining familial, genetic, and clinical risk scores, it is possible to segment the 20%-30% of individuals at the highest risk of developing YOD with less biological resilience for early intervention^[111].

Likewise, while the early use of cheap generic medications such as statin and renin-angiotensin system inhibitors are likely to be cost-effective in preventing cardiovascular-renal events in young patients with type 2 diabetes^[3], the cost-effectiveness of new drugs such as glucagon-like peptide 1 receptor agonist (GLP1-RA), sodium-glucose-cotransporter 2 inhibitor (SGLT2i), and non-steroidal mineralocorticoid receptor antagonist^[112] in young patients remain uncertain despite their high lifetime risk for complications^[113]. In this connection, diagnosis of familial hypercholesterolemia followed by cascade screening has been shown to be cost-effective for preventing premature cardiovascular disease through early detection and intervention^[114]. While definitive trials are needed to prove the value of genetic testing, RCTs have demonstrated that the provision of personalized^[115,116] and genetic information on the risk of diabetes complications empowered self-management and reduced negative emotions^[117-119].

USING BIOGENETIC MARKERS TO INCREASE THE PRECISION OF DIAGNOSIS AND TREATMENT

There are considerable overlaps in clinical presentations and phenotypes amongst people with autoimmune type 1 diabetes, LADA, MODY, type 2 diabetes, and other atypical forms of diabetes in young people. Once diabetes develops, glucolipotoxicity, inflammation, and oxidative stress can cause dedifferentiation and apoptosis of beta-cells and perpetuate glycemic deterioration^[22,120]. For the same set of risk factors (e.g., smoking, obesity), there are considerable inter-individual variations in rates of decline of beta-cell function^[81]. An estimated 50% of beta-cell function might have been lost at the time of diagnosis of diabetes^[121]. Early optimization of glycemic control could restore beta-cell function^[122] and delay treatment escalation^[56,57]. These data support the use of biomarkers to improve the precision of diagnosis and treatment to preserve beta-cell function^[123]. In the ongoing PRISM-RCT, we observed the importance of nature and nurture in these young patients in whom varying combinations of genetic predispositions, lifecourse factors, timeliness of diagnosis, lifestyles, and access to care can result in different presentations, trajectories, and outcomes [Figures 3 and 4 and Table 2].

In Hong Kong Chinese patients with YOD, analysis of stored samples indicated that 8% had LADA, but the majority had not been given early insulin treatment. Compared to their peers with classical type 1 diabetes, patients with LADA had a 2.8 times higher risk of ESKD, likely due to poor glycemic control with delayed insulin treatment. Amongst patients treated with insulin, the mean reduction in HbA1c at 6 months was

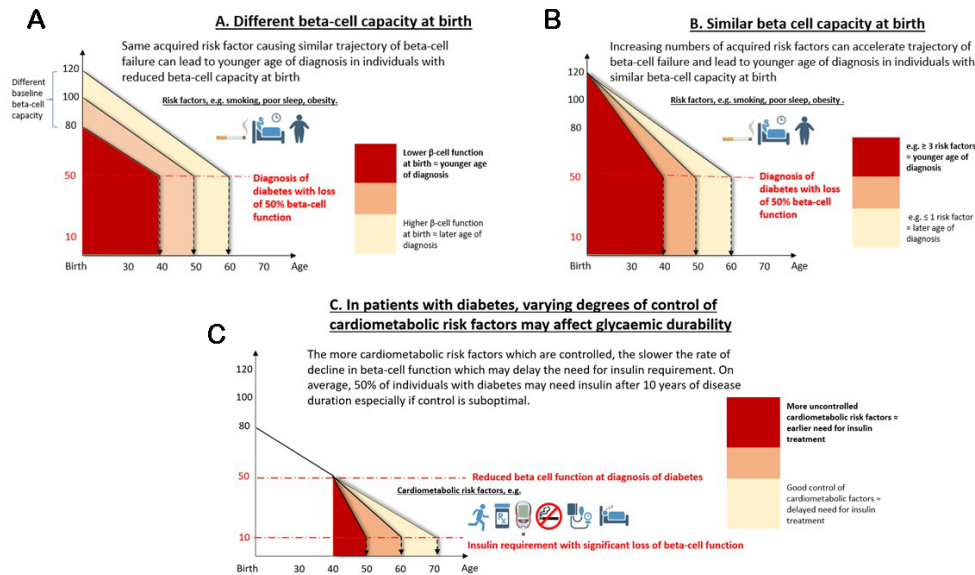


Figure 3. A conceptual framework indicating the decline in beta-cell function due to natural aging, metabolic stress, and inflammation (e.g., obesity, use of tobacco, psychosocial stress, poor sleep, infection), which can influence the age of onset of diabetes. For a given trajectory of beta-cell function, those with reduced beta-cell capacity are more likely to decompensate early. With the onset of diabetes, ongoing lipoglucotoxicity and inflammation can further accelerate beta-cell loss, resulting in insulin requirement. Reducing metabolic stress, especially in people with vulnerable beta-cell function, may delay the onset of diabetes and insulin requirement^[128].

2.3% in patients with LADA versus 0.7% in those without autoantibodies, calling for early detection of LADA to avoid delayed insulin treatment^[124,125].

Between 1995 and 1998, fasting, stimulated, and random CPs were measured in 280,539 inhabitants in Skaraborg from Sweden, of whom 3.2% had diabetes. Amongst 1,093 patients with well-defined diabetes types, all three CP measurement protocols were robust in discriminating type 1 from type 2 diabetes, based on receiver operator curve (ROC) analysis, with random CP having the best performance. The optimal cut-off value was 0.50 nmol/L for random CP, 0.42 nmol/L for fasting CP, and 0.60 nmol/L for stimulated CP^[126]. Other researchers proposed using fasting plasma CP < 250 pmol/L with or without autoantibodies to indicate absolute or severe insulin deficiency^[46]. In our prospective analysis, Chinese patients with type 2 diabetes who had GADA positivity and low CP had the fastest progression rate to insulin treatment with a high risk of severe hypoglycemia. These patients should benefit from a basal-bolus insulin regimen to optimize glycemic control. Patients with GADA but residual CP level had a similar risk of insulin requirement as their peers without autoimmune type 2 diabetes. Counter-intuitively, patients with high CP, suggestive of insulin resistance, were more likely to progress to insulin treatment^[125]. In a cohort of Chinese of working age, we used fasting plasma CP and glucose to derive Homeostasis model of assessment insulin resistance (HOMA-IR) and HOMA-beta to estimate insulin resistance and deficiency. In keeping with their contributory roles in diabetes^[127], both HOMA-IR and HOMA-beta predicted incident diabetes in people with normal glucose tolerance. In patients with YOD, these indexes independently predicted early insulin requirement^[128]. Due to these non-linear relationships of CP, the estimation of HOMA-IR and HOMA-beta, which takes prevailing PG into consideration, should be more informative. The use of HOMA indexes and autoantibodies will help physicians make more precise diagnoses and treatments.

The growing number of glucose-lowering drugs with different mechanisms of action calls for better patient segmentation to prioritize treatment selection^[22]. Using HOMA indexes, GADA, age, BMI, and age of diagnosis, researchers classified patients with type 2 diabetes into five subtypes. Patients with severe insulin resistance had a high risk of chronic kidney disease, while those with autoimmune or severe insulin deficiency required early insulin treatment^[129]. These studies had been replicated in other populations, including Chinese, in whom severe insulin-deficient type was more common and mild age-related diabetes was less common than their European counterparts. In all five subtypes of diabetes, Chinese patients had an earlier age of diagnosis, lower BMI, HOMA-beta, and higher HbA1c^[130,131]. In a cross-sectional analysis, Chinese patients with YOD had lower beta-cell function with a steeper negative relationship between beta-cell function and disease duration than that in their late-onset counterparts^[81].

NEED FOR RANDOMIZED CONTROLLED TRIAL GUIDED BY PHENOTYPES TO INFORM PRACTICE

Despite the organ-protective effects of SGLT2i and GLP1-RA, such evidence mainly came from high-risk patients with complications. Optimal glycemic control remained the cornerstone in diabetes management, and given the variable phenotypes suggestive of contribution from different etiologies, more studies are needed to guide treatment based on phenotypes or genotypes^[132]. For example, in the Trimaster Study, patients with type 2 diabetes and an estimated glomerular filtration rate of 60-90 mL/min/1.73m² were more responsive to DPP4i than SGLT2i. Patients with low BMI (< 30 kg/m²) were also more responsive to DPP4i than thiazolidinediones^[133]. Apart from its proven benefits in preventing diabetes, metformin also reduces the risk of vascular, renal, cancer, and pneumonia events and all-cause death in type 2 diabetes^[134]. There is also evidence suggesting that patients with predominant insulin deficiency may benefit from the addition of insulin secretagogues (e.g., SU), prandial insulin regulators (e.g., GLP1-RA, DPP4i, AGI), or insulin treatment, while those with insulin resistance, often due to obesity, might benefit more from weight-neutral or weight-reducing therapies such as GLP1-RA and SGLT2i^[135,136]. In a proof-of-concept analysis, we stratified patients with type 2 diabetes by CP and insulin treatment and reported that patients with low CP and treated with insulin had the lowest mortality rate^[137].

In the VERIFY Trial, newly diagnosed patients with type 2 diabetes treated with combination therapy of metformin and DPP4i had more durable glycemic control and 30% reduced risk of progression to insulin treatment compared to those treated with metformin monotherapy followed by DPP4i only with rising HbA1c^[138]. These effects were particularly evident in patients with YOD^[123]. In a real-world database, patients with type 2 diabetes, the majority of whom were on metformin and/or SU, those with additional DPP4i within 2 years of diagnosis had a 30% reduced risk of insulin treatment compared to those with additional DPP4 after 3-5 years of diagnosis^[57]. These findings highlight the importance of early diagnosis, early intervention, and early control in preserving beta-cell function, especially in patients with compromised beta-cell function. Against a backdrop of the declining use of SU, increasing popularity of SGLT2i, and advocacy of using GLP1-RA to replace insulin, the importance of better classification cannot be emphasized enough to ensure timely and appropriate treatment for maximizing efficacy (e.g., SU in patients with HNF1 α - and HNF4 α -MODY) and reducing side-effects (e.g., insulin analogs in patients with LADA or severe insulin insufficiency to avoid diabetic ketoacidosis and severe hypoglycemia). Despite their heterogeneous phenotypes and treatment responses, there is a lack of RCT data to guide diagnosis and treatment in these high-risk patients with YOD^[12].

PSYCHOSOCIAL-BEHAVIORAL NEEDS AND LIFECOURSE MANAGEMENT

Perinatal development, environmental exposure, socioeconomic status, migration, education, and health behaviors^[139] can interact in a complex manner to cause childhood obesity, which can track into adulthood

Table 2. Lifecourse factors that may influence the onset, trajectory, and consequences of diabetes (also refer to Figure 3)

Infancy and childhood	Adolescence	Middle age	Old age
<ul style="list-style-type: none"> • Ethnicity and migration • Common and rare genetic variants • Other familial factors (e.g., hemoglobinopathy, chronic hepatitis B infection) • Epigenetics and perinatal development • Low birth weight 	<ul style="list-style-type: none"> • Childhood illness (e.g., malignancy and steroid use) • Childhood obesity • Formation of habits and lifestyles • Education • Socioeconomic status 	<ul style="list-style-type: none"> • Obesity, metabolic syndrome, and fatty liver • Lifestyles (e.g., unhealthy diet, physical inactivity, poor sleep) • Psychosocial stress • Other risk conditions (e.g., depression, gestational diabetes, PCOS, ...) • Endocrinopathy and drug use 	<ul style="list-style-type: none"> • Micro/macrovacular complications • Chronic kidney disease • Heart failure • Cancer • Dementia • Frailty

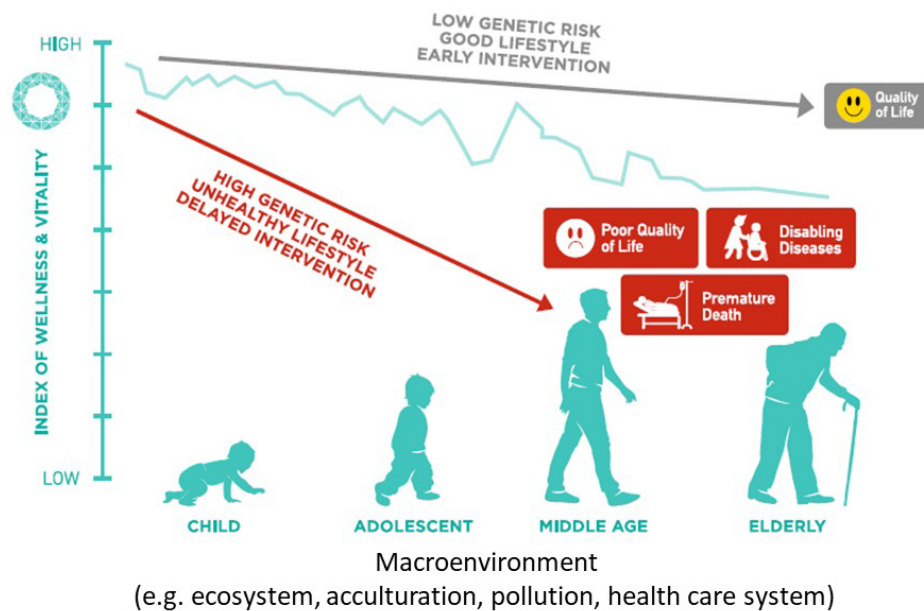


Figure 4. A conceptual diagram showing the complex interactions between nature and nurture where multiple lifecourse factors can predispose, precipitate, and perpetuate the onset and trajectories of diabetes resulting in markedly different outcomes, strongly influenced by genetic factors, early childhood development, environmental exposures, lifestyles, and access to care and education (reproduced with permission from GemVCare)^[151].

and bring forward the age of onset of diabetes. Other familial factors, such as chronic hepatitis B infection and hemoglobinopathy, have been associated with diabetes in some ethnic groups^[94,140]. Medical histories such as pancreatic disease, gestational diabetes, polycystic ovary syndrome, thyroid disease, tuberculosis, and mental illness may provide clues regarding the predisposition, precipitation, and perpetuation of YOD^[71,141,142]. A family history of diabetes affecting multiple generations with or without syndromic features may alert the possibility of MODY or monogenic diabetes^[67]. Understanding patient-reported outcome measures (PROMs) such as quality of life, competing priorities, psychosocial stress from work or family, interpersonal relationships, and life events^[143] may help care providers address negative emotions, maladjustment, and poor adherence frequently encountered in young patients with diabetes^[101,144-146] [Figure 3 and 4, Table 2].

PRACTICE ENVIRONMENT, CLINICAL ACUMEN AND PERSON-ORIENTATED CARE

A correct diagnosis is key to a meaningful dialogue between doctors and patients for informed and shared decision-making^[147,148]. This can only be achieved through comprehensive profiling, good doctor-patient relationships, regular reviews, and quality care. However, the busy working environment, short consultation

time, and frequent changes of care providers had made this approach challenging. The many technological advances focusing on procedures have further contributed to the increasing organ-based and fragmented healthcare practices^[149].

Reducing genomic medicine to practice for improving the precision of diagnosis and therapy^[150,151] must be aligned with reform in undergraduate/professional education and practice environments to facilitate implementation^[117]. Genomic medicine is only one of the many facets of person-orientated care which begins with good history taking, physical examination, and value-based investigations. This should allow physicians to prioritize a list of differential diagnoses followed by definitive or empirical treatment with anticipated outcomes, and action plans if the outcome is not achieved. Doctors interested in the field of diabetes need to stay abreast of the advances in genomic medicine, data analytics, and drug development and learn how to use lay language to communicate probabilities, uncertainties, and complexities. They are in the best position to assess the utility of using clinical/genetic risk scores or algorithms to segment patients for targeted treatment, exclude hormonal or drug-induced forms of diabetes, and order comprehensive genetic profiling to diagnose rare or syndromic forms of diabetes. For research-orientated physicians, setting up registers^[152] will provide a powerful tool to assess the values of using new technologies and approaches aimed at addressing the many needs of a young person with diabetes^[17,101,153-155]. The adoption of this person-orientated approach will bring back the science and arts of clinical medicine which is particularly relevant to patients with YOD given the implications of misdiagnosis, misclassification, and mismatched treatment.

PRISM: precision medicine to redefine insulin secretion and monogenic diabetes (PRISM) in Chinese patients with young-onset diabetes

Complexity is a key feature in internal medicine. For the same disease, different people can have different clinical presentations. For the same clinical presentation, different people can have different underlying causes. For the same treatment, different people can have different responses. It is against this background that the authors embarked upon a pragmatic 3-year RCT [Precision medicine to redefine insulin secretion and monogenic diabetes (PRISM)] where 884 patients with type 2 diabetes diagnosed before the age of 40 and aged less than 50 years underwent structured clinical assessment and comprehensive biogenetic profiling including measurement of HOMA-indices, CP, and GADA to diagnose LADA and assess beta-cell function. These patients had genome-wide genotyping for computing polygenic risk scores for beta-cell function and complications. They also had targeted gene-sequencing to detect mutations of genes for MODY and monogenic diabetes. Other PROMs included psychosocial-behavioral factors and quality of life. Half of these patients were randomized to receive 1-year intensive counseling and personalized treatment guided by their biogenetic profiles and psychosocial needs, delivered by a specialist-led multidisciplinary team in a diabetes center away from busy clinics aimed at attaining multiple treatment targets. After this 1-year multi-component management^[154,156], these patients will return to their usual clinics for follow-up with yearly review at the diabetes center while the other half receive usual care. All patients will undergo re-evaluation at 3 years. The primary outcome of PRISM is the incidence of all diabetes-related endpoints and the secondary outcome is control of cardiometabolic risk factors <https://clinicaltrials.gov/ct2/show/NCT04049149>. The results will be analyzed within the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation and Evaluation)^[157] to inform planners, practitioners, and policymakers about the resources, infrastructure, personnel, logistics, and technology needed to reduce precision medicine in YOD to practice and their cost-effectiveness. This project commenced in January 2020 and completed recruitment in September 2021, and the 3-year study period will end in September 2024^[158].

CONCLUSION

Diabetes is a societal, public health and personal challenge. The rapid changes in our ecosystem, physical and food environment, cultures, lifestyles, values, and perspectives have unmasked biological defects in vulnerable individuals at risk of developing diabetes at a young age. These individuals need to be diagnosed, treated, and controlled early to prevent complications, maintain earning power, and preserve quality of life. Decision makers including governments, payors, and healthcare planners are tasked with creating a health-enabling environment, building capacity, and ensuring access to affordable medications, care, and support in collaboration with industry. Likewise, care providers have the responsibility to identify unmet needs and discover new knowledge to improve outcomes. Against this backdrop, physicians standing between patients and technologies, equipped with knowledge in human biology, pathophysiology, clinical medicine, drug mechanisms, and care delivery, should spearhead the use of genomic medicine and holistic care to reclassify diabetes and implement personalized solutions in people with or at risk of developing YOD. By combining research and practice, there is a real possibility that we can use personalized and genomic data to transform care and save patient lives^[3].

DECLARATIONS

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Authors' contributions

Conceptualized and wrote the first draft with contribution and finalized the paper for submission: Chan JCN
Provided critical comments and approved the final manuscript: Chan JCN, Chow E, Kong A, Cheung E, O T, Lim C, Fan B, Tsoi S, Fan Y, Shi M, Ozaki R, Ma R, Luk A

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Chan JCN and Ma R hold patents for using genetic markers to predict diabetes and its complications for personalized care. Chan JCN, Ma R, and Lim C are cofounders of a start-up biotech company partially supported by the Technology Start-up Support Scheme for Universities (TSSSU) of the Hong Kong Government Innovation and Technology Commission. All other coauthors have no conflict of interest to declare.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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