Understanding diabetes heterogeneity: key steps towards precision medicine in diabetes

Richard David Leslie[1]*, FAoP. Professor of Diabetes and Autoimmunity

Ronald Ching Wan Ma[2,3,4]*, FRCP. Professor

Paul W Franks[5,6,7,8], PhD. Professor

Kristen J Nadeau[9], MD. Professor of Paediatrics

Ewan R Pearson[10], FRCP. Professor of Diabetic Medicine

Maria Jose Redondo[11], MD. Professor of Paediatrics

***These authors should be considered joint first authors**

[1] Blizard Institute, Barts and Royal London Medical School, London, UK

[2] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong SAR, China;

[3] Chinese University of Hong Kong-Shanghai Jiao Tong University Joint Research Centre in Diabetes Genomics and Precision Medicine, Hong Kong Institute of Diabetes and Obesity, The Chinese University of Hong Kong, Hong Kong SAR, China;

[4] Laboratory for Molecular Epidemiology in Diabetes, Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China

[5] Novo Nordisk Foundation, Tuborg Havnevej 19, 2900 Hellerup, Denmark

[6] Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, Malmo, Sweden.

[7] Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Department of Medicine, [8] University of Oxford, Oxford, UK.

[8] Harvard T.H. Chan School of Public Health, Boston, MA, USA

[9] University of Colorado Denver - Anschutz Medical Campus

[10]Population Health & Genomics, School of Medicine, University of Dundee

[11]Texas Children's Hospital, Baylor College of Medicine

Correspondence:

Richard David Leslie (r.d.g.leslie@qmul.ac.uk)

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Summary

Diabetes is highly heterogeneous yet diagnosed by measuring a single blood-borne metabolite, glucose, irrespective of aetiology. Whilst pragmatically helpful, disease classification can become a burden, limiting advances in research and medical care. Here, we describe diabetes heterogeneity, highlighting recent approaches that could facilitate management by integrating three disease models across all forms of diabetes, namely, the 'Palette Model', 'Threshold Model' and 'Gradient Model'. Since progression to diabetes, further worsening of established diabetes and the subsequent emergence of diabetes complications are kept in check by multiple processes designed to prevent or circumvent metabolic dysfunction, the impact of any given disease risk factor will vary from person to person depending on their background diabetes-related propensity and environmental exposures. Defining the consequent heterogeneity within diabetes, both in terms of diabetes risk and risk of complications, should improve health outcomes today, and shine a light on avenues for novel therapy in the future.

Search strategy and selection criteria

We searched PubMed for published articles from Jan 1, 2010 to December 7, 2022, with the search terms including: “heterogeneity AND diabetes”, “classification AND diabetes”, “autoantibodies AND diabetes”, “phenotyping AND diabetes”, “diabetes subtypes”. We also searched the reference lists of articles identified by this search strategy and selected those we judged to be relevant. Review articles are cited in several instances to provide readers with more details and more references than we had space to cite.

Introduction

Diabetes carries a substantial burden, affecting approximately >500 million people worldwide (1), at a global cost estimated at nearly 1 trillion USD (2). That burden is expected to increase in the coming years, particularly in Africa, the Middle East, South Asia, and Latin America (1).

The pathophysiology and clinical phenotype of diabetes is highly heterogeneous. It is a disease diagnosed solely by an elevation in blood glucose, often with little regard for the aetiological processes that caused it. Some types of diabetes, such as type 1 diabetes (T1D) or monogenic diabetes, are often adequately defined by their distinct aetiologies; others, most notably type 2 diabetes (T2D), are not. Type 1 diabetes is defined by the autoimmune destruction of the beta-cells and accounts for ~2-10% of all diabetes cases, with its prevalence varying from one population to the next. The most common form of diabetes, T2D, accounts for 90-95% of all cases. Unlike other forms of diabetes, most cases of T2D are diagnosed through a process of exclusion, with other known explanations for chronic hyperglycaemia having been considered and rejected. Thus, the precise pathophysiology of T2D in any given case is usually unknown, and there is substantial variation in clinical presentation, treatment requirements and prognosis. When the aperture is widened to the global scale, such uncertainty is even more striking, given different diabetes phenotypes across ethnicities and geographic locations (3, 4).

Challenges of applying classification to a heterogeneous disease

In clinical medicine, disease classification is often applied to categorise different diseases to facilitate making decisions on clinical care, and to stimulate epidemiological research. The rationale for this approach is that medical practice is structured around establishing categorical diagnoses to guide management. When therapeutic options are limited, such an approach is reasonable as was the case with insulin therapy in 1922. However, when there is a range of options, as is now the case, disease classification can become an obstacle in recognizing heterogeneity, even within a given category (Table 1) (5). For example, individuals with a monogenic mutation associated with maturity onset of diabetes of the young (MODY) can show different phenotypes when carrying that mutation on different polygenic backgrounds, so that someone with Glucokinase (GCK)-MODY (usually not requiring medical intervention) can show progressive hyperglycaemia when carrying additional genetic variants for T2D or with the development of adiposity-induced insulin resistance. Here we will focus on the heterogeneity of diabetes in general, not monogenic diabetes, but this example

highlights how it may be inappropriate to simplify complex interactions that contribute to common diseases like diabetes.

Despite these limitations, disease classification does facilitate clinical diagnosis, prescribing practices, as well as global comparisons of health-related data. Growing appreciation of diabetes heterogeneity prompted an update in 2019 of the previous World Health Organization (WHO) classification of diabetes. Table 1 summarizes the current classification (6), as well as some important considerations when considering the diagnosis. For example, monogenic forms of diabetes would need to be considered in someone presenting with youth-onset diabetes, especially if there is strong family history of diabetes. Conversely, among individuals with weight gain, other endocrinopathies such as Cushing's syndrome may need to be considered.

Beta-cell destruction or dysfunction is the key pathophysiological defect underpinning most cases and forms of diabetes (7, 8). By inference, it may not be possible or necessary to group people with diabetes into specific categories. However, recognizing the 'risk-continuum' of pathophysiological processes that contribute to hyperglycaemia can provide a better guide to our understanding of diabetes, and with that, better prediction and treatment. Future approaches to disease classification should be based on defining categories with shared pathophysiology, so that the numbers of "subtypes" would be variable, and dependent on data quality and the statistical methodology being used for the clustering.

Several emerging approaches to diabetes classification have been adopted, including the integration of the "Palette Model" and the "Threshold Model" (9). Here, we will use these models, and add a third, the "Gradient Model", to add the dimension of severity of common chronic diseases, including diabetes (Figure 1). The Palette Model identifies a wide range of disease-risk factors (as with different colours on an artist's palette), contributing to disease in different ways in different individuals, such as islet autoimmunity and insulin resistance in the same person. The Threshold Model, on the other hand, highlights how a combination of diabetogenic factors, which may or may not cross the threshold for clinical diabetes (9) (10)(Figure 2). For example, an individual with mild islet autoimmunity may only develop clinical diabetes in the presence of T2D-associated genes (11) or insulin resistance (12). As a result, the disease phenotype could reflect a combination of diabetes-related mechanisms (13) which interact to modify the disease's natural course (14) (15). This dynamic is captured in the Gradient Model, allied to the Threshold Model, given that disease risk factors operate within time-specific windows, so that the presence and/or severity of diabetes, after disease-onset, may change, e.g., individuals with T2D can remit when insulin sensitivity improves and individuals with T1D can have a 'honeymoon' off insulin therapy. Moreover, not all individuals at high genetic risk of either T1D or T2D will develop islet autoimmunity or metabolic dysfunction respectively, while not everyone with islet autoimmunity or metabolic dysfunction develops diabetes. By implication, these three Models highlight the importance of allostasis through regulatory pathways, be they immune or metabolic, to reduce disease progression. Whilst none of these conceptual models alone can fully account for the complexity of diabetes, each model does offer a better appreciation of that heterogeneity, which underlies diabetes.

Heterogeneity in diabetes – biological variation or error?

Understanding diabetes heterogeneity should enhance our ability to predict disease incidence, treatment response, and prognosis. Ideally, a physician would want precisely defined, long-term (sometimes lifelong) measures of those environmental and biological features causing the disease and its subsequent trajectory. Instead, current data is sparse and imperfectly characterised i.e., often with considerable systematic [bias] and non-systematic error. Clinically, heterogeneity in diabetes is a consequence of variations either in 'biological' processes underlying the disease phenotype (signal) or error in the 'quantification' of that phenotype (noise). Decoding heterogeneity requires that signal to be successfully parsed from noise.

Many established environmental features drive diabetogenic exposures including sedentary behaviour, certain diets, stress, sleep disturbance, and smoking. Accurate and precise quantification of these exposures may help resolve some heterogeneity within diabetes, yet doing so is challenging, as such exposures are often complex, difficult to assess without systematic and non-systematic error, and conveyed over extended periods from birth through adulthood (16-18). The impact of biological variants and diabetogenic exposures on disease-related cellular networks and phenotypes have only recently been explored. These 'biological variants' include variations in DNA, epigenetic marks, RNA, proteins, hormones, and metabolites. The process of quantification of these variants is subject to technical variation and this may mislead interpretation of their impact on diabetes heterogeneity. Variations in the assessment of blood glucose also exacerbate diabetes heterogeneity: diabetes is typically diagnosed using random, fasting and post-challenge blood glucose measurements, or with HbA1c, each reflecting different features of glycaemic regulation. Fasting glucose, for example, is influenced mainly by gluconeogenesis and glycogenolysis, whereas post-challenge glycaemia is mainly determined by peripheral insulin resistance and the beta-cell response (19) (20). Whilst insulin resistance is a key pathophysiological defect in T2D (21), recovery of first phase insulin secretion identifies subjects who have remission of T2D following weight loss with reduction in hepatic and pancreatic fat (22), highlighting the key role of beta-cell function in the development of T2D. Using few point-estimates of time-varying biological features, such as glycaemia and/or autoantibodies, are also error prone owing to a 'regression dilution effect' (23). There are additional contextual factors (e.g. stress, ambient temperature, recent exercise) that limit test reproducibility and variability in sample handling and storage that can introduce error into assessments and obstruct the study of diabetes heterogeneity.

Heterogeneity within Autoimmune Diabetes

The discovery of insulin in 1922 readily divided diabetes into insulin-dependent cases, who required it for their very survival, and those who did not. Since children often presented with ketoacidosis, which is life-threatening without insulin treatment, their disease was seen as a juvenile-onset insulin-dependent form of diabetes, later called type 1 diabetes (T1D). Appreciation of the heterogeneity within diabetes also comes with uncertainty about the disease nosology, especially since current classification relies on clinical features and biomarkers which are not pathognomonic of underlying disease aetiology (24). Furthermore, epidemiological studies suggest that the majority of clinically defined cases of T1D are diagnosed in adulthood (22), whether in China (65% of total T1D cases) or USA (59%) (24) (25); indeed, in the UK Biobank a significant proportion of those diagnosed with diabetes over the age of 30 years had an elevated GRS for T1D (26).

The Palette Model proposes that variable elements can cluster in any given individual at a given time. Genetics and environment combine and lead to diabetes in any given individual by engaging diverse pathways at a given time. For example, genetic determinants of islet autoimmunity (e.g., HLA and non-HLA alleles associated with T1D) and processes typically associated with T2D, such as impaired beta-cell function or insulin resistance, may interact with microorganisms (viruses and the gut microbiome), dietary factors (vitamin D and gluten exposure), and factors associated with industrialization i.e., heavier BMI, hygiene, pollution and overcrowding. Pathophysiological processes that are highly prevalent in the population, such as today are obesity-related factors, can appear in combination other mechanisms, including islet autoimmunity.

The Threshold Model advances the concept that the combined effect of various diabetogenic influences must reach a critical threshold to induce diabetes. Genetic susceptibility alone may never result in clinical diabetes, and even identical twins who share a common environment may remain discordant for islet autoimmunity and T1D (27). Moreover, islet autoimmunity, when mild, may never lead to diabetes, as demonstrated by individuals who have persistent single autoantibody positivity without progression to diabetes. Even, those relatives of T1D cases carrying the protective genotype *HLA DQA1*0102/DQB1*0602*, whilst not developing diabetes, can have abnormal glucose tolerance and reduced insulin secretory capacity (28). However, such individuals can progress to diabetes as other factors accumulate, such as insulin resistance due to obesity (12) (29, 30) or concurrent T2D-associated genes (11, 13). In the Threshold Model, the number and combination of factors (e.g., genetics, environment) may vary. At one extreme, a single gene mutation e.g. *AIRE* or *FOXP3*, can cause insulin-dependent diabetes, at the other extreme, pancreatectomy or pancreatitis can do the same (31). Similarly, aggressive islet autoimmunity can lead to diabetes without requiring additional factors. The appearance of diabetes-associated autoantibodies in early life seems to reveal two distinct endotypes, one associated with insulin (proinsulin) autoantibodies and HLA DR4 (DR4PRO) (also called T1D endotype 1 or T1DE1), and the other associated with glutamic acid decarboxylase autoantibodies (GADA) and HLA DR3 (DR3GAD) (also called T1D endotype 2 or T1DE2), (25). The former identifies a cohort with an earlier peak incidence (typically diagnosed under age 7 years), insulin autoantibody as the first islet autoantibody to appear, rapid progression to multiple autoantibodies and more severe insulin secretory loss (low serum C-peptide as a proxy for insulin), allied with more marked islet inflammation (high levels of CD20 and CD8 cells infiltrating islets). On the other hand, DR3GAD endotype is usually diagnosed over age 12 years with GADA as the first and often only autoantibody to appear, less severe islet inflammation, as well as insulin secretory loss (32). T1DE1 is almost exclusive to very early childhood and T1DE2 to older individuals. At the individual level these endotypes are distinct and do not co-exist, yet at the group level they are not clearly delineated, with intermediate ages at diagnosis reflecting a continuum extending to the prevalence of multiple autoantibodies and the severity of both islet inflammation and C-peptide loss (33) (34).

The Gradient Model captures the notion that combinations of genetic and environmental factors can determine the velocity and severity of the disease process. High genetic risk with multiple serum autoantibodies at a young age are each associated with earlier progression to T1D and lower fasting C-peptide at diagnosis. Conversely, individuals can undergo remission when beta-cell function and/or insulin sensitivity improve, as with the 'honeymoon' period and following pregnancy. Both Threshold and Gradient Models account for that variable severity of insulin secretory loss once

diabetes develops, while the gradient effect extends to disease risk before clinical onset with greater insulin secretory loss in the DR4PRO endotype compared with the later onset DR3GAD endotype (Figure 2). T1D genetic risk, including the association with HLA Class 1 haplotypes, is also less striking in older cases, (35). While histologically, heterogeneity in disease severity (13) can even be detected within islets, given that not all insulin-containing cells are destroyed, while whole lobules of the pancreas can remain unaffected, so-called pancreatic 'vitiligo' (32, 36). Although a full description is beyond the scope of this article, race, ethnicity and ancestry are additional important modifiers of disease development and course. For example, elevated BMI increases progression to T1D in non-Hispanic White (by 36%), but in Hispanic children by 400% (37). Studies are underway to extend research beyond European and Chinese ancestry cohorts (38-40). Finally, and importantly, there could be utility in defining endotypes within T1D if they impact management e.g., studies suggest that immune therapy with teplizumab and GAD-alum might be more beneficial in DR4PRO and DR3GAD cases respectively, though these proposals need validation (41) (42). In T1D cases aged 7 years or more, a non-immune based agent, verapamil, known to reduce endoplasmic reticular stress in the beta cell, also appears to limit progressive decline of C-peptide post-diagnosis (43, 44).

Identifying T1D in the adult population can be challenging, as T2D becomes increasingly prevalent with age and cases can masquerade as T2D when they do not require insulin therapy, at least initially. Especially since, in cases presenting with GADA, many do not require insulin at diagnosis and have variable rates of progression to insulin therapy. Some, likely have false positive GADA, that is, the limited assay specificity provides a false signal, and have T2D (45) (46). The remainder may have an attenuated T1D phenotype or reflect the pleiotropic effects of variable disease-risk loci (24, 47) (48), the former, now called slowly evolving autoimmune diabetes of adulthood, and previously also referred to as latent autoimmune diabetes of adults (LADA), can initially masquerades as T2D (Table 1)(see Case1). However, combining clinical features, autoantibodies, C-peptide and genetic risk score (GRS) can help differentiate T1D (49) (50). Increasingly, clinics measure GADA in adult-onset cases, in combination with random blood C-peptide and glucose, to determine risk of progressing to insulin dependence (Figure 5). Identifying adults with T1D should also improve management, whether by informing prognosis relating to insulin dependence, risk of other autoimmune diseases including disease risks in relatives, or avoiding potentially less suitable adjunctive therapy (51).

Even cases with established T1D show that the severity of insulin deficiency correlates with clinical risk. In a recent study of 6,000 cases with poor glycaemic control (HbA1c 8.0-8.5%, 63-68 mmol/mol), over an average period of 5.2 years, those with fasting C-peptide >0.20 nmol/L had lower insulin requirement, HbA1c, and risk for both ketoacidosis and hypoglycaemia compared with cases with undetectable C-peptide (34). By inference, even minimal endogenous insulin secretion has a buffering activity on glucose homeostasis detectable many years post-diagnosis (33, 52). Efforts to limit the progression of the disease process using novel therapies, whether before clinical diagnosis following the appearance of immunologic and metabolic abnormalities, as found with teplizumab, or at clinical diagnosis, are worthwhile, given that there is a gradient effect so that the severity of insulin deficiency correlates with prognosis.

Heterogeneity within Type 2 diabetes (T2D)

Diabetes aetiology is highly heterogenous reflecting the many routes whereby defects can result in raised blood glucose. In the context of this underlying heterogeneity, the fact that T2D is a diagnosis of exclusion, where all diabetes that cannot be otherwise classified is grouped, makes the T2D heterogenous and poorly defined. In people labelled as T2D, there are varying contributions from factors that reduce beta-cell function and/or insulin sensitivity, such as genetics, aging, obesity, poor diet, physical inactivity, inadequate sleep, circadian disruption, stress and illness. Such non-genetic effects are striking when considering differences according to age at onset. Ideally, clinical recognition of this heterogeneity should improve our treatment and ability to predict progression and complications. Current management and guidelines of T2D (53) do little to incorporate disease heterogeneity into their recommendations.

Several recent studies have utilised a Palette Model to quantify T2D heterogeneity applying machine learning methods to two key types of data: 1) simple clinical measures or deeper phenotyping at diagnosis, or 2) grouping genetic risk variants based upon their aetiological processes to generate partitioned polygenic scores (pPS) and explore how T2D phenotypes differ in people with the genetic burden.

Utilising a "hard clustering" approach based on defined traits (age at diagnosis, presence of diabetes-associated autoantibodies, BMI, HbA1c, beta-cell function and indices of insulin resistance), diabetes heterogeneity was distilled using selected sets into five subtypes (54). These subtypes include a cluster of severe autoimmune diabetes (SAID), as well as four other forms, encompassing: severe insulin deficient diabetes (SIDD), severe insulin resistant diabetes (SIRD), mild obesity-related diabetes and mild age-related diabetes (54). In line with the Gradient Model, subtypes were associated with different disease trajectories e.g. severe insulin deficient diabetes had more rapid progression to insulin requirement, and severe insulin resistant diabetes had a worse renal prognosis (54) as well as being more likely to develop hepatic fibrosis (55). Subsequent studies showed that the T2D risk variants differed between subtypes, for example, the severe insulin resistant subtype was not associated with the classic T2D risk variant at *TCF7L2*, in contrast to the other non-autoimmune subtypes (56). In addition, subjects within the SIRD cluster were more likely carriers of the rs738409(G) variant in *PNPLA3*, which has been linked with NAFLD (57).

Although clinical features associated with these five adult diabetes subtypes tend to be consistent across different ethnicities (58) (59), "pigeonholing" individuals has inherent limitations, especially at the boundaries of hard clusters where the data points have similar distance from two different centroid. In contrast, utilizing "soft clustering", or "fuzzy clustering", allows individuals to be defined by more than one characteristic, given overlapping defects can contribute to diabetes in any one individual as proposed by the Palette Model (60). Such "fuzzy" or "soft" clustering has two main advantages over "hard" clustering methods. Firstly, memberships can be combined with other information. In particular, when membership of a cluster reflects probabilities, results can be combined from different sources using Bayes' theorem. Secondly, that membership for any given subject enables membership of a 'second best' cluster that is almost as good as the 'best' cluster, a phenomenon often not apparent when using other clustering techniques (61).

One such soft clustering approach, "archetypes clustering", applied to 726 deeply phenotyped adults with T2D from the IMI-DIRECT study (62), was consistent with the Palette Model: many people in the

middle of the palette show diabetes onset driven by many small defects, so they cannot be reliably allocated to a discrete subgroup, whereas in line with a Threshold Model, those at extremes of the palette can be allocated to discrete subgroups (Figure 3). Using this approach, while 65% of adults could not be reliably allocated to a discrete subgroup, the remainder could be allocated, with a >60% probability, to one of four clusters characterised by distinct pathophysiological mechanisms, and rates of glycaemic deterioration over 3-years. Finally, an alternative approach did not attempt to allocate people to discrete clusters, instead recognising the phenotypic distribution as continuous within adults with T2D (63); a non-linear dimensionality reduction approach using reverse graph embedding (DDRtree) was applied to nine routine clinical measures in 23,000 adults at diagnosis. The resulting tree structures visually represent phenotypic heterogeneity in this population, but also shows how that heterogeneity maps to risk of macro- and micro-vascular disease, progression to insulin requirement, and differences in drug response (Figure 4).

Another approach to clustering by phenotype employs genetic aetiology. By partitioning polygenic scores of different pathophysiological defects (e.g. reduced beta-cell function, obesity, lipodystrophy, altered liver metabolism), or other traits that capture these defects, five partitioned polygenic scores (pPS) were generated in adults (64) (65) using a fuzzy clustering approach. Every adult with T2D was allocated a score for each of these pPS; consistent with the Palette Model, most were in the middle of the 'palette'. Nevertheless, some adults with T2D had a high genetic burden for a particular pPS and consistent phenotypes (e.g., lipodystrophy, beta-cell deficiency, obesity with insulin resistance, differences in cardiovascular risk and renal disease) (65). Recent analysis showed that subjects with diabetes with different pPS have different rates of progression to diabetes-related outcomes. For example, those with higher obesity pPS have higher risks of developing end-stage renal disease and coronary heart disease, whereas those with elevated beta-cell dysfunction pPS have higher risk of proliferative diabetic retinopathy (66).

It is now clear that environmental, phenotypic and genetic heterogeneity are associated with heterogeneity in diabetes outcomes and drug response, an effect that underpins the Threshold Model of diabetes. That heterogeneity also results in variation in the severity of disease as in the Gradient Model, for example, in relation to progression of diabetes towards need for insulin (67) (68) (69). Although this concept of diabetes heterogeneity has been appreciated for some time, it has yet to be translated systematically into clinical diabetes care. However, a number of recent studies have progressed the field of precision medicine to the point of clinical implementation using simple clinical phenotypes. By recognising differences in sex, BMI and renal function, several studies could predict differences in drug responses to common treatments, i.e. sulphonylureas, DPP4 inhibitors, thiazolidinediones and SGLT2 inhibitors (70, 71). Importantly, observational adult primary care data and post-hoc analysis of randomised controlled trials found that reduced renal function can be used to preferentially select DPP4 inhibitor over an SGLT2 inhibitor and, from the Trimaster 3-way cross-over study, to select pioglitazone over DPP4 inhibitors when individuals have a BMI>30 kg/m^2 (72). These studies pave the way for incorporation of phenotypic heterogeneity into routine clinical care, guiding treatment choice. More work is required before genetic information is used for clinical management in T2D – although there are robust genetic determinants of drug response (reviewed in (73)), likely implementable when genetic data are routinely embedded into medical record systems.

Heterogeneity in non-autoimmune diabetes in youth

Historically, T2D was thought to occur almost exclusively in adults, as a consequence of factors noted above, most notably those linked with ageing. However, that is changing and while the overall incidence of youth-onset T1D still outnumbers youth-onset T2D, there has been a marked increase in the latter in multiple populations from Canada, the United States, through the Middle-East, to China (74, 75),(76, 77) (78). As with adult-onset T2D, youth-onset diabetes is also heterogeneous (see Case 2). The Treatment Options for Diabetes in Adolescents and Youth (TODAY) study in the United States (79) showed that most youths with T2D have obesity and are pubertal, with a very sedentary lifestyle, strong family history of T2D and/or *in utero* exposure to T2D or gestational diabetes, while in the United States they tend to be of underrepresented race/ethnicity (80). However, in line with a Threshold Model, only the minority of youth with these risk factors develop T2D, therefore other factors, both genetic and non-genetic, are likely needed to reach the threshold to develop diabetes.

Using the Palette Model, genetic factors (e.g., HLA and non-HLA alleles), including those typically associated with T2D, such as lower beta-cell function, insulin resistance and environmental factors noted above, but extending to adverse childhood experiences, can lead to diabetes in any given youth by engaging diverse pathways at a given time. Employing the Threshold Model, that interaction between genes and environment likely must reach a critical threshold to induce diabetes. Genetic abnormalities, such as those at determine insulin resistance, lower beta-cell function, or T2D-associated genes (11) may never result in clinical diabetes unless additional factors e.g., obesity or puberty exacerbate the condition. As with the Gradient Model, any combination of these factors once diabetes develops can determine disease severity. Conversely, individuals can undergo remission when insulin sensitivity improves, as when exiting puberty, or following bariatric surgery. The association between obesity and T2D is stronger in youth with younger age at presentation, while prepubertal T2D, albeit rare, appears almost exclusively in children with elevated BMI (81).

As with adult-onset T2D, phenotype clustering occurs in youth. The SEARCH study classified 2,291 recently diagnosed youth aged <20-years using diabetes autoantibodies (DAA) and insulin sensitivity (IS), the latter estimated using HbA1c, waist circumference and triglycerides, validated against hyperinsulinemic-euglycaemic clamps (82). Four categories were described based on presence or not of autoimmunity and insulin resistance. The largest categories were DAA+/IS+ve (54.5%) or DAA-/IS- ve (15.9%), which aligned with provider clinical diagnosis in 90% of cases. The DAA-/IS-ve group also had a greater urinary albumin: creatinine ratio than other groups (83). Since DAA+/IS-ve group (19.5%) had similar prevalence and levels of DAA and similar distribution of HLA risk genotypes as the DAA+/IS+ve group, thus may represent T1D in youth with obesity. The remainder (10.1%) without DAA but insulin sensitive may represent a combination of undetected autoimmunity and monogenic diabetes requiring further investigation. Using these same four categories SEARCH also found that the T1D GRS was highest in DAA+/IS+ve and lowest in the DAA-/IS-ve groups, while the converse held true for the T2D GRS. The genetic probability of T1D identified those without DAA most likely to progress to insulin requirement (39).

Just as defining T1D in adulthood is difficult, it is also difficult to determine T2D in youth given its increasing incidence, coupled with rising rates of obesity. The multi-centre SEARCH for Diabetes in Youth study in the US showed that *HNF1A, HNF4A,* and *GCK* mutations causing MODY accounted for 1.2% of diabetes cases and 7–15% of all youth cases without diabetes-associated autoantibodies (84). MODY should be considered in autoantibody-negative diabetes cases, even when obesity is present. Supporting that conclusion, the TODAY study, found that 4.5% of youth clinically diagnosed

with T2D and obesity had genetic variants consistent with MODY (85). Both insulin secretory loss and insulin sensitivity vary greatly in youth onset T2D. Recent data from both adolescents and adults with T1D and T2D found that whole-body insulin sensitivity in normal-weight youth with T1D is roughly equivalent to insulin sensitivity in nondiabetic youth with obesity, while youth with obesity plus T1D have reduced insulin sensitivity similar to youth with T2D (86). Further, adjunctive treatment with metformin (87) (88) and bromocriptine quick-release (89) have been shown in youth with T1D to lower insulin dose and improve insulin resistance, BMI, blood pressure, carotid intimal media thickness (90), and aortic stiffness (with metformin), and blood pressure and aortic stiffness (with bromocriptine). Interestingly, the metabolic syndrome phenotype characteristic of insulin resistance in youth T2D differs from that in T1D; low HDL cholesterol and adiponectin concentrations and elevated triglycerides and ectopic fat (liver, visceral and muscle fat) typical of the former are less common in the latter. Therefore, a metabolic syndrome phenotype can support the diagnosis of T2D. As noted above, in youths as in adults, those with a T2D phenotype, but single GADA, present a diagnostic challenge, and the phenotype of youth should be assessed to personalize treatment and address co-morbidities (Fig 4) (91).

Some of the conclusions about the differences between adult- and youth-onset diabetes are likely to be confounded by ethnicity, socio-demography, and temporal factors, as these tend to differ by age-group. For example, the phenotype of youth-onset T2D differs from adults, including a strong female predominance (79) (92), although some features are confounded by other factors including ethnicity, e.g., female preponderance is not apparent in Asia (93). The clinical course of youth-onset T2D is more aggressive than adult-onset T2D, with more rapid insulin secretory loss, poorer response to oral medications, and earlier onset of diabetes-related complications (see Case 4). Glycaemic failure rates and decline in insulin secretory function were more than twice higher in the TODAY study (comparing metformin alone or in combination with rosiglitazone or intensive lifestyle therapy) than in similar adult trials, despite youth having a shorter diabetes duration (94), e.g. therapy failure rate with metformin alone was 51.7% in TODAY vs. 12% in the adult ADOPT study (95). Similarly, the Restoring Insulin Secretion (RISE) Consortium, comparing 3 months of insulin glargine then 9 months metformin with 12 months of metformin, it was found that youth with T2D had lower insulin sensitivity and higher insulin secretion than adults, yet insulin secretion declined more rapidly in youth than adults in whom it was stable. Multiple studies also showed the much earlier onset of diabetes-associated complications despite shorter diabetes duration (96) (97) (98) (99) (100). These observations argue for careful categorising of youth with diabetes and aggressive treatment of their glycemia, co-morbidities and diabetes complications.

Looking to the future

To understand disease heterogeneity, one should capture the nature of that variability and define how, in any given individual, it is related to the disease pathogenesis, risk and outcome. Here we integrated three models: starting with multiple risk factors on a palette, their combination may attain a given threshold to affect a given individual to cause diabetes, while the impact of those risk factors once diabetes has developed, as well as leading up to the diagnosis, will create a gradient of disease severity, both for T1D and T2D.

We envisage integrating genetic, demographic and phenotypic data to define disease risk and disease-outcome in a given individual (51, 101) (102), recognising that it may not always be possible to assign individuals to a distinct diagnostic category. Recognition of the different pathophysiological pathways contributing to hyperglycaemia, including beta-cell dysfunction, adipose tissue dysfunction, altered incretin response etc. has highlighted the opportunity to better tailor treatment

according to underlying pathophysiology (103). Interestingly, some of the pathways leading to diabetes converge at the insulin-secreting cell endoplasmic reticulum whose stress response is regulated by gene variants common to both major types of diabetes (8); by addressing that stress response it should be possible to protect the insulin-secreting cell, indicating that early therapy could better prevent diabetes, irrespective of its cause (43) (44). Proteomic or metabolite studies should aid identification of at-risk cases e.g., using machine learning to proteomic profiles from a single fasted sample found that only three proteins (RTN4R, CBPM and GHR) could identify individuals at risk of T2D (104).

Since lifestyle and metformin can both limit progression from impaired glucose tolerance to T2D, identifying that risk at an even earlier stage should be valuable. Not least when we can exploit an arsenal of new drugs to reduce risk. We already define risk for microvascular and macrovascular disease with BMI, hypertension and dyslipidaemia. Furthermore, in line with BMI impacting progression through preclinical stages (14, 29, 30), it is already incorporated in a predictive model for T1D (102). When GRS is eventually used clinically, its utility could be expanded to diagnose diabetes type, guide treatment selections and predict treatment success, as well as define risk of vascular complications and other conditions such as coeliac disease. Such biomarkers and risk scores need to be developed into easy-to-use tools to communicate risk to clinicians and patients to guide clinical decision. Screening programmes must be made available, both locally and globally, and tailored to different ethnic groups. For example, despite GRS for T1D being different between China and Europe (105, 106), it should be possible to define a "cosmopolitan" GRS that can be used in ethnically -diverse populations, which is problematic in admixed populations, in addition to ethnicity-specific GRS (reviewed in (38)). Likewise, a multi-ethnic GRS for T2D has also been generated (66).

Defining heterogeneity of disease risk or complications risk within types of diabetes should improve the outcome of interventions, and enable us to identify factors which account for that heterogeneity. For example, endotypes identified in T1D may define the optimum immune therapy and that approach offers a signpost towards targeted therapy to be exploited in the future in all forms of diabetes. There is an ongoing international effort, led by the American Diabetes Association and European Association for the Study of Diabetes, to review the current evidence on diabetes diagnosis, classification and prognostication, with the ultimate aim to improve precision medicine in diabetes (5).

Finally, there are two important elements to population screening. First, it should not be limited to GRS, a relatively crude tool when taken in isolation, but should be integrated into an individualised package which considers demographics, family history and a broad range of clinical features as well as laboratory-based features, including proteomics (24, 107). Second, as with all screening programmes, it will be essential that the benefits and the limitations of screening are fully explained and that a robust system is in place to deal with uncertainties and with queries as they arise. As more user-friendly tools such as risk calculators or pathway-specific scores are developed, they should be incorporated into clinical service to improve diabetes care. It will require widespread engagement across different sectors to fully realize the potential of precision medicine to improve diabetes care.

Conflict of Interest:

RDL is on the Advisory Boards of Diamyd and Provention and has received educational grants from Novo-Nordisk, Eli Lily, Sanofi, Astra Zeneca and MSD. RCWM has received research funding from AstraZeneca, Bayer, Novo Nordisk, Pfizer, Roche Diagnostics (HK) Limited and Tricida Inc. for carrying

out clinical trials, and has received speaker honorarium or consultancy in advisory boards from AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Merck and Kyowa Kirin. All proceeds have been donated to the Chinese University of Hong Kong to support diabetes research. RCWM is a cofounder of GemVCare, a diabetes technology start-up, established through support from the Hong Kong Government Technology Start-up Support Scheme for Universities (TSSSU). ERP has received honoraria for speaking from Lilly, Novo and Illumina. The other authors have no conflicts to disclose.

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Contributions statement:

RDL, RCWM, PWF, KJN, ERP, MJR all contributed to the conceptualisation, data curation, formal analysis, visualization, writing original draft, and writing-review and editing of the revised manuscript. RDL and RCWM contributed equally and should be considered joint first authors.

Box- Illustrative cases

Case 1- A lean fit man presents at age 33 with diabetes diagnosed on the basis of both oral glucose tolerance and HbA1c. He has a family history of T1D and his monozygotic twin has T1D diagnosed at age 14 years with HLA-DR4 and GADA alone. Multiple testing for diabetes-associated autoantibodies were initially positive at an earlier age but subsequently negative and his random serum C-peptide was >600 pM. He had thyroid autoantibodies but was euthyroid. Started on metformin he was intolerant to it and put on a DPP-4 inhibitor. He remains on a DPP-4 inhibitor 15 years later with HbA1c <53 mmol/mol/ 7.0%.

Case 2- A 43 year-old Chinese man was found to have hypertension at health check, and was also found to have elevated blood glucose of 13mmol/l, with preceding weight loss of 20 lbs. BMI 21.7 kg/m^2. HbA1c 119 mmol/mol /13% at presentation. Family history of diabetes present. Started metformin and sitagliptin initially by primary care physician and referred for specialist evaluation. HbA1c improved and condition then stable with HbA1c 44 mmol/mol /6.2% on metformin alone. Further evaluation showed adequate fasting C-peptide of 1026pmol/l, and GADA and anti-IA2 antibodies were negative. Gene screening panel for monogenic forms of diabetes including Lamin A/C gene were all negative. GRS showed high polygenic risk for T2D.

Case 3- A 10 year-old girl presented with polyuria and polydipsia (HbA1c was 108 mmol/mol /12% and fasting blood glucose 250 mg/dL / 14 mmol/l), marked ketonuria, and autoimmune primary hypothyroidism (initial TSH 15.8, free T4 1.0 ng/dl [0.7-1.9] and positive thyroid peroxidase autoantibodies). She had acanthosis nigricans, was in puberty with height at the 75th centile and weight BMI both above 97th centile (i.e. obesity). She also had high triglycerides, low HDL and elevated liver enzymes. Antibodies against GAD, insulin, islet cell and zinc transporter were all negative. Her parents were overweight with dyslipidaemia and hypothyroidism. She was initially treated with levothyroxine and insulin infusion. The latter was then replaced with long-acting insulin and metformin. Subsequently, insulin was stopped and metformin continued.

Case 4- A 12 year-old Asian (from Indian subcontinent) boy was diagnosed one year earlier with diabetes ketoacidosis and presumed T1D with single GADA positive (negative for IA-2, insulin and ZnT8 autoantibodies). He did not have HLA DR3 or DR4. A screen for MODY genes was negative. His father had T2D. The patient was started on insulin, but he was able to come off insulin 3 weeks after onset, and 8 months post-diagnosis had a HbA1c of 38 mmol/mol /5.6% with random C-peptide 773 pM, though he remains GADA positive.

Learning Points from the cases:

- Diabetes with GADA is not invariably and initially insulin-requiring (case 1, case 4)
- Asian and African cases may not fit into phenotypes as designated by European and American studies (case 2, case 4) e.g. without high risk HLA variants or obesity.
- C-peptide can help decide whether insulin treatment is imperative (case 1, case 2)
- Even ketoacidosis in children is not inevitably associated with early insulin-dependence (case 3, case 4)

Figure legends.

Figure 1. Conceptual diagram illustrating three different models to illustrate heterogeneity of common diseases including the Palette Model, the Threshold Model and the Gradient Model. Upper panel highlights the general concept of the models, whilst the lower panel provides examples when the models are applied in the context of diabetes heterogeneity. The Palette Model illustrates how multiple risk-factors (genetic and non-genetic) can contribute to a given disease. The Threshold Model illustrates how, in any given individual, some but not necessarily all, risk factors will be of sufficient severity that the altered tissue function crosses a threshold leading to clinical disease. The Gradient Model illustrates how the same disease-risk factors leading to the clinical disease will impact the severity of that clinical disease post-diagnosis, which will vary between individuals. In the top figure, a circular dot represents risk-factors associated with diabetes, be they genetic, non-genetic or disease-associated pathways and networks. In the Threshold Model, each colour represents those same processes in given individuals of sufficient intensity, operating in tandem, to lead to clinical disease. Once the disease develops, it will be of variable severity as shown in the Gradient Model, and that severity will reflect the intensity of those factors leading to the disease in the first place.

In the figure depicting the palette model, each colour represents example of an underlying aetiological process, such as:

Green = lipodystrophy

Blue = obesity and insulin resistance

Red = beta-cell deficiency

Purple = disorders of incretin action

Yellow = beta-cell autoimmunity

Most people with T2D are 'grey' and represent a mixed aetiology.

In the threshold model, increasing severity from yellow to red indicate varying severity of the defect in for a particular tissue dysfunction, e.g. insulin secretory dysfunction, and hence increasing risk of diabetes once a threshold is reached for the diagnosis of diabetes

In the gradient model, individuals can be viewed as being on a continuum of risk post-diagnosis of "T1D" or "T2D", in terms of different prognosis, including progression to insulin.

Figure 2. Conceptual diagram illustrating the heterogeneity of diabetes in terms of underlying pathophysiological defects, relative contribution of genetic factors, and its impact on progression to hyperglycaemia. Figure adapted from Redondo et al, Diabetologia 2020 (9).

Figure 3. A visualisation of the heterogeneity of diabetes, based upon an extension of the Palette Model (60) and reproduced from reference (62).
Each colour represents an aetiological process, and each dot, a person with diabetes, with increasing depth of colour representing a greater contribution to the diabetes aetiology. For example:

Green = lipodystrophy

Blue = obesity and insulin resistance

Red = beta-cell deficiency

Purple = disorders of incretin action

Yellow = Beta-cell autoimmunity

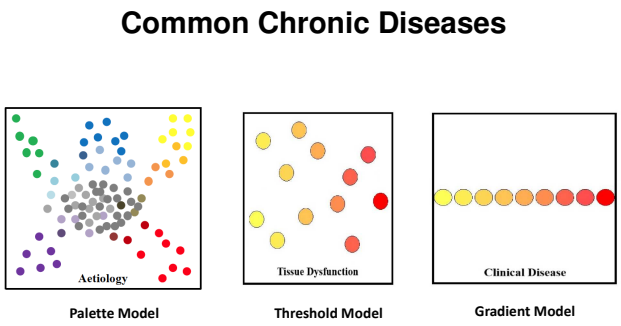
Most people with T2D are 'grey' and represent a mixed aetiology; some with T2D are deeper in colour as they have diabetes due predominantly do a defect in that pathway. The aetiological drivers of T1D and monogenic diabetes are largely distinct but there are people who have overlap in aetiology for their diabetes. PC1 and PC2 represent the principal components 1 and 2, respectively.

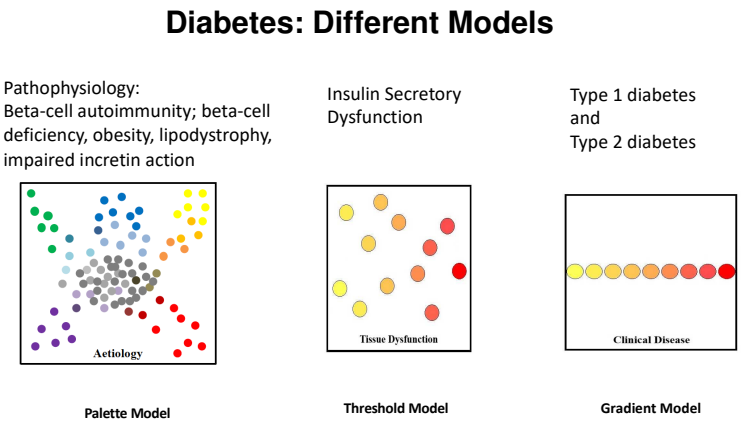
Figure 4. Schematic diagram highlighting the phenotypic heterogeneity of diabetes. People with newly diagnosed T2D can be represented on the tree based upon nine phenotypic characteristics. The phenotypic values are overlayed on a tree structure to visualize the distribution of the nine phenotypic traits over the tree structure. Magenta colour indicates high value whereas green colour indicates low value of the phenotype. Figure reproduced from Nair et al, Nature Medicine 2022 (63).

Figure 5. Suggested algorithm for the evaluation of diabetes at presentation according to age and disease duration exploiting diabetes-associated autoantibodies, C-peptide and T1D GRS.

Key: T1D GRS: T1D genetic risk score
AABBCC (see text): Age, Autoimmunity, BMI, Background, Control (HbA1c), Complications.

Figure 1.


Common Chronic Diseases
Aetiology
Tissue Dysfunction
Clinical Disease
Palette Model
Threshold Model
Gradient Model


Diabetes: Different Models
Pathophysiology:
Beta-cell autoimmunity; beta-cell deficiency, obesity, lipodystrophy, impaired incretin action
Insulin Secretory Dysfunction
Type 1 diabetes and Type 2 diabetes
Aetiology
Tissue Dysfunction
Clinical Disease
Palette Model
Threshold Model
Gradient Model

637 Figure 2.

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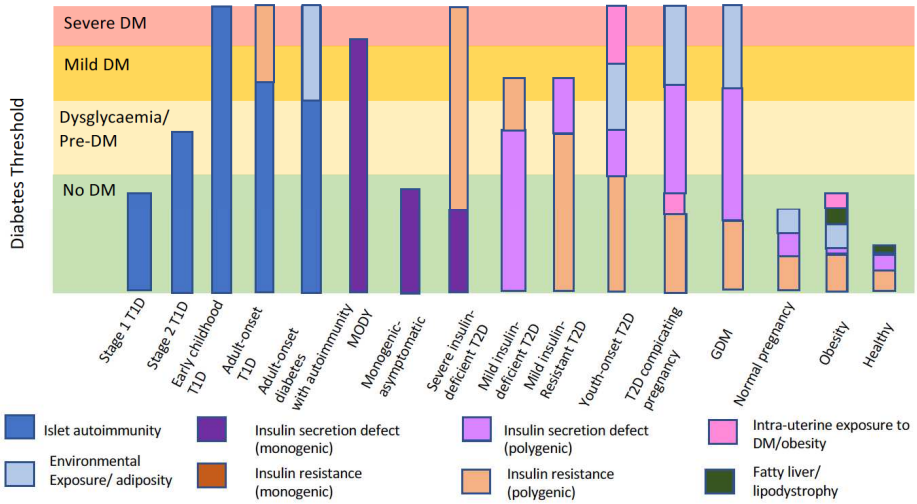

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Figure 3.

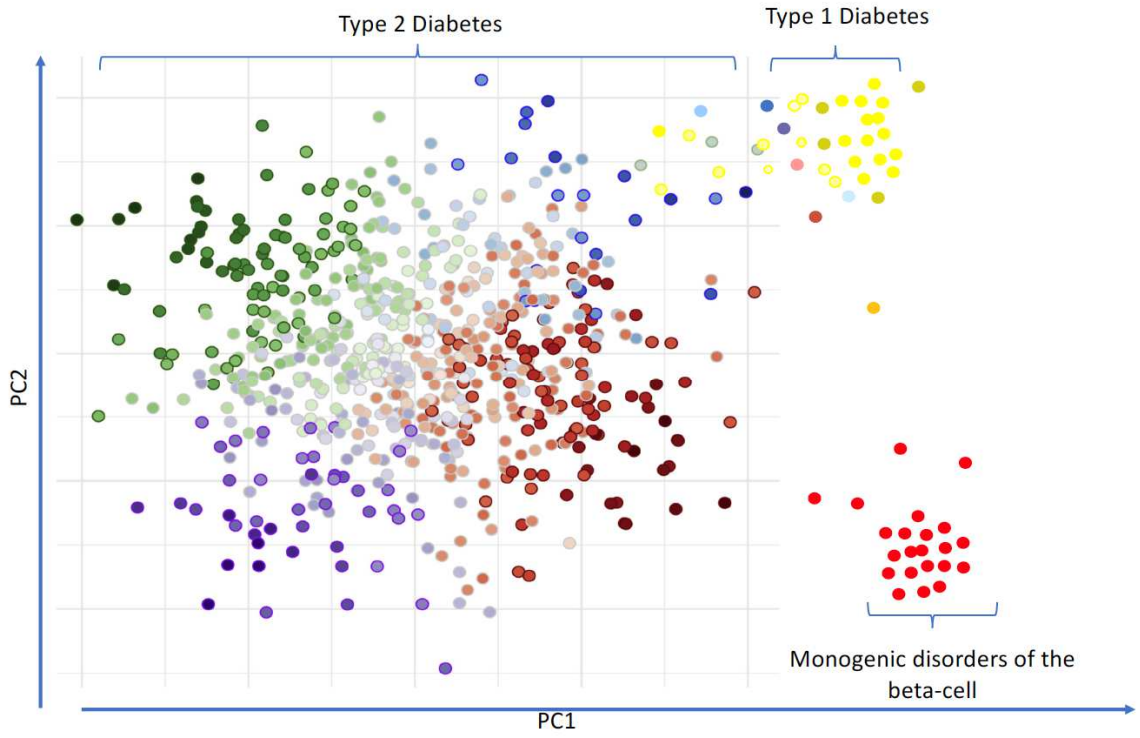
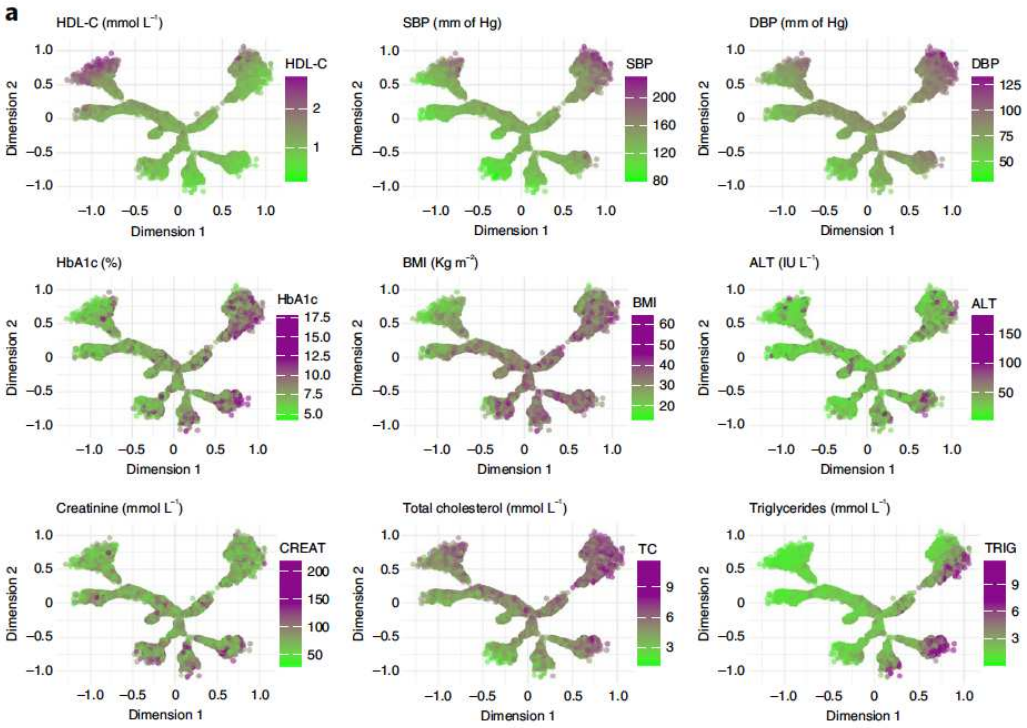

Type 2 Diabetes
Type 1 Diabetes
PC2
PC1
Monogenic disorders of the beta-cell

Figure 4.


a
HDL-C (mmol L⁻¹)
SBP (mm of Hg)
DBP (mm of Hg)
HbA1c (%)
BMI (Kg m⁻²)
ALT (IU L⁻¹)
Creatinine (mmol L⁻¹)
Total cholesterol (mmol L⁻¹)
Triglycerides (mmol L⁻¹)
Dimension 1
Dimension 2

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671 Figure 5.

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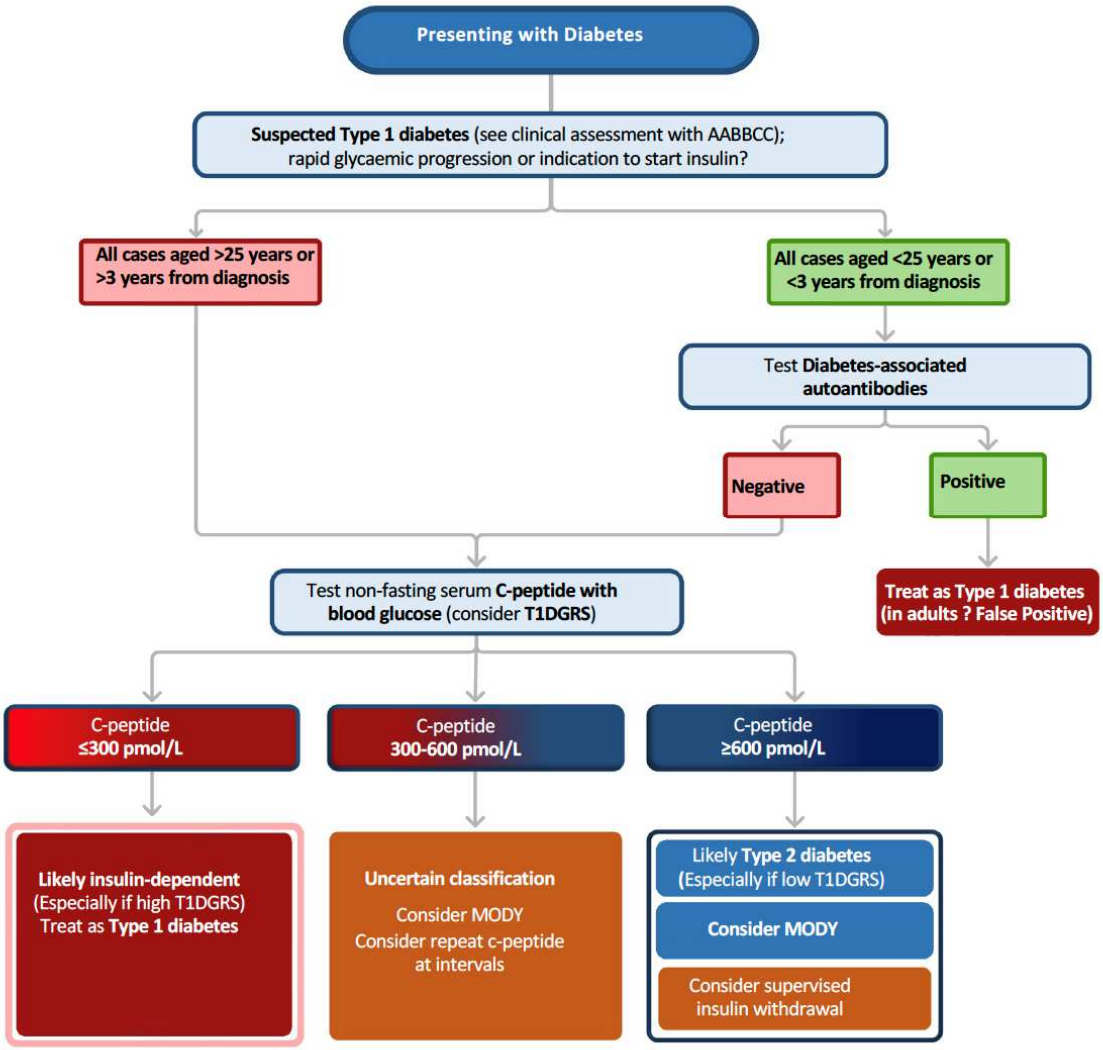

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678 Table 1. Types of diabetes according to current 2019 WHO classification (table adapted from (6))

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Types of diabetes	Brief description	Clinical implications	Updates from previous classification
Type 1 diabetes (T1D)	Immune-mediated beta-cell destruction and absolute insulin deficiency. Onset most commonly in childhood or early adulthood	Requires insulin	T1D subclasses now removed
Type 2 diabetes (T2D)	Most common type, various degrees of beta-cell dysfunction and insulin resistance. Commonly, but not invariably, associated with overweight, obesity, inactivity and metabolic syndrome.	Individuals assumed to have "T2D" when not fitting apparent T1D or other forms. Variable demographics and disease course. Different treatments now for different pathophysiologies	T2D subclasses now removed
Hybrid forms of diabetes			
Slowly evolving, immune-mediated diabetes of adults	Similar to slowly evolving T1D in adults, with a single GAD autoantibody, initial preservation of beta-cell function, often may have features of metabolic syndrome	Variable course but ultimately often require exogenous insulin.	Change in nomenclature-previously referred to as Latent Autoimmune Diabetes of Adults (LADA)
Ketosis-prone diabetes	Presents with ketosis and insulin deficiency, which resolves, at least initially. Variable pathophysiology includes T1D and T2D.	May require insulin initially, but with variable disease cause and course	
Other specific types			

Monogenic diabetes - Monogenic defects of beta-cell function - Monogenic defects in insulin action	Caused by specific genetic mutations, with presentation ranging between the neonatal period and early adulthood. Caused by specific mutations leading to severe insulin resistance in absence of obesity	Different pancreatic and extra-pancreatic clinical manifestations with specific treatment implications.	Updated nomenclature to highlight specific genetic defects
Type 3 diabetes (Diseases of exocrine pancreas)	Caused by various injury to the pancreas	Exocrine pancreas now implicated in T1D and T2D diabetes	
Endocrine disorders	Occurs in diseases with excessive production of hormones that antagonize insulin action	Treatment of underlying condition may improve glycaemia	
Drug or chemical-induced	Secondary to chemicals that affect insulin secretion or action	May be reversible; consider switching responsible medication	
Infection-related diabetes	May be due to direct virus-related beta-cell destruction; systemic inflammation; stress-related insulin resistance; etc	May or may not be reversible	
Uncommon specific forms of immune-mediated diabetes	Associated with rare immune-mediated diseases		
Other genetic syndromes sometimes associated with diabetes	Rare genetic or chromosomal disorders linked to diabetes through various mechanisms	Variable implications on treatment, with some requiring early insulin treatment	
Unclassified diabetes	For cases that do not fit		

	into any of the categories		
Hyperglycaemia first detected during pregnancy			
Diabetes mellitus in pregnancy	T1D or T2D first diagnosed during pregnancy	May be confused with gestational diabetes mellitus (GDM). Associated with increased risk of pregnancy complications.	
Gestational diabetes mellitus (GDM)	Hyperglycaemia first presenting only in pregnancy, with high-risk of later progression to T2D	Affects significant proportion of pregnancies using current thresholds of diagnosis.	Defined by the WHO 2013 criteria for GDM

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