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Type 1 diabetes presenting in adults: Trends, diagnostic challenges and unique features

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Abstract

Type 1 diabetes (T1D) has been historically regarded as a childhood-onset disease; however, recent epidemiological data indicate that adult-onset T1D accounts for a substantial proportion of cases worldwide. There is evidence that adult-onset T1D is associated with the classic T1D triad of elevated genetic risk, the presence of islet-specific autoantibodies and progression to severe insulin deficiency. In this article, we review our understanding of the commonalities and differences between childhood and adult-onset T1D, and we highlight significant knowledge gaps in our understanding of the diagnosis, incidence, trajectory and treatment of adult-onset T1D. Compared to children, adults presenting with T1D exhibit differences in genetic risk, immunologic profiles and metabolic outcomes, including differences in the type and number of autoantibodies present, genetic associations and total genetic burden, rates of C-peptide decline, the persistence of C-peptide in long-duration disease and glycaemic control. In addition, obesity and metabolic syndrome are increasingly common in adults, which not only blurs the clinical distinction of adult-onset T1D from type 2 diabetes (T2D) but also likely contributes to differences in metabolic outcomes and rates of progression. Because T2D is so prevalent in the adult population, adult-onset T1D is misclassified as T2D in at least one in three cases, leading to delays in appropriate treatment. Current diagnostic tools, including autoantibody testing and C-peptide measurement, are underutilised or lack specificity in distinguishing adult-onset T1D from atypical T2D. Additionally, the impact of different responses to disease-modifying therapy between adults and children is unclear. Addressing these knowledge gaps requires expanded epidemiological studies, diverse patient registries and refined classification criteria to improve early detection and treatment strategies. A deeper understanding of adult-onset T1D will be critical to reduce the burden of misdiagnosis, lead to earlier diagnosis and treatment and optimise population-based screening approaches in this under-recognised population.

Plain Language Summary

Type 1 diabetes (T1D) is an autoimmune disease that causes metabolic and nutritional complications due to the destruction of insulin-producing pancreatic β cells. T1D was formerly known as "juvenile diabetes" because it was assumed that most

cases occurred in childhood; however, recent epidemiological data show that nearly half of all T1D cases are diagnosed in adulthood. Despite the high prevalence of adult-onset T1D, there are challenges with correctly diagnosing T1D in adulthood, and significant knowledge gaps remain regarding the incidence, trajectory, and treatment of adult-onset T1D. In this article, we summarize the current understanding of commonalities and differences between childhood and adult-onset T1D. Particularly, we highlight age-related differences in genetic risk, immunologic profiles, and metabolic outcomes and complications. Finally, we highlight key gaps in our understanding of adult-onset T1D that need to be addressed to reduce the burden of misdiagnosis and allow for better screening and treatment of T1D in adulthood.

KEYWORDS
basal insulin, beta cell function, diabetes complications, type 1 diabetes

1 | EPIDEMIOLOGY OF ADULT-ONSET TYPE 1 DIABETES

Type 1 diabetes (T1D) has historically been viewed as a disease with childhood onset; however, increased recognition/identification of adults with T1D and recent epidemiological studies show that adult-onset T1D represents a substantial number of T1D cases worldwide.[1,2] Even though yearly childhood T1D incidence is higher, data from several countries suggest that adult-onset T1D is more prevalent than childhood-onset T1D,[3–6] as adulthood represents many more years at risk. For example, disease incidence among a US population of commercially insured individuals demonstrated a lower incidence rate for adults 20–64 years of age (18.6/100000) compared to youth 0–19 years of age (34.3/100000); however, the total number of adult-onset T1D cases in the 14-year period (2001–2015) was higher in adults than children (19 174 adult-onset cases versus 13 302 childhood-onset cases).[3]

A recent systematic review from 32 countries and regions highlighted several substantial knowledge gaps that exist in our understanding of the prevalence of adult-onset T1D.[1] Key takeaways from this comprehensive analysis include: (1) adult-onset T1D incidence closely parallels the patterns observed in childhood-onset disease: 92% of included studies showed higher incidence in men compared to women; (2) higher rates were found in Nordic populations compared to Asian populations; (3) the incidence of T1D onset in adulthood is substantial, but there is no clear pattern of elevated risk with increasing age within the adult population (58% of included studies reported an increased incidence with age and 42% of studies reported decreased incidence with increasing age) and (4) there is a general lack of data and understanding of the epidemiology of adult-onset T1D, particularly in low-and middle-income countries.

Taken together, these epidemiologic data show that adult-onset T1D represents a large number of newly diagnosed cases, in many instances accounting for nearly half of all new cases of T1D.[2–8] However, our understanding of the incidence and trajectory of adult-onset T1D lags behind our understanding of childhood-onset T1D due to a paucity of natural history data, especially prior to seroconversion, and frequent misclassification of diabetes subtype when diagnosed in adulthood. Importantly, some cases of T1D presenting in adulthood are labelled as 'latent autoimmune diabetes in adults' (LADA), but it remains controversial as to whether there are true epidemiological, clinical or pathophysiological distinctions between adult-onset T1D and LADA. Furthermore, this artificial subdivision may contribute to misclassification and suboptimal treatment. In this article, we refer to T1D presenting in adulthood as a singular entity, while acknowledging that there is heterogeneity within this population, including differences in rates of C-peptide decline within adults that is not well understood.

2 | DIAGNOSTIC CHALLENGES AND UNIQUE FEATURES

As the prevalence and burden associated with adult-onset T1D is better recognised, the question of how to most accurately identify disease in adults becomes increasingly important. Identification of adult-onset T1D is important because the hallmark of progressive autoimmune β cell loss commonly necessitates the use of exogenous insulin as the mainstay of treatment. The erroneous treatment of those with adult-onset T1D with therapeutics normally used to treat type 2 diabetes (T2D), including dietary modification or oral agents, leads to poor glycaemic control and a higher risk of acute and chronic complications.[9–12] In addition to allowing for correct therapeutic management, an accurate diagnosis for T1D in adulthood is clinically important for several additional reasons: (1) qualification for treatment with emerging immunotherapies for T1D, (2) optimal family screening and monitoring, (3) qualification for continuous glucose monitors and other diabetes technology, which may be restricted by third party and government payers, and (4) proper monitoring for additional associated autoimmune conditions in affected individuals.

The most prevalent form of diabetes in adults is T2D, which accounts for 90%–95% of all diabetes cases in adults. This proportion is in contrast to paediatric diabetes, where T1D accounts for >90% of

all diabetes cases. The low prior odds of a person with newly diagnosed adult-onset diabetes having T1D raises a real challenge for accurately identifying T1D in adults. As a result, many cases of adult-onset T1D are initially incorrectly diagnosed as T2D in clinical care. Additionally, the difference in prior odds of T1D between children and adults means that individual features that are either highly suggestive or confirmatory of paediatric diabetes are less discriminative on their own in adults.[9] Features considered to be associated with T1D (lower body mass index, ketoacidosis at presentation, islet autoantibodies) can also be present in T2D. In adults, presentation with any of these features on their own is more likely to be associated with 'atypical' T2D rather than classical T1D, due to the overwhelming prior odds of T2D in this age group.

By self-report, misclassification of adults presenting with T1D occurs in nearly 38% of people.[10] A UK registry study showed that a remarkably similar percentage of people ultimately diagnosed with adult-onset T1D due to progression to severe insulin deficiency were initially clinically diagnosed with T2D and treated with non-insulin therapies.[13] An analysis of electronic health record (EHR) data in the United States showed a similar rate of diabetes misclassification in adults, with 30%–40% of T1D cases being misclassified as T2D.[14] Conversely, misclassification of T2D as T1D also occurs and influences the average clinical features of adult T1D studies by inadvertently including T2D cases.[9] For example, one study demonstrated that one-sixth of people with a clinical diagnosis of T1D in adulthood had persistently high levels of C-peptide, low frequency of autoantibody positivity and low genetic risk for T1D, suggesting a misclassification. Interestingly, 22% of the individuals who were misclassified as having T1D and then reclassified were able to stop insulin therapy.[15] This misclassification becomes even more important as the availability of EHR data for medical research is coupled with newly developed algorithms or 'computable phenotypes' that can be applied to find T1D cases.[16] There is a need for close scrutiny to ensure that EHR-derived diagnoses are correct, and these algorithms need to be validated against standard and robust biomarker confirmed definitions of T1D. A study by Thomas et al. highlighted that all EHR/biobank definitions of T1D are imperfect and vary in accuracy, sensitivity and specificity, and this is extremely important to consider due to increasing dependence on EHR data in epidemiology, clinical care and medical research.[17]

Given the challenges in accurately identifying adult-onset T1D, an important question is how both clinical features and biomarkers can be combined to aid in classification. Autoantibodies serve as the most reliable biomarker available for T1D diagnosis, and a recent major shift in thinking in the T1D field has been the recognition and adoption of pre-clinical stages of T1D based on the presence of autoantibodies.[18] Stage 1 T1D is defined by the presence of two or more autoantibodies in the absence of abnormal glucose; stage 2 disease is defined by two or more autoantibodies and dysglycaemia and Stage 3 is defined as clinical diagnosis of new-onset T1D. The majority of natural history studies in T1D, especially those that have informed this new staging paradigm, were undertaken in children. An example is the landmark meta-analysis of several birth cohort studies by Ziegler, which showed that over 80% of children with two or more autoantibodies progressed to a clinical diagnosis of T1D by the end of childhood.[19]

Whether this exact staging paradigm and progression risk is identical and/or valid for application in adults remains to be fully demonstrated. Cross-sectional cohorts like the TrialNet Pathway to Prevention study have shown that progression from either single or multiple autoantibody positivity to clinical T1D diagnosis is slower in adults compared to children.[20] In addition, within TrialNet, the 5-year rate of progression to diabetes in multiple autoantibody-positive adults was only ~15%.[21] A number of epidemiological studies have been performed in adults following either the development of autoantibodies or Stage 3 diabetes onset (Table 1). However, there is very little data on when incident adult cases first developed autoimmunity, and there are no natural history studies of adults that include time before seroconversion. Therefore, there are major knowledge gaps in the understanding of when autoantibodies develop in those who progress to a diagnosis of adult-onset T1D, the length of time it takes to progress to T1D, and how this progression differs compared to childhood-onset T1D. It is important to address these differences between children and adults to facilitate screening for adult-onset T1D, to inform natural history studies and to identify adults who could be treated before the clinical onset of T1D. In the following sections, we summarise what is known about the unique genetic, immunologic and metabolic features of adult-onset T1D. In addition, we highlight knowledge gaps and opportunities to increase our understanding of adult-onset T1D (Table 2 and Figure 1).

2.1 | Genetic and immunologic features of adult-onset T1D

Approximately 50% of the heritability of childhood-onset T1D is attributed to variation in human leukocyte antigen (HLA) alleles, with over 75 additional loci now associated with T1D in the largest genome-wide association study to date.[22] Compared to childhood-onset disease, adult-onset T1D cases show lower disease concordance rates between twins,[23] less high-risk HLA heterozygosity[24] and more protective genotypes,[25,26] leading to overall lower genetic risk scores (GRS)[4,27] in adult compared to childhood-onset T1D. In one of the earliest large adult T1D studies, Howson included over 1300 individuals with a clinical diagnosis of insulin-treated T1D, combined with at least one positive autoantibody and highlighted a high degree of genetic overlap between adult- and childhood-onset T1D, with very similar impacts on the risk of genetic loci (HLA and non-HLA) known to associate with paediatric T1D. Despite this similarity, a universal observation is that genetic risk for T1D seems to slightly reduce with age, whether measured as individual risk allele frequencies, frequency of high-risk HLA, or when combined into a polygenic score as a T1D GRS. A slightly reduced T1D GRS with increasing age of paediatric diagnosis has been shown multiple times,[28,29] and more recently,

TABLE 1 Epidemiological studies of adults with autoantibody positivity and T1D.

Study	Cohort	Findings	References
Pre-stage 3 diagnosis			
TrialNet pathway to prevention	Relatives of individuals with T1D are screened for autoantibodies and monitored longitudinally	Risk of progression from autoantibody positivity to Stage 3 T1D is lower in adults versus children	20,21,89
Diabetes prevention Trial of type 1 diabetes (DPT-1)	The DPT-1 study enrolled multiple autoantibody-positive individuals and tested the efficacy of either parenteral or oral insulin in delaying the progression to Stage 3 disease	Similar declines in β-GS and insulin sensitivity in those progressing to T1D when split by age above and below 14 years. In addition, DPT-1 data was used by Sosenko et al to model the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS), which is based on log-BMI, age, log-fasting C-peptide and post-challenge glucose and C-peptide sums from 2-h oral glucose tolerance tests. The DPTRS accurately predicts T1D risk in autoantibody-positive individuals	61,90
Post-stage 3 diagnosis			
TrialNet	Individuals from TrialNet intervention studies	Age affected decline in C-peptide and β-GS post diagnosis	68,73
European registry study	Adults and children with T1D and post diagnosis C-peptide	Positive correlation between age at T1D diagnosis and fasting C-peptide; more rapid decline of β-cell function in those with very young age of diagnosis	91
Startright	Autoantibody confirmed clinical T1D	Similar rate of C-peptide decline post-diagnosis across adults above and below 35 years	31
T1D Exchange	Cross-sectional study of clinical T1D, including those with short and long-duration disease	Adults have more frequent and higher persistent C-peptide	92
UNITED	Cross-sectional study clinical T1D	Older age of diagnosis associated with C-peptide levels	93
SDRNT1BIO	Cross-sectional study clinical T1D	Older age associated with higher C-peptide level. Associations with T1D and T2D genetic risk. C-peptide associated with reduced complications.	94,95
Diabetes control and complications trial (DCCT)	Randomised trial of intensive glycaemic control	Higher C-peptide reduces risk of complications	96–98

Thomas confirmed this trend by comparing T1D GRS between adults and children in the ADDRESS 2 study,[30] a UK diabetes cohort study[13] and Startright (a cohort of autoantibody confirmed clinical T1D).[31] There are fewer novel loci that have been discovered when studying the age of diagnosis alone, and they have only focused on large samples of paediatric diabetes. Therefore, it is unclear if we will obtain more genetic insights into adult-onset T1D as larger samples of adult cases are collected, and we are able to perform association studies across the full age range of diagnoses. In aggregate, adult T1D has been much less genetically studied than paediatric diabetes, but the best evidence to date highlights considerable overlap in children and adults, albeit with a slightly reduced overall genetic burden when aggregated as a T1D GRS.

Adult-onset T1D has similar autoantibody associations as childhood-onset T1D, with GAD65, IA2, ZnT8, insulin and islet cell autoantibodies all being present in adult-onset T1D. However, adults diagnosed with T1D most often present with GAD65 positivity,[26,27,32–36] and adults are more likely to be single autoantibody positive at diagnosis compared to both children and adolescents.[37] Importantly, high levels of GAD65 positivity are closely associated with a rapid decline in C-peptide, deteriorating metabolic control and the need for insulin treatment, suggesting that measurement of GAD65 autoantibodies is valuable both as a diagnostic and prognostic tool.[38–40] Additionally, while reversion of multiple autoantibody status occurs in slightly more than 4% of people overall, adults were more likely than children to become zero or single antibody positive after being identified as multiple antibody positive.[41] It is worth noting that for some autoantibodies, there is evidence that normal ranges may be different in adults and children. For example, ZnT8 autoantibodies have a higher normal range in individuals <30 years of age.[42] It is also important to note that a significant proportion of a background population will be autoantibody positive based on the way normal ranges and positive tests are defined (commonly by an autoantibody titre >97.5th or 99th percentile of a reference population). Thus, caution must be applied when analysing data from cohorts where there is the possibility of a false-positive autoantibody test.[9,43] Furthermore, at the individual level, autoantibody false positives can have a tremendous impact on screening efforts that are increasingly being applied in the general population.

Beyond autoantibody phenotypes, T1D is associated with changes in both innate and adaptive immune cell signatures and function. In addition to analyses performed in living cohorts, studies of pancreata collected from individuals soon after death or from organ donors are available in a number of biorepositories. These tissues

TABLE 2 Current gaps in understanding of type 1 diabetes presenting in adults.

Category	Gaps
Epidemiology	• Limited data on adult-onset T1D prevalence, especially in low- and middle-income countries. • Lack of diverse international registries for adult-onset T1D. • Accuracy of diagnosis within cohorts, the medical record, and in insurance claims can influence epidemiological data and conclusions.
Genetics and immunological features	• Unknown timing of autoimmunity onset in adults. • Unclear progression rates from autoantibody positivity to clinical T1D in adults. • 'Biologic' false positives for autoantibodies have been proposed, but this is a poorly defined term. • Uncertainty around genetic risk differences between adult- and childhood-onset T1D. • Tissue biorepositories are useful but still have limited numbers of donors.
Metabolic features	• Limited understanding of the extent of metabolic differences between adult- and childhood-onset T1D. • Need for better biomarkers to predict disease course in both adults and children. • Limited analysis of longitudinal C-peptide trends in adults prior to seroconversion, after seroconversion and after Stage 3 onset. • Unclear role of insulin resistance in both adult- and childhood-onset T1D. • What are the factors that account for discrepancies observed between cohorts examining the impact of age on C-peptide decline? • Is C-peptide decline a continuous gradient or are there critical inflection points? If the latter is true, do these inflection points differ by age either in timing, severity or underlying aetiology? • Are there differences in exocrine pancreas loss across the lifespan?
Diagnosis, classification and treatment	• High rate of misclassification as T2D in adults due to overlapping clinical features. • Limited validated diagnostic tools and biomarkers for distinguishing adult-onset T1D from atypical T2D. • Genetic tests and risk scores have not been integrated into clinical use for either children or adults. • Lack of consensus on optimal screening and classification strategies for adult-onset T1D. • Limited guidance on best treatment approaches, especially for those adults initially misclassified as T2D. • Unclear impact of misclassification on long-term outcomes and complication status. • Limited guidance on the development of personalised goals for glycaemic management and complication avoidance.

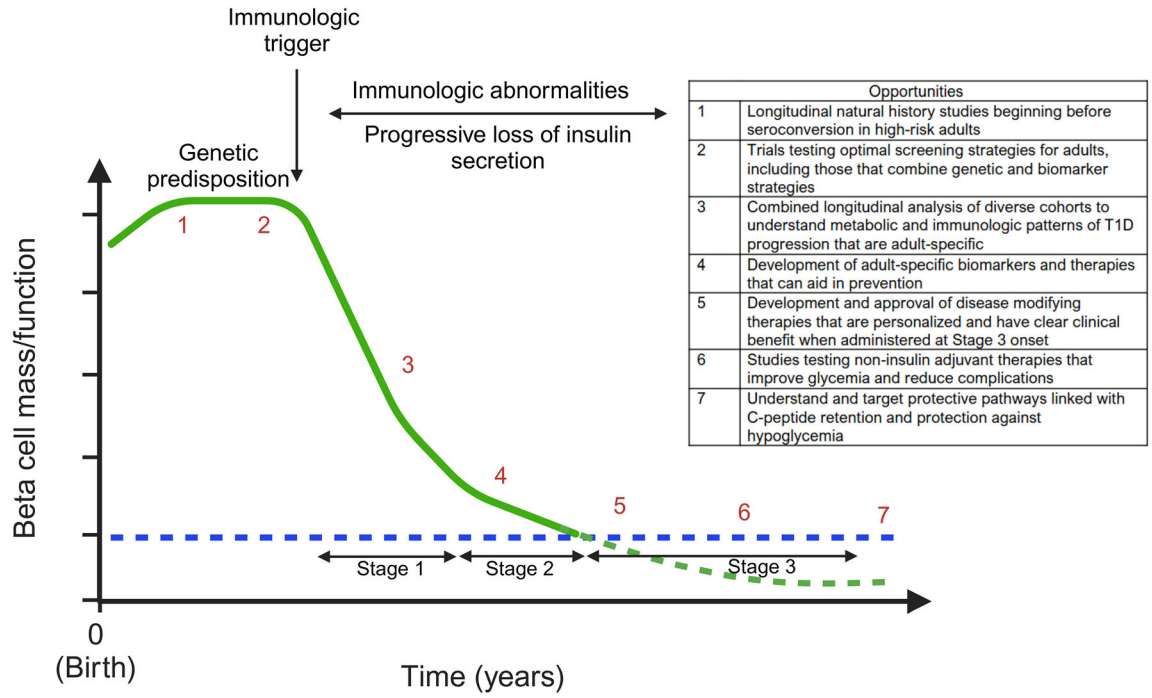

FIGURE 1 Opportunities to increase our understanding of type 1 diabetes presenting in adults.

have enabled centralised analysis using multi-omics approaches, as is done in the Human Pancreas Analysis Program, as well as investigator-initiated studies, as is the model for the Network for Pancreatic Organ Donors with Diabetes (nPOD).[44–46] Limitations of these collections are that they provide a purely cross-sectional view of disease pathogenesis, sample sizes are limited, and organ donors

often undergo prolonged hospitalisations and intensive care before death. However, analysis of these tissues provided unique insight into age-related differences in the pancreas of individuals with T1D. Age-stratified analyses have shown that the frequency of insulitis decreases with increasing disease duration and is more commonly observed in those with an early age of T1D onset.[47,48] The composition of insulitic lesions also varies with age. In those diagnosed with T1D in early childhood, insulitic lesions are characterised as 'hyperimmune' with an increased proportion of both CD8+ T cells and CD20+ B cells.[49] Consistent with an exaggerated immune response, islets from younger individuals have higher proinsulin expression and reduced insulin expression.[50] Similarly, residual insulin-containing islets are more prevalent in those with a later age of onset.[51]

How immune phenotypes in the pancreas relate to circulating immune signatures is not clear. A number of studies have described changes in adaptive and innate immune signatures in T1D, but the impact of age on these signatures has not been well studied. One study attributed age-related changes in immunoregulatory phenotypes and regulatory T cells as a reason for reduced age-related T1D incidence.[52] A recent large cross-sectional analysis of >800 individuals across the lifespan using flow cytometry highlighted a number of age-associated findings. Age was associated with increased numbers of $CD4^+$ T cells and decreased numbers of B cells and $CD8^+$ T cells, as well as shifts from naive to memory cell populations in adaptive immune cells. Overall, T1D was associated with an accelerated aging phenotype, and this was independent of sex, race, ethnicity and a polygenic T1D risk score.[53]

2.2 | Metabolic features of adult-onset T1D

The development of the T1D staging system has provided a standardised framework to study disease prior to and after the onset of clinical disease. This paradigm has been useful in segmenting disease evolution for clinical trial purposes. However, whether diabetes evolution represents a continuous gradient of metabolic severity or whether there are metabolic inflection points or distinct disease mechanisms and trajectories within or between T1D stages is unknown. Notwithstanding this uncertainty, there are some analyses of differences in metabolic phenotypes between adults and children both before and after Stage 3 T1D onset. Notably, fewer studies have been performed prior to the onset of Stage 3 T1D, and in those that have reported comparisons, an age-stratified analysis may not have been the primary question. For example, in an analysis of data from the natural history TrialNet Pathway to Prevention study, patterns of C-peptide loss and glycaemia were determined in autoantibody-positive individuals who progressed to T1D after <5 and ≥5 years of follow-up. Progressors with <5 years of follow-up were younger at study entry and had a younger age of diabetes diagnosis compared to those who progressed at ≥5 years of follow-up. The median age of T1D onset in progressors with <5 years of follow-up was 11.6 years compared to a median age of onset of 17.0 years in progressors ≥5. Interestingly, within 3 years of diagnosis, patterns of change in C-peptide AUC and other measures derived from oral glucose tolerance tests were similar between the two groups, suggesting that the progression of β cell failure follows a predictable pattern in both younger and older individuals.[54]

While C-peptide AUC has been adopted by most clinical trial networks to report β cell function, this measure fails to account for the prevailing glycaemia and may provide incomplete information about β cell function, particularly before clinical diabetes diagnosis. In addition, changes in C-peptide AUC have not correlated well with clinical markers of metabolic homeostasis, including glycaemic control and exogenous insulin use.[55–57] However, when endogenous insulin secretion is analysed relative to the concomitant glucose concentration via a parameter termed β cell glucose sensitivity (β-GS), there is better correlation between β cell function and clinical measures including haemoglobin A1c and exogenous insulin use.[58–60] Along these lines, β-GS was modelled using data from oral glucose tolerance tests performed in the Diabetes Prevention Trial of T1D (DPT-1) cohort. This analysis showed that β-GS was reduced to a similar extent in young (<14 years of age) and older (>14 years) progressors at the time of study entry (median of 2.24 years prior to the onset of Stage 3 T1D). In addition, the slope of decline in β-GS from study entry to a diagnosis of diabetes was not different between younger and older study progressors to diabetes,[61] even when slopes were analysed for the entire duration of follow-up or discretely at one year prior to diagnosis.

At the time of clinical diagnosis (i.e., Stage 3 onset), absolute values of C-peptide may be different between children and adults. Adults have higher serum and urinary C-peptide levels.[62,63] Similarly, among individuals with T1D diagnosed within the last 10 weeks, there was a positive association between age of diagnosis and insulin secretory rates (ISR) during a 4-h mixed meal tolerance test.[64] It is unclear if these differences are driven primarily by adiposity, body mass index and insulin resistance or if they represent a bona fide difference in disease pathogenesis between adults and children. Interestingly, adults are less likely to present with ketoacidosis at the time of diagnosis,[65] and many adults do not require immediate insulin therapy, although misclassification of diabetes subtype in adults may account for the observed delays in the need for insulin therapy. Even among children, though, a later age of disease onset has been associated with a longer 'honeymoon' period,[66] and adults are more likely to experience a clinical remission.[67,68] While factors including socioeconomic status and access to care complicate these analyses, an older age of onset is associated also with better glycaemic control.[69] In long-duration disease, age influences glycaemic control, as adults typically have lower haemoglobin A1c levels.[70,71]

Longitudinal patterns of C-peptide loss following the onset of Stage 3 T1D have been studied in several cohorts, including as part of several intervention studies performed in the T1D TrialNet Network. Greenbaum and colleagues analysed patterns of decline in C-peptide AUC secreted in response to a mixed meal tolerance test two years post-diagnosis in 191 individuals from the placebo arms of two positive intervention studies and the entire cohort of one negative study. This analysis showed that C-peptide declined significantly

faster in participants 7–21 years of age compared to those over the age of 21 years.[72] A second analysis included data four years post-diagnosis in 507 individuals from five TrialNet intervention studies, including all participants from three negative studies and placebo-treated individuals from two positive studies. At this time point, individuals >18 years old were more likely to have detectable C-peptide. In addition, adults were also more likely to exhibit a clinical remission, which was defined as an insulin dose-adjusted haemoglobin A1c value ≤9.[68] Similar findings have been observed in other living cohorts of individuals with long-duration disease and in tissue biorepositories of organ donors with T1D, where both have shown that residual C-peptide secretion or detectable serum C-peptide is more likely to be observed in individuals diagnosed at an older age.[51]

Recently, Gitelman and colleagues confirmed an effect of age on the rate of decline of β cell function by modelling longitudinal changes in β-GS from mixed meal tolerance test data collected from placebo-treated individuals from nine Stage 3 intervention studies performed in TrialNet and other clinical networks. In this study, β-GS exhibited a more rapid decline in children (<12 years of age) as compared to adolescents (age 12–18) and adults (>18 years of age).[73] It is interesting to note that in the Greenbaum study, C-peptide AUC demonstrated a comparable decline in both children (<12 years of age) and adolescents (age 12–17),[72] suggesting that β-GS could provide a more nuanced view of changes in β cell function across different age groups.

However, several additional papers have failed to confirm an effect of age on rates of C-peptide decline post-diagnosis. Steele and colleagues evaluated ISR during a 4-h mixed meal tolerance test and found no relationship between age or BMI and the slope of decline in ISR.[64] Likewise, an analysis of 1549 individuals from two studies performed in the UK described two phases of C-peptide decline; the first phase was characterised by an initial exponential fall over the first 7 years, followed by a period of relative stability. Interestingly, neither the overall pattern nor duration of these two phases differed in individuals above or below the median age of diagnosis in the cohort, which was 10.8 years.[74] A recent analysis of changes in C-peptide AUC in 649 children (<10 years of age), adolescents (10–17 years) and adults (≥18 years of age) followed in the INNODIA cohort similarly showed no impact of age on the rate of decline.[37] Children were noted to have lower absolute C-peptide levels, but rates of decline across the three age groups were similar, with the caveat that children younger than five had a fasting C-peptide measured and did not undergo evaluation with a mixed meal tolerance test. Finally, data from nearly 1800 robustly characterised individuals with adult-onset T1D showed that age of onset was not associated with a T1D GRS or rate of C-peptide decline.[31]

Thus, in aggregate, there remains considerable uncertainty on the extent to which age impacts the rate of β cell loss either before or after clinical diagnosis of T1D. Numerous factors could drive the observed differences between various studies, including differences in sample size, cohort demographics (including genetics), age cut-offs used to designate children and adolescents, the choice of physiologic test, methods used to model C-peptide data and even the assays used to measure C-peptide. For example, the study by Steele et al. had a relatively small sample size, while the UK analysis utilised longitudinal and cross-sectional data as well as results from urinary C-peptide and random non-fasting C-peptide levels. In contrast, the INNODIA and TrialNet studies both had relatively large sample sizes and nearly identical protocols for physiologic testing, yet the impact of age on C-peptide decline was different between the studies. It will be important to determine whether there are environmental factors, genetic differences or potentially ascertainment or measurement biases that could account for differences between studies. Thus, more studies are needed to understand discrepancies observed between cohorts, and future studies may benefit from the combined analysis of multiple cohorts. There are still unresolved questions about the best methods to accurately measure β cell loss, the different levels in C-peptide between adults and children when analysed cross-sectionally, whether decline rates and disease activity are different before and/or after disease, and how this correlates with appearances at the islet level. These questions are important considerations when considering intervention and monitoring in clinical trials and clinic settings.

A recent study suggested that 62% of adults with T1D in the United States are overweight or obese.[75] Therefore, there are likely to be complex interactions between adult-onset T1D and metabolic features more commonly observed in adulthood, including weight, metabolic syndrome, insulin resistance and hyperlipidaemia. These additional metabolic factors may influence T1D progression and prevention, response to treatment following a Stage 3 T1D diagnosis and the development of complications.[76] In fact, analyses in TrialNet suggest that insulin resistance is associated with a modest increased risk of progression from autoantibody positivity to a clinical T1D diagnosis.[77] Further highlighting this complex interaction between metabolic features and adult-onset T1D is emerging data indicating that glucagon-like receptor-1 (GLP-1) agonists may have utility as an adjuvant therapy for T1D. Although GLP-1 agonists are only FDA approved in obesity and T2D, recent findings and a meta-analysis suggest that GLP-1 treatment has moderate beneficial effects in T1D, including decreased haemoglobin A1C, weight loss and reduced insulin requirements without increasing the risk for severe adverse events.[78,79] Additionally, SGLT2 inhibitors are being used increasingly in T1D,[76] where their use is associated with reduced insulin requirements, improved glycaemic variability, weight loss and reduced haemoglobin A1C levels.[80] SGLT2 inhibitor use can be associated with diabetic ketoacidosis, so caution is required, and detailed expert consensus guidance for their use in T1D has been published by others.[81] Long-term outcome studies are needed to understand whether the use of non-insulin therapies offers the same protection against cardiovascular and renal complications in adult-onset T1D as has been observed in T2D.[80]

Finally, in recent years, there has been increasing recognition that T1D is not only a disease of the endocrine pancreas, but that exocrine pancreas loss is also a key feature of T1D. This concept is perhaps best illustrated by the consistent findings in organ donors and living individuals that pancreas weight or volume is decreased in those with T1D. This decreased pancreas weight is most pronounced

during the first year after diagnosis and continues to decline through five years post-diagnosis.[82–84] Importantly, individuals at increased genetic risk for T1D and those with multiple autoantibodies also show a decrease in pancreas weight.[83,84] This finding of decreased total pancreas weight in T1D has been shown in adults and children; however, it is not known whether there are age-related differences in pancreas loss.

3 | APPROACHES FOR CLASSIFICATION: PRACTICAL AND ASPIRATIONAL

Given the high rate of initial disease misclassification, how then does the practicing clinician reliably identify individuals with adult-onset T1D? A high level of vigilance is necessary, and the simple AABBCC mnemonic can serve as a reminder to consider age, other autoimmunity, BMI, background (i.e., family history), control and comorbidities when considering diabetes aetiology.[8] The development of actual data-driven tools to identify adult-onset T1D is needed and under active development. Among single features, age at diagnosis (<40 years), low BMI (<25 kg/m^2) and progression to insulin therapy within 3 years of diagnosis are the best predictors of T1D.[85] Classification models that integrate several key features are increasingly being applied and tested. In one study, the use of five variables, including clinical features (age of diagnosis, body mass index) and biomarkers (autoantibodies and GRS) had high accuracy in identifying recently diagnosed adults who had a rapid insulin requirement.[27]

A recent consensus report from the EASD and the ADA includes a staged approach to diagnosing adults with suspected T1D,[86] and this diagnostic algorithm appeared in the 2025 ADA Standards of Care.[87] Caveats to this approach include the acknowledgement that most recommendations have been based on data from White European populations, and limited information is available from more diverse populations. Secondly, while features such as age of onset, BMI, history of autoimmunity, the presence of classical symptoms and severity of hyperglycaemia are useful in building a case for an individual, no single clinical feature can accurately distinguish T1D from T2D.[8,27] Thus, overlap in the clinical features between T1D, T2D, and even atypical and monogenic diabetes subtypes may often lead to continued uncertainty of diagnosis, even when autoantibodies and C-peptide measurements are available. In this setting, longitudinal monitoring of C-peptide may allow for detection of progression to severe insulin deficiency, which necessitates treatment with insulin, whatever the clinical diagnosis. Finally, elements of the approach are opinion-driven, reflecting a lack of rigorous and validated data to drive clinical decision-making. For example, the idea of false-positive autoantibody results, either biological or technical, is not considered in the guidelines but has been an area of significant controversy.[9] Additional studies are needed to understand if increased attention to adult-onset T1D and these new diagnostic algorithms will reduce misclassification in the future.

Nonetheless, in adults with suspected T1D, guidelines suggest that the first step should be autoantibody testing, beginning with the measurement of GAD antibodies. If GAD is negative, IA-2 and ZnT8 should be measured. Measurement of insulin antibodies can be added in those not treated previously with insulin. A positive autoantibody result is taken to be indicative of a T1D diagnosis; however, in individuals <35 years of age who lack clinical features of T2D or monogenic diabetes, a negative autoantibody result should not influence the diagnosis, as up to 15% of true T1D cases will be autoantibody negative.[88] Additionally, for these autoantibody negative individuals <35 years of age, monogenic diabetes must be considered based on the presence of one or more features: (1) haemoglobin A1C <58 mmol/mol (<7.5%) at diagnosis; (2) a parent with diabetes; (3) clinical features of monogenic diabetes, including renal cysts, partial lipodystrophy, maternally inherited deafness and severe insulin resistance in the absence of obesity or (4) a probability of having monogenic diabetes per the Exeter MODY calculator that exceeds 5% (diabetesgenes.org/exeter-diabetes-app/ModyCalculator). If one or more of these features is present, testing should proceed with measurement of C-peptide in those individuals treated with insulin. If the result is >200 pmol/L, genetic testing for monogenic diabetes should be undertaken. A C-peptide level <200 pmol/L is consistent with a diagnosis of T1D. For those lacking features of either monogenic diabetes or T2D, T1D is likely confirmed.

The diagnostic approach is less clear for those >35 years of age, especially in those with mixed clinical features. In this case, clinical decision-making is suggested, with the acknowledgement that a trial of non-insulin therapy may be appropriate. Such a decision should come with education and counselling about the signs and symptoms of worsening metabolic status and ketoacidosis. Measurement of C-peptide can be undertaken in those with disease duration of more than 3 years. If C-peptide is >600 pmol/L, a diagnosis of T2D is more likely, while a value <200 pmol/L is consistent with a diagnosis of T1D. For those with intermediate values (>200 pmol/L but <600 pmol/L), the guidelines suggest rechecking when the individual is >5 years from diagnosis.

The practical aspects of checking C-peptide can be challenging in the clinical setting. Per the ADA Standards of Care, C-peptide can be measured on a randomly collected sample as long as it is within 5 h of food intake, and the sample should have concurrent measurement of glucose. If C-peptide is >600 pmol/L, no further consideration is needed. However, if C-peptide is <600 pmol/L and the concurrent glucose is <4 mmol/L (<70 mg/dL), the clinician should consider repeating the test. Finally, an acute hyperglycaemic crisis can be associated with β cell dysfunction that is partially reversible, so testing should be performed at a time when blood glucose levels are more stable.[87]

4 | CLOSING

Adult-onset T1D accounts for the majority of newly diagnosed T1D cases each year; however, knowledge gaps exist regarding the diagnosis, classification, treatment and natural history of adult-onset T1D. Compared to children, adults presenting with T1D have different genetic risk, immunologic profiles and metabolic outcomes, yet different diagnostic criteria or treatment plans based upon age at diagnosis

have not been developed, highlighting several key questions for the field: (1) should age be treated as a continuous variable for T1D in biological studies, classification and treatment?; (2) is it feasible and preferable to develop different guidelines for T1D diagnosis and treatment for children versus adults?; (3) do the newly defined stages of pre-clinical T1D apply equally to children and adults? and (4) would adult-specific standards for T1D diagnosis decrease misclassification of diabetes subtype?

Table 2 and Figure 1 summarise the knowledge gaps and opportunities to increase our understanding of adult-onset T1D. A better understanding of the clinical features and natural history of adult-onset T1D will reduce the burden of misdiagnosis and could lead to optimised population-based screening in this underrecognised population.

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CONFLICT OF INTEREST STATEMENT

CEM has served on advisory boards related to T1D research clinical trial initiatives: Isla Technologies, Avotres and DiogenX. CEM has patent (16/291668): Extracellular Vesicle Ribonucleic Acid (RNA) Cargo as a Biomarker of Hyperglycaemia and Type 1 Diabetes and provisional patent (63/285765): Biomarker for Type 1 Diabetes (PDIA1 as a biomarker of β-cell stress). RAO reports consulting income from Janssen, Provention Bio, Sanofi, and Novo Nordisk, honoraria from Sanofi and Novo Nordisk, and advisory board membership for Sanofi. RAO receives research funding from NIDDK, Breakthrough T1D, The Leona M and Larry B Helmsley Charitable Trust, and Randox Ltd. The University of Exeter has a licensing and Royalty agreement with Randox for a 10 SNP T1D GRS biochip.

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