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REVIEW

Continuous glucose monitoring as a tool in early-stage type 1 diabetes

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Abstract

Continuous glucose monitoring (CGM) has transformed diabetes management by providing continuous, real-time insights into glucose dynamics, while enhancing the lived experience of individuals with type 1 diabetes. In established type 1 diabetes, CGM-derived measures of glucose management, such as time in range, time above range, time below range and glycaemic variability, have become integral tools to optimise therapy, reduce episodes of hypoglycaemia and guide clinical decision-making. More recently, CGM has emerged as a promising tool to detect early hyperglycaemia and other glucose abnormalities in individuals with early-stage type 1 diabetes, for whom current screening and staging methods, including fasting glucose, HbA_{1c} and the OGTT, remain limited by episodic sampling, participant burden and variable reproducibility. This review examines the rationale, evidence and practical considerations for integrating CGM into early-stage type 1 diabetes research and clinical frameworks. We discuss its potential to complement existing metabolic and immunological markers, as well as the technical, analytical and regulatory challenges that must be addressed for CGM to serve as a reliable tool for screening, staging and monitoring and as a clinical endpoint in early-stage type 1 diabetes.

Keywords Continuous glucose monitoring · Progression · Review · Stage 1 diabetes · Stage 2 diabetes · Type 1 diabetes

Abbreviations

CGM	Continuous glucose monitoring
DKA	Diabetic ketoacidosis
DPTRS	Diabetes Prevention Trial–Type 1 Risk Score
EMA	European Medicines Agency
FDA	Food and Drug Administration
IVGTT	Intravenous glucose tolerance test
MMTT	Mixed-meal tolerance test
OGTT	Oral glucose tolerance test
SMBG	Self-monitoring of blood glucose

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Introduction

The rising global incidence of type 1 diabetes combined with the persistently high and, in some regions, increasing rates of diabetic ketoacidosis (DKA) underscore the urgent need for targeted public health strategies [1–3]. Screening and monitoring programmes to detect type 1 diabetes in the early stages of disease mitigate the risk of DKA [4].

Symptomatic type 1 diabetes (stage 3) occurs when an insufficient number of functional beta cells remain to maintain glucose homeostasis [5, 6]. This clinical presentation is preceded by progressive beta cell loss driven by autoimmune destruction over months or years [7–10]. This offers an opportunity for earlier detection and intervention, through timely monitoring before insulin is initiated. With the recent regulatory approval of teplizumab, the first disease-modifying drug for stage 2 type 1 diabetes, and other emerging interventions [11], emphasis is growing on identification of diabetes before stage 3. Currently, the oral glucose tolerance test (OGTT) remains the gold standard for staging and monitoring type 1 diabetes [7–9, 12, 13], but its invasiveness, cost, variability and poor tolerability [14–17] highlight the need for alternatives.

Interest is growing in leveraging the dynamic, real-time insights of continuous glucose monitoring (CGM) data to detect, stage and guide intervention in early-stage type 1 diabetes. Screening for type 1 diabetes is now increasingly offered not only to first-degree relatives but also to the general population, to identify individuals with early-stage disease, defined as the confirmed presence of two or more autoantibodies. In this context, CGM could help refine risk stratification, confirm early dysglycaemia or track disease progression, and support the timely identification of individuals who may benefit from disease-modifying therapies.

However, expanding the context of use of CGM in early-stage type 1 diabetes will require robust evidence. For example, CGM-derived glucose patterns and measures of variability may function as prognostic biomarkers by informing the likelihood or timing of disease progression. These metrics may also serve as predictive biomarkers, identifying individuals more likely to respond to an intervention when treatment response is the endpoint [18]. Recent reviews have highlighted the potential for CGM-derived diagnostic thresholds to assist in diagnosing early dysglycaemia and defining stage 2 disease [19, 20]. In this review, we synthesise current evidence on the use of CGM in early-stage type 1 diabetes, examining its potential applications in screening, staging and monitoring, and outline the key technical, analytical and regulatory considerations that will determine its future use and that must be addressed for its broader adoption.

Established staging and monitoring tools in early-stage type 1 diabetes

Islet autoantibodies

The presence of multiple islet autoantibodies remains a robust biomarker for early-stage type 1 diabetes, with the presence of two or more islet autoantibodies indicating that the autoimmune process has begun and the lifetime risk of progression to clinical (stage 3) type 1 diabetes approaches 100% [7–9, 21, 22]. The number, titre and type of autoantibody further inform the rate of progression [21, 23–25].

Glycaemic markers: OGTT and HbA_{1c}

In addition to the presence of two or more islet autoantibodies, staging of preclinical disease is currently guided by the level of glucose tolerance assessed by an OGTT and/or HbA_{1c} [7–9].

Early-stage type 1 diabetes is characterised by distinct metabolic phases in which individuals may alternate between dysglycaemia (stage 2) and normoglycaemia (stage 1), complicating staging and risk stratification. In TrialNet, stage 2 eligibility requires two abnormal serial assessments, defined by impaired fasting glucose (6.1–6.9 mmol/l), impaired glucose tolerance at 120 min (7.8–11.0 mmol/l) or elevated intermediate OGTT values (≥11.1 mmol/l) [26]. It is important to note that these criteria derive from the strict dysglycaemia definition used in the pivotal TrialNet TN-10 study [27], which formed the basis for teplizumab approval. The ADA applies broader fasting glucose (5.6–6.9 mmol/l) and HbA_{1c} (39–46 mmol/mol [5.7–6.4%]) thresholds and only the 120 min OGTT value, without intermediate values [9]. The Fr1Da study showed a higher 2 year progression risk when using TrialNet criteria (62.9%) than when using ADA criteria (32.2%) [28].

An increase in HbA_{1c} levels has also been suggested as a specific indicator of progression to stage 3 type 1 diabetes [29–31], with a ≥10% rise over 3–12 months suggestive of increased risk of progression to stage 3 within 2 years [32]. However, HbA_{1c} is relatively insensitive, lags behind real-time glucose values and is influenced by multiple factors [33]. Consensus guidance therefore recommends combining ADA and TrialNet definitions to robustly distinguish normo- and dysglycaemia for staging accuracy, alongside metabolic monitoring, education on diabetes/DKA symptoms, and psychosocial support [13].

Rationale for evaluating CGM in early-stage type 1 diabetes

There is a growing momentum towards the use of CGM in early-stage type 1 diabetes to address key unmet needs required for effective general population screening programmes.

The need for continuous surrogate markers of beta cell health

The decline in functional beta cell mass due to autoimmune destruction typically occurs months or years before clinical diagnosis [34, 35]. The evolution of disease onset is heterogeneous in rate and metabolic manifestation [36–38]; hence, beta cell function or 'health' is best conceptualised by the disposition index, which captures the hyperbolic relationship between insulin secretion and sensitivity [39–42].

The AUC of C-peptide during dynamic testing (i.e. OGTT, mixed-meal tolerance test [MMTT] or intravenous glucose tolerance test [IVGTT]) is widely accepted as a surrogate marker of beta cell function and as a trial endpoint [27, 43–47]. The earliest detectable abnormality, loss of the first-phase insulin response (FPIR), is most sensitively measured using a hyperglycaemic clamp or IVGTT [39, 48–50], although these methods are considered impractical for large-scale use.

Additional biomarkers such as the proinsulin:C-peptide ratio [51–53] and pragmatic composite indices such as the BETA-2 score [54–57], M120 risk score [58], progression likelihood score [36], Quantitative Risk Score [59], Index60 and Diabetes Prevention Trial–Type 1 Risk Score (DPTRS) [60–63] have shown value in tracking beta cell decline, predicting progression and identifying early treatment response [64]. More complex modelling approaches such as the oral minimal model [65, 66] allow estimation of insulin sensitivity and beta cell responsivity from OGTT data, possibly offering greater granularity in dissecting metabolic heterogeneity in the early stages of disease [38, 39, 67].

However, even the most sophisticated indices are constrained by their reliance on intermittent OGTT testing, making it difficult to pinpoint the timing of beta cell functional changes [68]. Cohort studies demonstrate that autoantibody-positive individuals can move between normoglycaemia (stage 1) and dysglycaemia (stage 2) [69, 70]. Longitudinal data from TrialNet showed that 36% of individuals with an abnormal OGTT reverted to normoglycaemia at their next assessment [71]. It is plausible that many of these periods of metabolic recovery and decline are masked by the limitations of conventional testing intervals and tools.

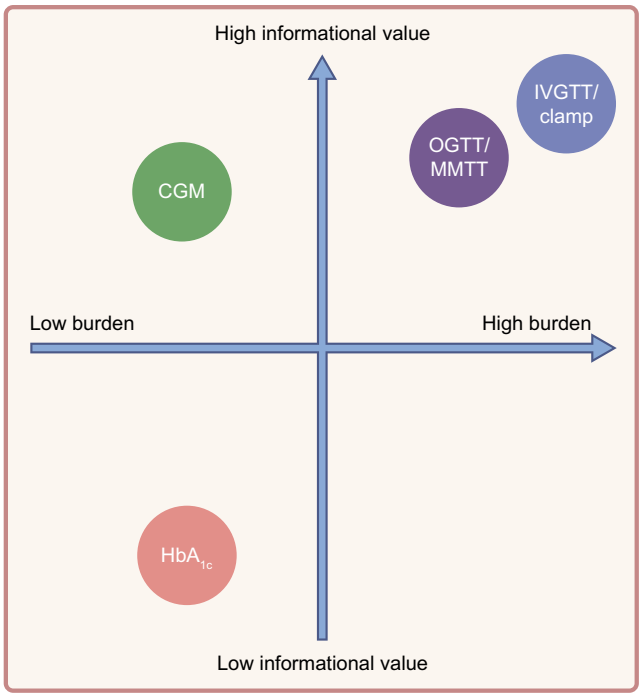

Fig. 1 Schematic of the relative burden (invasiveness, cost, tolerability, logistics) and informational value (capturing disease staging, beta cell function and risk of progression) of current metabolic monitoring tools in early-stage type 1 diabetes. This figure is available as part of a downloadable slideset

The need for minimally invasive and scalable surveillance

To enable earlier detection of type 1 diabetes and intervention at scale, screening must be delivered to the general population, as the majority (>85%) of affected individuals do not have an affected first-degree relative [12, 72, 73]. However, the gold standard OGTT [7–9, 12] is invasive, time-consuming and often distressing for young children [14, 74], requiring preparatory carbohydrate loading, prior fasting, cannulation, ingestion of a glucose load and multiple blood draws over 2 h. In addition, practical limitations such as the need for immediate processing to avoid glycolysis and sample degradation, the need for specialised facilities, and poor reproducibility necessitate repeated monitoring in both children and adults [14–17, 74], limiting scalability. CGM offers a minimally invasive alternative for disease surveillance and risk stratification [13, 19, 75] in both adults and very young children [76]. Moreover, as it is widely recommended for monitoring in established type 1 diabetes, many diabetes professionals have experience in its use.

As general population screening initiatives emerge worldwide [77–81], follow-up strategies must balance informative value with accessible, low-burden monitoring technologies

(Fig. 1) to improve early detection, risk stratification and long-term adherence.

Current recommendations and clinical implementation of CGM in type 1 diabetes

Until recently, monitoring of clinical type 1 diabetes relied primarily on self-monitoring of blood glucose (SMBG). In 2022, the UK National Institute for Health and Care Excellence marked a major shift by recommending CGM for all individuals with type 1 diabetes [82, 83]. Similar updates from the ADA, International Society for Paediatric and Adolescent Diabetes (ISPAD) and American Association of Clinical Endocrinology (AACE) [84–86] further broadened access, transitioning CGM from a specialised technology for select subgroups into the gold standard of routine clinical care.

Current landscape of CGM in early-stage type 1 diabetes

To identify relevant studies examining CGM in early-stage type 1 diabetes, we conducted a targeted narrative search of MEDLINE via PubMed (January 2000–September 2025) using the terms 'continuous glucose monitoring', 'CGM', 'screening', 'autoantibodies' and 'progression'. Citation searching was also performed. Inclusion criteria were (1) studies using CGM in individuals with islet autoantibodies, stage 1 or stage 2 type 1 diabetes; (2) studies reporting glycaemic metrics or progression endpoints; and (3) studies published in English. Exclusion criteria were studies in established type 1 diabetes, type 2 diabetes or maturity-onset diabetes of the young, or those lacking CGM-derived metrics. We identified 14 studies that have examined CGM in early-stage type 1 diabetes (Table 1), primarily using cross-sectional comparisons (autoantibody status or stage) or progression endpoints to stage 3 and often focusing on thresholds for time above specific glucose cut-offs (Fig. 2).

Early small studies demonstrated that autoantibody-positive individuals had higher mean glucose levels, glycaemic variability and time above 7.8 mmol/l glucose than autoantibody-negative control individuals [87], both as a group and among those who progressed to stage 3 [88, 89]. Steck et al were the first to propose a predictive threshold, identifying that spending ≥18–20% time above 7.8 mmol/l glucose signalled an increased risk of progression to stage 3 type 1 diabetes [88].

Subsequent larger cohorts have refined these thresholds: ≥18% time ≥7.8 mmol/l glucose predicted progression in children with two or more autoantibodies [90], the Autoimmunity Screening for Kids (ASK) cohort demonstrated that >10% time spent above 7.8 mmol/l glucose was strongly predictive of progression to stage 3 within a year in individuals with one or more autoantibody [91], and the TrialNet Pathway to Prevention (TNPTP) cohort reported that a value as little as ≥5% of time spent at ≥7.8 mmol/l glucose was predictive of progression to stage 3 in autoantibody-positive individuals [92]. A recent study, however, demonstrated that a threshold of ≥10% of time above 7.8 mmol/l glucose had low specificity and was associated with limited risk for stage 3 type 1 diabetes, particularly in those with stage 1 disease, while a composite progression score combining SD with time above 7.8, 8.9 and 10.0 mmol/l glucose achieved superior discrimination than any single metric (AUC 0.88) [93]. A small study from the Belgian diabetes registry identified that time above 6.7 mmol/l glucose was the most effective univariate CGM predictor of progression, although the OGTT-derived AUC glucose outperformed CGM in univariable models; combining CGM features with HbA_{1c} improved performance [94].

In a study by Ylescupidez et al, while 29 of 48 daytime CGM-derived metrics were found to significantly differ between progressors and non-progressors, the predictive utility of individual measures, and even of combined panels including CV, mean glucose, IQR, SDwsh (within-participant average hourly SD) and hypo-/hyperglycaemic index, remained modest and consistently inferior to OGTT-based indices such as Index60 and DPTRS [95]. However, combining CGM-derived features with participant characteristics or standardised liquid meal protocols improves discrimination, with incremental AUCs and postprandial percentage time spent at >10.0 mmol/l glucose distinguishing antibody-negative from antibody-positive groups, and integration with genetic risk scores achieving ROC AUCs up to 0.93 [96–98].

Cross-sectional analyses have consistently shown graded increases in glycaemic variability (SD, CV, mean amplitude of glycaemic excursion [MAGE]) and time above 7.8, 8.9 and 10.0 mmol/l glucose across control, stage 1 and stage 2 individuals [76, 93, 99]. Very young children (mean age ~4 years) with multiple autoantibodies also displayed higher variability and increased time above 7.8 mmol/l than antibody-negative control children (SD 1.1 vs 0.9 mmol/l, CV 17.3% vs 14.7%, time >7.8 mmol/l 8.0% vs 3.3%) [76]. In some settings, thresholds >10.0 mmol/l were more discriminative than those >7.8 mmol/l, particularly postprandially [96].

Across studies, time above 7.8 mmol/l glucose consistently signals higher risk, although thresholds vary from as little as 5% to as high as 20% (Table 1, Fig. 2). Nonetheless, recent recommendations have formalised the use of 7.8 mmol/l glucose as a staging threshold, defining stage 2 as ≥10% and stage 3 as ≥20% of time above this level, confirmed by additional non-CGM glucose measures [13]. A recent meta-analysis highlighted that higher CGM cut-offs increase specificity at the expense of sensitivity, possibly

Table 1 Summary of studies evaluating CGM to stage and predict progression in early-stage type 1 diabetes (*n*=14)

Study[a]	Population (antibody status, age [years])	CGM model and wear duration[b]	Key CGM metrics measured	Key outcomes
Steck (2014) [88]	*N*=23 ≥2 Aab (*n*=14), age 13.8 ± 3.5 0 Aab (*n*=9), age 13.6 ± 2	Dexcom SEVEN 5–7 days	Mean glucose, max. glucose, SD, CV, TA7.8 mmol/l, TA11.1 mmol/l, AUC	≥18–20% TA (≥) 7.8 mmol/l could be used to predict progression to T1D in Aab-positive children: TA (≥) 7.8 mmol/l: 31.0 ± 18.0% in progressors (*n*=5) vs 12.0 ± 7.0% in non-progressors (*n*=9), *p*=0.04
Van Dalem (2015) [89]	*N*=51 ≥2 Aab (*n*=22), median (range) age 19 (12–41) 0 Aab (*n*=20), median (range) age 18 (12–40) Stage 3 T1D (*n*=9), median (range) age 20 (13–36)	Medtronic iPro2 5 days	SD, CV, IQR, TA7.8 mmol/l	CGM measurements (SDday, IQRday and CVday) above the range of those from healthy control individuals had higher diagnostic efficiency for detecting or predicting dysglycaemia than elevated SMBG variables (Rangeday and SDday) (77–82% vs 73%) Those who developed IGT or diabetes during follow-up (*n*=5) had higher GV variables than those who remained euglycaemic (*n*=12)
Helminen (2016) [87]	*N*=20 ≥2 Aab (*n*=10), age 9.8 ± 4.1 0 Aab (*n*=10), age 9.9 ± 4.5	Dexcom G4 Platinum 7 days	Mean glucose, max. glucose, range, SD, TA7.8 mmol/l, TA11.1 mmol/l, AUC, MAGE	Aab-positive individuals have higher average glucose and glucose variability than matched Aab-negative control individuals: Glucose (mmol/l): 5.4 ± 0.6 vs 4.7 ± 0.3, *p*=0.018 SD (mmol/l): 1.2 ± 0.5 vs 0.8 ± 0.2, *p*=0.04 TA (≥) 7.8 mmol/l: 5.9 ± 7.0% vs 0.4 ± 0.4%, *p*=0.04
Steck (2019) [90]	*N*=23 ≥2 Aab (*n*=23), age 13.9 ± 3.8 progressors, 16.6 ± 4.5 non-progressors	Dexcom SEVEN Plus or Dexcom G4 Platinum 5–7 days (on multiple occasions)	Mean glucose, max. glucose, SD, CV, range, TA6.7 mmol/l, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, TA11.1 mmol/l, AUC	≥18% TA (≥) 7.8 mmol/l predicts progression to T1D in Aab-positive children: TA (≥) 7.8 mmol/l: 24.0 ± 17.0% in progressors (*n*=8) vs 8.0 ± 6.0% in non-progressors (*n*=15), *p*=0.005
Kontola (2022) [99]	*N*=46 0 Aab (*n*=9), median (range) age 9.3 (3.9–15.2) 1 Aab (*n*=6), median (range) age 12.3 (7.4–13.1) ≥2 Aab (*n*=31), median (range) age: stage 1 (*n*=12), 9.7 (5.1–25.4); stage 2 (*n*=11), 15.1 (4–20.2); stage 3 (*n*=8), 9.7 (4.5–19.7)	Dexcom G6 10 days	Mean glucose, CV, MAGE mean, HBGI mean, CGM estimated HbA_{1c}, TA7.8 mmol/l, TA11.1 mmol/l, TA13.9 mmol/l, TB3.9 mmol/l, TB3.0 mmol/l, TIR3.9–7.8 mmol/l, AUC, OGTT metrics	CGM can identify asymptomatic individuals in stage 3 T1D and dysglycaemic individuals in stage 2 T1D prior to an OGTT: TA (≥) 7.8 mmol/l: median (IQR) 3.95% (2.21–6.19) (0 Aab) vs 5.95% (3.6–10.3) (stage 1) vs 44.5% (17.0–43.2) (stage 3), *p*<0.01 TIR3.9–7.8 mmol/l: 94.0 ± 2.7% (0 Aab) vs 90.9 ± 4.9% (stage 1) vs 67.8 ± 13.4% (stage 3), *p*<0.001 CV: 15.5 ± 1.8% (0 Aab) vs 19.8 ± 1.9% (stage 1) vs 30.8 ± 6.5% (stage 3), *p*<0.001
Steck (2022) [91]	*N*=91 ≥1 Aab (*n*=91), median (IQR) age 10.5 (6.8–13.2) progressors, 11.7 (8.1–14.5) non-progressors	Dexcom G4 Platinum or Dexcom G6 7–10 days, (every 6 months)	Median glucose, SD, CV, range, TA6.7 mmol/l, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, TA11.1 mmol/l, MAGE, MODD, AUC	>10% TA (>) 7.8 mmol/l is associated with high risk of progression to stage 3 T1D in Aab-positive individuals: TA (≥) 7.8 mmol/l: median (IQR) 21.0% (13.0–33.0) in progressors (*n*=16) vs 3.0% (1.0–7.0) in non-progressors (*n*=75), *p*<0.0001

Table 1 (continued)

Study[a]	Population (antibody status, age [years])	CGM model and wear duration[b]	Key CGM metrics measured	Key outcomes
Montaser (2023) [96]	*N*=60 0 Aab (*n*=21), age 27 ± 9.9 1 Aab (*n*=18), age 23.5 ± 11.9 ≥2 Aab (*n*=21), age 20.7 ± 10.2	Dexcom G4 Platinum 7 days	Mean glucose, SD, CV, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, TB3.9 mmol/l, TB3.0 mmol/l, LBGI, HBGI, ADRR, post-SLMM CGM metrics	Three metrics differed between groups: TA (>) 10.0 mmol/l, *p*=0.040 (negative vs 1 Aab *p* = 0.352, negative vs ≥2 Aab, *p* = 0.012, 1 Aab vs ≥2 Aab, *p*= 0.144) Overnight CGM incremental AUC, *p*=0.005 (negative vs 1 Aab *p* = 0.012, negative vs ≥2 Aab *p* = 0.005, 1 Aab vs ≥2 Aab *p* = 0.012) TA (>) 10.0 mmol/l for 75 min post standard liquid meal, *p*=0.004 (negative vs 1 Aab *p* = 1.000, negative vs ≥2 Aab *p*= 0.012, 1 Aab vs ≥2 Aab *p*= 0.018) TA (>) 7.8 mmol/l was not as predictive as TA (>) 10.0 mmol/l
Wilson (2023) [92]	*N*=105 0 Aab (*n*=10), median (IQR) age 16.3 (15.1–18) ≥2 Aab (*n*=95): median (IQR) age: stage 1 (*n*=53), 17.2 (11.7–36.4); stage 2 (*n*=42), 15.5 (11.6–37.5)	Dexcom G4 Platinum 7 days	Mean glucose, SD, CV, max. glucose, min. glucose, range, TA6.7 mmol/l, TA7.8 mmol/l, TA8.9 mmol/l, CONGA, DySF, MAGE, MODD	≥5% TA (≥) 7.8 mmol/l was predictive of progression to stage 3 T1D in Aab-positive individuals: TA (≥) 7.8 mmol/l: 8.0 ± 8.0% in progressors (*n*=29) vs 4.7 ± 6.0% in non-progressors (*n*=66), *p*=0.03
Ylescupidez (2023) [95]	*N*=93 ≥2 Aab (*N*=93), stage 1 (*n*=58), stage 2 (*n*=35); age 18.2 ± 13.3 progressors, 26.6 ± 15.2 non-progressors	Dexcom G4 Platinum 7 days (three occasions, 6 months apart)	CV, SD, range, TA7.8 mmol/l, TA11.1 mmol/l, time 3.3–7.8 mmol/l, ADRR, CONGA, GRADE, HBGI, MAGE, MODD, max. glucose	4/7 OGTT metrics and 29/48 CGM metrics were statistically different between Aab-positive progressors and non-progressors including: TA (>) 7.8 mmol/l: median (IQR) 5.45% (2.16–11.02) in progressors (*n*=34) vs 2.46% (0.7–6.45) in non-progressors (*n*=59), *p*=0.026 Individual CGM metrics did not exceed an AUC of 70% for prediction of T1D. Combining CGM metrics improved the adjusted ROC AUC for prediction of subsequent T1D to 76.6% Index60 and DPTRS had the highest unadjusted ROC AUC for prediction of subsequent T1D
Haynes (2024) [76]	*N*=55 0 Aab (*n*=24), age 4.7 ± 1.9 ≥2 Aab (*n*=31), age 4.4 ± 1.8	Dexcom G6 14 days (consecutive days, with two consecutive sensors)	Mean glucose, CV, SD, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, TA11.1 mmol/l, TB3.9 mmol/l, TB3.5 mmol/l, TB3.0 mmol/l, MAGE, CONGA	Very young Aab-positive children have higher SD, CV and TA (>) 7.8 mmol/l than Aab-negative children: SD (mmol/l): median (IQR) 1.1 (0.9–1.3) vs 0.9 (0.8–1.0), *p*<0.001 CV: 17.3% (16.0–20.9) vs 14.7% (12.9–16.6), *p*<0.001 TA (>) 7.8 mmol/l: 8.0% (4.4–13.0) vs 3.3% (1.4–5.3), *p*=0.005
Montaser (2024) [97]	*N*=42 0 Aab (*n*=21), age 27 ± 9.9 ≥2 Aab (*n*=21), age 20.7 ± 10.2	Dexcom G4 Platinum 7 days	Mean glucose, CV, range, IQR, TA6.7 mmol/l, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, TB3.9 mmol/l, TB3.0 mmol/l	Three metrics differed between groups: CV, *p*=0.028 Range, *p*= 0.035 TA (>)10.0 mmol/l, *p*= 0.04 In a classifier model, CV, range, TA8.9 mmol/l, Gmax and IQR were the most significant features capturing variability and dysglycaemia in the two risk groups

Table 1 (continued)

Study[a]	Population (antibody status, age [years])	CGM model and wear duration[b]	Key CGM metrics measured	Key outcomes
Desouter (2025) [94]	*N*=34 ≥2 Aab (*N*=34), median (IQR) age 16.6 (13.4–23.4)	Medtronic iPro2 5 days (semi-annually)	Mean glucose, SD, CV, IQR, TA6.7 mmol/l, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, AUC glucose	Considerable inter- and intra-variation TA6.7 mmol/l and TA7.8 mmol/l increased in progressors (*n*=17) within the last 3 years before diagnosis compared with most non-progressors (*n*=17) In a univariate prediction model TA (≥) 6.7 mmol/l was the most effective CGM metric (AICc=75) at predicting progression to stage 3 T1D OGTT-derived AUC glucose outperformed CGM TA (≥) 6.7 mmol/l (AICc=71.1). A multivariable CGM model of mean glucose and IQR achieved a similar AIC (AICc=72.5)
Huber (2025) [93]	*N*=97 0 Aab (*n*=33), median (IQR) age 11 (10–13) ≥2 Aab (*n*=64), median (IQR) age: stage 1 (*n*=46), 9 (7–11), stage 2 (*n*=18), 9.5 (7.3–11.8)	Dexcom G6 10 days (multiple occasions)	Mean glucose, SD, CV, max. glucose, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, TA11.1 mmol/l, TB5.6 mmol/l, TB4.4 mmol/l	Several CGM parameters were significantly different between Aab-negative control individuals and those with stage 1 and stage 2 T1D, including: TA (>) 7.8 mmol/l: stage 1: median (IQR) 11.3% (5.5–26.9); stage 2: 31% (16.1,44.6); control: 6.6% (3.2–16.2%) (control vs stage 1 p= 0.04, control vs stage 3 p= 0.0003, stage 1 vs stage 2 p= 0.01) A composite progression score using SD, TA (>) 7.8 mmol/l, TA (>) 8.9 mmol/l and TA (>) 10.0 mmol/l could identify those who progressed to stage 3 (*n*=11) (AUC 0.88 [95% CI 0.77, 0.99], p<0.0001) TA (>) 7.8 mmol/l ≥10% had a very low specificity and was associated with a low risk for stage 3 type 1 diabetes
Montaser (2025) [98]	*N*=39 1 Aab (*n*=18), age 23.5 ± 11.9 ≥2 Aab (*n*=21), age 20.7 ± 10.2	Dexcom G4 Platinum 7 days	CV, TA7.8 mmol/l, TA8.9 mmol/l, TA10.0 mmol/l, AUC glucose	Post standardised liquid mixed meal TA (>) 10.0 mmol/l differed between groups (p=0.020) A model combining T1D genetic risk score and incremental AUC glucose differentiated groups with ROC AUC of 0.93 (95% CI 0.83, 1.00)

Values are mean ± SD unless otherwise stated

[a]Studies listed were identified through a targeted narrative search of MEDLINE via PubMed (January 2000–September 2025)

[b]CGM was blinded in all studies except for that by Kontola et al [99], in which CGM was unblinded on request

Aab, autoantibody; AICc, corrected Akaike information criterion; CONGA, Continuous Overall Net Glycaemic Action; DySF, Dynamic Stress Factor; GRADE, Glycaemic Risk Assessment Diabetes Equation; Gmax, maximal glucose amplitude; HBGI, High Blood Glucose Index; IGT, impaired glucose tolerance; LBGI, Low Blood Glucose Index; MAGE, mean amplitude of glycaemic excursion; MODD, mean of daily differences; ROC, receiver operating characteristic; SLMM, standardised liquid mixed meal; T1D, type 1 diabetes; TA, % time above (specified as ≥ or > in results depending on the study); TB, % time below; TIR, time in range

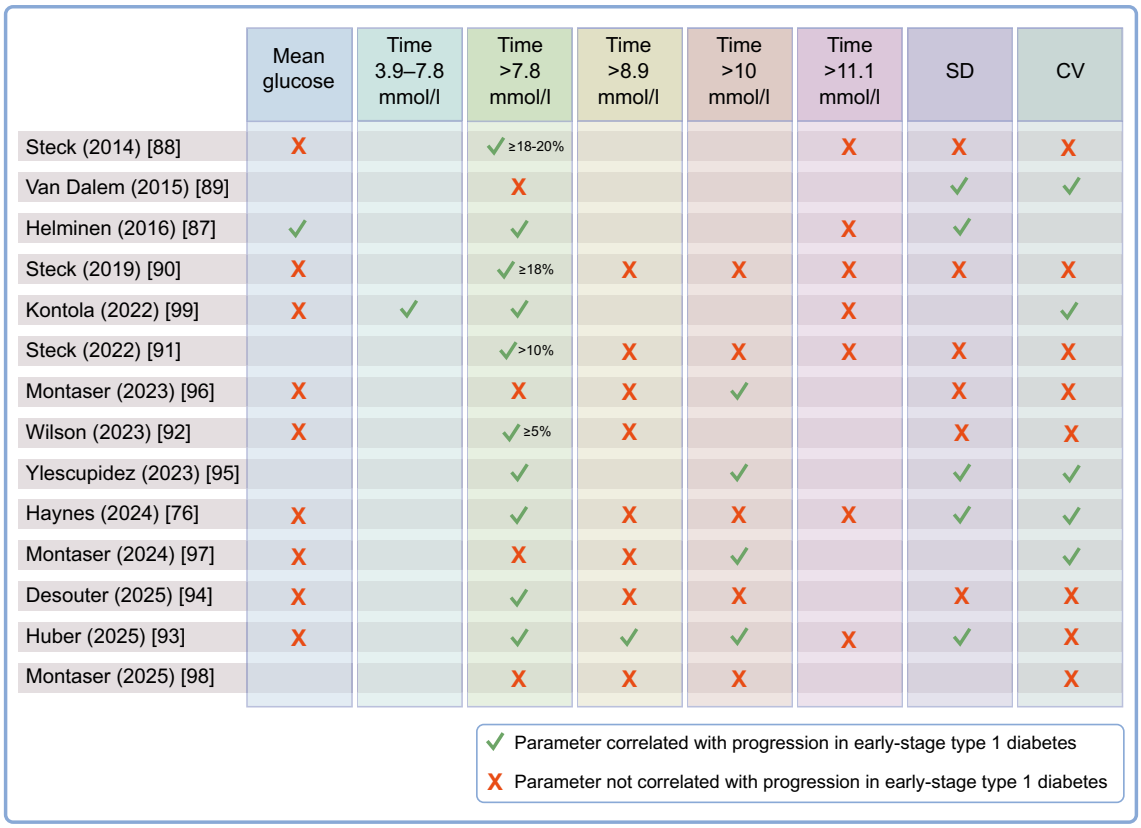

Fig. 2 CGM metrics associated with progression in early-stage type 1 diabetes. Green ticks indicate metrics significantly correlated with progression in early-stage type 1 diabetes, while red crosses indicate no significant association. Blanks represent where information was not reported. T1D, type 1 diabetes. This figure is available as part of a downloadable slideset

missing some high-risk individuals, and that predictive performance is strengthened when metrics are interpreted alongside factors such as sex, family history and autoantibody profile [100].

CGM as a tool to guide initiation of insulin or immunotherapy

Current consensus is lacking on the use of CGM to guide insulin initiation in early-stage type 1 diabetes, although recent recommendations support a 'treat-to-target' approach [101]. However, early use of insulin carries risks, given the absence of defined dosing strategies, with potential for hypoglycaemia and uncertain long-term adherence before overt symptoms appear.

The role of CGM in monitoring responses following immunotherapy is also currently undefined, but clinical trials increasingly include CGM metrics as secondary endpoints. CGM can detect early hyperglycaemic patterns that may reflect declining beta cell function, but treatment effects on C-peptide do not always translate into short-term CGM improvements, as seen in the INNODIA MELD-ATG trial, where low-dose antithymocyte globulin preserved stimulated C-peptide but did not improve CGM-derived time in range at 12 months [102].

Potential pitfalls for CGM use in early-stage type 1 diabetes

Heterogeneity Heterogeneous study designs may reduce the pre-test probability of progression in some analyses [91, 94]. Several of the studies to date compared multiple antibody-positive individuals with antibody-negative individuals [76, 87–89, 92, 93, 97] while others compared any individual with one or more antibody with antibody-negative individuals [91, 94]. Some studies focused on progression to stage 3 type 1 diabetes in individuals with multiple autoantibodies [90, 92, 95], while others relied on cross-sectional data to distinguish groups by antibody status or type 1 diabetes stage [87, 88, 93, 99]. Further inconsistency arises from thresholds reported as '>7.8 mmol/l' vs '≥7.8 mmol/l', a small distinction that nonetheless alters classification between cohorts. Notably, age-related discrepancies have been observed in normoglycaemic individuals without diabetes. While time above 7.8 mmol/l glucose is typically low in younger adults [103], a recent larger analysis of an older

population demonstrated that ~10% of time spent above 7.8 mmol/l glucose is expected, even when stratified to include only those under 60 years of age and without obesity (BMI <30 kg/m^2) [104]. Differences in glycaemic profiles in the population without diabetes have been shown to change with age [105, 106]. This likely reflects physiological changes associated with ageing [107], such as declining insulin sensitivity, altered postprandial responses and reduced physical activity levels. This underscores the need for caution when applying uniform glycaemic thresholds across age groups, and hence age-specific thresholds may be necessary when using CGM for staging within adult screening programmes, in order to avoid false-positive findings. Despite the availability of data from large, normative studies [103, 104, 108], there is currently no consensus on what constitutes a 'normal' CGM profile [19].

Study numbers The small number of studies to date using CGM in early-stage type 1 diabetes have resulted in around 779 sets of CGM data (Table 1). In part this is due to CGM being a relatively new tool, with the US Food and Drug Administration (FDA) approving the first commercially available device in 1999 [109]. Further, there are limited data on adult populations with early-stage disease, with few studies having a mean age >18 years [96, 97].

Sensor types Four studies to date used a Dexcom G6 or newer sensor, whereas the remaining ten studies used older generation devices (Dexcom G4, Medtronic iPro 2 and Dexcom SEVEN) (Table 1). It is likely that device-dependent differences play an important role in the heterogeneity observed. However, such differences are not confined to older models [110, 111]. A recent comparative study demonstrated that even current generation systems can diverge substantially, resulting in mean glucose differing by up to 1.1 mmol/l and time in range (3.9–7.8 mmol/l) varying by nearly 20% [112]. Such discrepancies highlight that CGM-derived metrics are not interchangeable across devices [113, 114]. This variability in part reflects inconsistency in comparator methods in sensor development and calibration, with capillary vs venous plasma sampling producing ranging biases depending on the measurement method [115–117], contributing to more than 5% bias existing between individual devices of the same brand [117–119]. This has motivated calls to action to standardise comparator type, sampling frequency and analytical performance to ensure comparability [116, 119, 120], which we support.

Surrogate for beta cell health CGM does not directly measure beta cell health, which is better assessed through metabolic tests and modelling [39]. This underscores a broader challenge: glycaemia-based tools may be highly sensitive but less specific indicators of underlying pathophysiology. Glucose represents a surrogate of beta cell health, and CGM adds a further layer of indirection by monitoring interstitial rather than plasma glucose. CGM offers a practical method for detecting glucose abnormalities but cannot disentangle whether observed dysglycaemia arises from defects in insulin secretion, sensitivity or both. CGM abnormalities near disease onset have been shown to parallel changes in OGTT-derived variables, although both exhibit substantial intra- and interindividual variability [94]. As such, OGTTs (including derived metrics) and CGM offer distinct yet complementary windows into beta cell health, underscoring the rationale for evaluating CGM in early-stage type 1 diabetes as either an adjunct or a pragmatic alternative to periodic metabolic tests. However, its role in staging and predicting disease or serving as a surrogate endpoint remains to be fully defined [93]. As data accumulate, novel CGM analyses may help stratify risk and define subgroups with divergent progression trajectories [97, 98, 100].

Practical considerations for CGM use in early-stage type 1 diabetes

Psychological impact and acceptability to the general public

Receiving a positive autoantibody result has been shown to cause significant initial distress, particularly for mothers of children receiving this [121–123]. The use of CGM as a method of quantifying risk could provide some reassurance due to the unpredictable nature of progression to stage 3 type 1 diabetes. A single study evaluating the acceptability of CGM in a cohort from the ENDIA study found that parents had largely positive experiences of using CGM, and felt that having additional knowledge about their child's glucose patterns helped them further understand the risk of progression to stage 3 type 1 diabetes [124].

However, the possibility of heightened anxiety, as is seen in established type 1 diabetes [125] due to increased visibility of glucose levels, needs better understanding [126]. Across multiple studies, perceived burdens of CGM include alarms and the volume and complexity of CGM data [126–128]. Additionally, pain and reactions at insertion sites are notable in type 1 diabetes [129], which has been reflected in concerns raised in studies of CGM in early-stage type 1 diabetes [19, 124]. This requires further study, including across age groups.

Blinded vs unblinded use

Positive autoantibody status alone has been associated with behaviour changes, including changes to meal planning, and increased blood glucose monitoring [130, 131], which may

be amplified with access to real-time data. It is therefore recommended in consensus guidelines that CGM should ideally be blinded for diagnostic and prognostic purposes [19] to minimise the influence of physiological and behavioural factors, such as meal timing, physical activity and stress. The study by Kontola et al is the only study to date that has provided unblinded CGM [99], with 35% of participants or their guardians requesting access to unblinded glucose data (median age of participants 11.7 years [range 3.9–25.4]). While unblinded systems can empower individuals and provide transparency [132], in this setting appropriate education would be necessary [19]. Given Kontola et al's experience [99] one might consider a hybrid approach, for example offering unblinding after a defined observation period. However, more studies are needed that compare blinded vs unblinded use in early-stage type 1 diabetes.

Duration and frequency of CGM wear

The optimal duration and frequency of CGM wear in early-stage type 1 diabetes remains under consideration. In established type 1 diabetes, multiple studies suggest that 12–15 days of data [133–135] are sufficient to provide reliable estimates of mean glucose, glycaemic variability and time in range, with strong correlations with 3 month glycaemic profiles [136–139]. This may be an appropriate target for the duration of CGM wear in early-stage type 1 diabetes in the context of prediction. The frequency of CGM use in early-stage type 1 diabetes must balance adequate data capture with participant burden and cost, arising from the device itself, the need for training and educational resources, and data interpretation. Current recommendations suggest repeat CGM screening every 6–36 months in adults, depending on the immune burden and risk of progression [13, 138, 140]. In children, frequency varies by age and immune burden, ranging from every 3 months in those aged under 3 years or with dysglycaemia to annually in those aged over 9 years in stage 1 [13, 19, 91]. However, considering the relatively common metabolic fluctuations in early-stage type 1 diabetes, prolonged CGM wear may be warranted in selected individuals to capture evolving glycaemic patterns; this requires further study.

Another important consideration is data quality. International consensus guidelines recommend ≥70% CGM wear time in established type 1 diabetes to ensure reliable metrics [137, 138] and that all CGM data should be analysed to avoid the introduction of bias [138]. However, these standards need further elucidation in early-stage type 1 diabetes.

Reliability

Although the accuracy of CGM devices has improved, even current generation devices show inter-device variability that affects derived metrics [110–112, 115, 119, 141]. These discrepancies reflect variations in calibration methods and signal processing, compounded by the absence of a universally standardised reference for factory calibration, underscoring the need for harmonised validation protocols across devices [116, 119, 120]. The current FDA approach for integrated CGM (iCGM) systems [142] defines device accuracy criteria for regulatory approval but does not standardise study design or comparator methodology; hence, devices may comply with special control requirements, yet differ in performance [114, 119, 143].

Beyond inter-device variability arising from systematic differences between manufacturers, models, and sensors of the same model, reliability is also shaped by data completeness and user acceptability; attrition due to incomplete data or participant refusal can limit both trial feasibility and real-world adoption. Biological and technical factors add further variability and indeed can result in deviations from the 'true' value over the period of wear. Local blood flow, hydration status and inflammatory responses at the insertion site can alter tissue fluid dynamics, while most sensors, relying on glucose oxidase-based electrochemistry, are susceptible to interference from other molecules. Depending on enzyme formulation and applied voltage, endogenous metabolites such as uric acid and ascorbic acid, as well as exogenous compounds including paracetamol (acetaminophen) and dietary components, can perturb current flow at the sensor tip and artificially shift reported glucose values [144]. User surveys also highlight perceived accuracy limitations under real-world conditions, including during dehydration or illness or with use of over-the-counter medications and vitamin C, although formal validation studies remain sparse for many of these scenarios [145]. It remains unclear if current CGM systems experience reduced accuracy across a broad range of physiological conditions; however, recent consensus statements suggest that modern CGM systems retain acceptable accuracy in people with advanced chronic kidney disease and on dialysis [146].

Finally, interstitial-to-plasma glucose lag remains a consideration. Although less likely to cause systematic misclassification in early-stage research, where analyses are retrospective and abnormalities modest, it remains a source of noise [147, 148].

Collectively, although individually small, these biological, behavioural and sensor related-sources of variability can accumulate, potentially influencing prognostic/diagnostic thresholds used in early-stage type 1 diabetes, and reinforce the need for rigorous standardisation before CGM metrics can be reliably accepted as regulatory endpoints.

Cost and access

In established type 1 diabetes, CGM has been shown to be cost-effective compared with SMBG, through reductions in

healthcare use, hospitalisations and diabetes complications [149, 150].

In early-stage type 1 diabetes, the cost-effectiveness of CGM is unknown. One can speculate that CGM might offset screening and monitoring costs by reducing reliance on resource-intensive tests such as the OGTT or by enabling earlier, risk-stratified interventions; however, formal economic assessments are required. These should ideally model multiple scenarios using real-world screening data and healthcare use rates to assess the value of CGM in early-stage type 1 diabetes.

Analysis of CGM data

Analytical approaches to CGM in early-stage type 1 diabetes are evolving. Most studies use simple descriptive metrics (e.g. percentage time above, below or within ranges), but such static summaries lose the richness of glucose as a continuous time series and are sensitive to missing or irregular data [151]. This has prompted calls for more advanced methods, including functional data analysis, machine learning and artificial intelligence [152], that could offer deeper insights into glucose dynamics.

Some emerging approaches show potential in early-stage type 1 diabetes. Glucodensity [153], which models glucose as a distributional function rather than discrete values, has uncovered risk phenotypes across normoglycaemic, type 2 diabetes and type 1 diabetes cohorts that are invisible to conventional metrics [153, 154]. Machine learning algorithms trained on 16 point OGTT curves have been applied to CGM data during standardised OGTTs, accurately identifying insulin resistance and beta cell dysfunction in a simple, at-home testing framework [155]. A similar testing framework has also been investigated in early-stage type 1 diabetes [97] using risk classifiers based on CGM summary features during a 2 h OGTT. While informative, this approach still compresses CGM data into static snapshots and may not fully capture important temporal dynamics describing underlying physiology.

Time series decomposition and forecasting approaches are also gaining traction, with recent work in type 2 diabetes showing that decomposed CGM traces can cluster representative glucose profiles and predict 6 month therapeutic responses [156], illustrating CGM's emerging potential as a predictive biomarker. Adapting these approaches could enhance CGM's prognostic value in early-stage type 1 diabetes by anticipating progression and detecting subtle metabolic inflections. As immunomodulatory trials expand, these approaches may eventually also inform the prediction of treatment response.

Furthermore, a recent FDA commentary underscores that, as CGM-derived endpoints gain prominence in regulatory decision-making, CGM data pose distinct statistical challenges, including epoch-level irregularities, data anomalies and non-random missingness, that must be handled transparently and consistently in trial analysis plans [157].

Table 2 Research priorities in CGM for early-stage type 1 diabetes

Duration	Priority
Short term	• Determine and agree internationally harmonised standards for CGM evaluation protocols between regulatory authorities and industry stakeholders to reduce inter- and intra-sensor variability • Define normative thresholds (age-specific) in antibody-negative control population and accompanying inter- and intra-sensor variability to inform CGM thresholds for staging and prediction • Determine acceptability of CGM wear in the early-stage type 1 diabetes general population compared with other metrics used in staging and monitoring (e.g. HbA_{1c}, OGTT, venous glucose) • Define the optimal frequency and duration of repeat CGM wear to monitor or predict progression • Define the optimal type 1 diabetes stage(s) for CGM use to predict progression • Quantify the impact of behaviour change with unblinded and blinded CGM wear and subsequent impact on staging and prediction of progression
Medium term	• Develop specific educational tools and guidance for clinicians and CGM users about the role of CGM in early-stage type 1 diabetes • Define the role of CGM in staging type 1 diabetes and as a surrogate prognostic biomarker for disease progression singularly and with other markers of beta cell health • Define the role of CGM in guiding the initiation of, and responses following, immunotherapy and/or insulin therapy • Evaluate the cost-effectiveness of CGM as an alternative to the gold standard measure (OGTT)
Long term	• Establish large general population CGM datasets for early-stage type 1 diabetes (children and adults) • Define the role of functional analysis and machine learning as alternative techniques to analyse CGM data in early-stage type 1 diabetes • Determine the long-term acceptability of CGM wear in early-stage type 1 diabetes individuals and develop support frameworks • Understand the factors that influence CGM uptake for equitable access to CGM in early-stage type 1 diabetes • Integrate CGM into regulatory biomarker qualification pathways for use as an endpoint in primary and secondary prevention trials

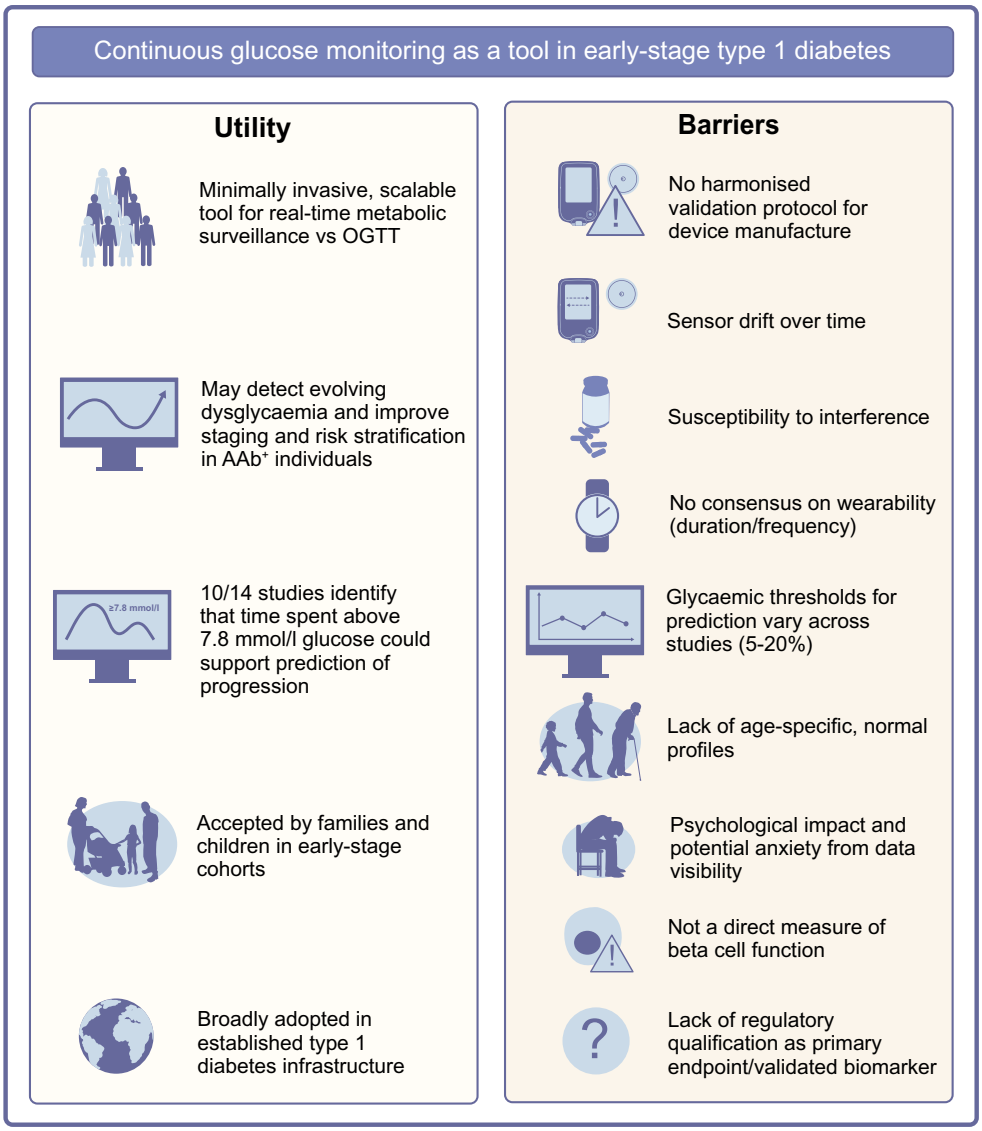

Fig. 3 Schematic overview of the potential utility of and key barriers to implementing CGM in early-stage type 1 diabetes. This figure is available as part of a downloadable slideset

Burden of monitoring and importance of acceptability in children

Beyond the technical and clinical considerations, the lived experiences of children and families must be recognised. Many children with stage 1 or 2 type 1 diabetes do not require intervention for years, making repeated clinical visits difficult to justify. Population-based screening will require follow-up strategies that prioritise acceptability, practicality and sustainability. Clear communication and education are essential to prevent disengagement. By offering a less burdensome option, CGM may improve adherence to and retention in longitudinal monitoring, especially when paired with psychosocial support and education [124, 126].

Regulatory perspectives

The FDA and European Medicines Agency (EMA) have acknowledged the clinical utility of CGM in the management of established type 1 diabetes, approving multiple devices to optimise glycaemic control and reduce hypoglycaemia risk. Their most recent guidance recognises CGM as a valuable tool but does not elevate it to a primary endpoint in prevention or preservation trials. The FDA's 2023 draft guidance [158] maintains HbA_{1c} as the primary endpoint, accepts CGM-based hypoglycaemic measures as validated, and treats other metrics such as time in range as exploratory. Similarly, the EMA's 2023 final guideline on diabetes trials [159, 160] encourages CGM use and explicitly accepts

24 h glucose profiles as secondary endpoints, but continues to require diabetes incidence (stages 1–2) or C-peptide/HbA_{1c} (stage 3) as primary endpoints. Neither agency has yet established a pathway for CGM as a primary endpoint in early-stage type 1 diabetes.

Moving towards such acceptance will require alignment with biomarker qualification frameworks such as FDA's BEST (Biomarkers, EndpointS, and other Tools) [18] and the EMA's process for novel biomarker validation, which emphasises analytical validity, clinical relevance and a defined context of use [161]. Recent FDA approvals of the Dexcom Stelo and Abbott's Rio and Lingo for adults who do not use insulin [162–164] underscore a regulatory openness to broader CGM applications, highlighting the potential relevance of CGM in early-stage type 1 diabetes.

To date, most evidence supports CGM's role as a prognostic tool. Its potential as a predictive biomarker, identifying subgroups most likely to benefit from immunotherapy or beta cell preservation strategies, remains to be explored. This distinction is critical for regulatory qualification and for defining the context of use in future implementation.

Looking ahead, prospective studies will be essential to establish CGM metrics as prognostic biomarkers for disease progression and supportive endpoints in intervention trials, particularly for patient selection, stratification and enrichment contexts where most successful biomarker qualifications have occurred [161]. Clear research priorities must be defined: Short-term efforts should focus on harmonising comparator methods and device validation; mid-term efforts on generating robust prospective evidence for CGM metrics as prognostic biomarkers; and long-term efforts on integration into regulatory biomarker qualification pathways (Table 2).

Conclusion

CGM has the potential to enhance assessment in early-stage type 1 diabetes, addressing critical unmet needs by providing minimally invasive, real-time assessments of glucose dynamics and detecting subtle, transient dysglycaemia that may be missed by intermittent testing. These features position CGM as a valuable complement or, in some contexts, a pragmatic alternative to the less practical gold standard OGTT. However, despite this promise, important barriers must be addressed. These include the need for appropriate contextualisation of comparative normal values, substantial inter-sensor variability (systematic differences between manufacturers, models, and sensors of the same model) and intra-sensor variability causing imprecision, bias and sensor drift over the wear period (arising from insertion effects, tissue changes, enzyme degradation or physiological conditions), uncertainty about optimal wear duration and frequency, lack of international standardisation, potential psychological burdens and unknown cost-effectiveness (Fig. 3).

Establishing CGM as a reliable tool for screening, staging and management in early-stage type 1 diabetes will require rigorous methodological validation, particularly if CGM-derived metrics are to be considered as prognostic biomarkers or trial endpoints. Prospective studies must define clinical validity, optimal implementation strategies and cost-effectiveness in early-stage disease. We therefore call for coordinated research efforts across academic, clinical, industry and regulatory partners to support the standardisation, integration and eventual regulatory qualification of CGM within early-stage type 1 diabetes frameworks.

Supplementary Information The online version contains a slideset of the figures for download available at https://doi.org/10.1007/s00125-026-06707-4.

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sium at the 61st Annual Meeting of the EASD in 2025. JV is a member of Sanofi's Advisory Committee for the BR1DGE programme. JV also serves on the Steering Committee of Sanofi's TH1NK Ahead initiative. The authors declare that there are no other relationships or activities that might bias, or be perceived to bias, their work.

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References

1. Gregory GA, Robinson TIG, Linklater SE et al (2022) Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: a modelling study. Lancet Diabetes Endocrinol 10(10):741–760. https://doi.org/10.1016/S2213-8587(22)00218-2
2. Cherubini V, Grimsmann JM, Åkesson K et al (2020) Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents. Diabetologia 63(8):1530–1541. https://doi.org/10.1007/s00125-020-05152-1
3. Wolfsdorf J, Craig ME, Daneman D et al (2009) Diabetic ketoacidosis in children and adolescents with diabetes. Pediatric Diabetes 10(s12):118–133. https://doi.org/10.1111/j.1399-5448.2009.00569.x
4. Hummel S, Carl J, Friedl N et al (2023) Children diagnosed with presymptomatic type 1 diabetes through public health screening have milder diabetes at clinical manifestation. Diabetologia 66(9):1633–1642. https://doi.org/10.1007/s00125-023-05953-0
5. Atkinson MA, Campbell-Thompson M, Kusmartseva I, Kaestner KH (2020) Organisation of the human pancreas in health and in diabetes. Diabetologia 63(10):1966–1973. https://doi.org/10.1007/s00125-020-05203-7
6. Rodriguez-Calvo T, Richardson SJ, Pugliese A (2018) Pancreas pathology during the natural history of type 1 diabetes. Curr Diab Rep 18(11):124. https://doi.org/10.1007/s11892-018-1084-3
7. Insel RA, Dunne JL, Atkinson MA et al (2015) Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 38(10):1964–1974. https://doi.org/10.2337/dc15-1419
8. Besser REJ, Bell KJ, Couper JJ et al (2022) ISPAD Clinical Practice Consensus Guidelines 2022: stages of type 1 diabetes in children and adolescents. Pediatric Diabetes 23(8):1175–1187. https://doi.org/10.1111/pedi.13410
9. American Diabetes Association Professional Practice Committee (2024) 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 48(Suppl 1):S27–S49. https://doi.org/10.2337/dc25-S002
10. Vercauteren J, EDENT1FI consortium (2025) Harmonising terminology for type 1 diabetes: the EDENT1FI lexicon initiative. Lancet Diabetes Endocrinol 13(11):P905-907. https://doi.org/10.1016/S2213-8587(25)00284-0
11. Allen LA, Dayan CM (2021) Immunotherapy for type 1 diabetes. Br Med Bull 140(1):76–90. https://doi.org/10.1093/bmb/ldab027
12. Sims EK, Besser REJ, Dayan C et al (2022) Screening for type 1 diabetes in the general population: a status report and perspective. Diabetes 71(4):610–623. https://doi.org/10.2337/dbi20-0054
13. Phillip M, Achenbach P, Addala A et al (2024) Consensus guidance for monitoring individuals with islet autoantibody-positive pre-stage 3 type 1 diabetes. Diabetes Care 47(8):1276–1298. https://doi.org/10.2337/dci24-0042
14. Sims EK, Geyer S, Johnson SB et al (2019) Who is enrolling? The path to monitoring in type 1 diabetes TrialNet's pathway to prevention. Diabetes Care 42(12):2228–2236. https://doi.org/10.2337/dc19-0593
15. Mooy JM, Grootenhuis PA, de Vries H et al (1996) Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. Diabetologia 39(3):298–305. https://doi.org/10.1007/BF00418345
16. Sacks DB (2011) A1C versus glucose testing: a comparison. Diabetes Care 34(2):518–523. https://doi.org/10.2337/dc10-1546
17. Chai JH, Ma S, Heng D et al (2017) Impact of analytical and biological variations on classification of diabetes using fasting plasma glucose, oral glucose tolerance test and HbA1c. Sci Rep 7(1):13721. https://doi.org/10.1038/s41598-017-14172-8
18. FDA-NIH Biomarker Working Group (2016) BEST (Biomarkers, EndpointS, and other Tools) resource. US Food and Drug Administration, Silver Spring, MD, USA
19. Mader JK, Wong JC, Freckmann G et al (2025) The use of continuous glucose monitoring to diagnose stage 2 type 1 diabetes. J Diabetes Sci Technol 19(4):1109–1127. https://doi.org/10.1177/19322968251333441
20. Narayan K, Mikler K, Maguire A, Craig ME, Bell K (2025) The current landscape for screening and monitoring of early-stage type 1 diabetes. J Paediatr Child Health 61(5):676–684. https://doi.org/10.1111/jpc.70016
21. Ziegler AG, Rewers M, Simell O et al (2013) Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 309(23):2473–2479. https://doi.org/10.1001/jama.2013.6285
22. Bonifacio E (2015) Predicting type 1 diabetes using biomarkers. Diabetes Care 38(6):989–996. https://doi.org/10.2337/dc15-0101
23. Felton JL, Redondo MJ, Oram RA et al (2024) Islet autoantibodies as precision diagnostic tools to characterize heterogeneity in type 1 diabetes: a systematic review. Commun Med 4(1):66. https://doi.org/10.1038/s43856-024-00478-y
24. Kwon BC, Achenbach P, Anand V et al (2022) Islet autoantibody levels differentiate progression trajectories in individuals with presymptomatic type 1 diabetes. Diabetes 71(12):2632–2641. https://doi.org/10.2337/db22-0360
25. Sims EK, Cuthbertson D, Ferrat LA et al (2025) IA-2A positivity increases risk of progression within and across established stages of type 1 diabetes. Diabetologia 68(5):993–1004. https://doi.org/10.1007/s00125-025-06382-x
26. Sosenko JM, Skyler JS, Herold KC, Palmer JP (2012) The metabolic progression to type 1 diabetes as indicated by serial oral glucose tolerance testing in the diabetes prevention trial-type 1. Diabetes 61(6):1331–1337. https://doi.org/10.2337/db11-1660
27. Herold KC, Bundy BN, Long SA et al (2019) An anti-CD3 antibody, teplizumab, in relatives at risk for type 1 diabetes. N Engl J Med 381(7):603–613. https://doi.org/10.1056/NEJMoa1902226

28. Hummel S, Koeger M, Bonifacio E, Ziegler A-G (2025) Dysglycaemia definitions and progression to clinical type 1 diabetes in children with multiple islet autoantibodies. Lancet Diabetes Endocrinol 13(1):10–12. https://doi.org/10.1016/S2213-8587(24)00337-1
29. Helminen O, Aspholm S, Pokka T et al (2014) HbA1c predicts time to diagnosis of type 1 diabetes in children at risk. Diabetes 64(5):1719–1727. https://doi.org/10.2337/db14-0497
30. Salami F, Tamura R, You L et al (2022) HbA1c as a time predictive biomarker for an additional islet autoantibody and type 1 diabetes in seroconverted TEDDY children. Pediatr Diabetes 23(8):1586–1593. https://doi.org/10.1111/pedi.13413
31. Stene LC, Barriga K, Hoffman M et al (2006) Normal but increasing hemoglobin A1c levels predict progression from islet autoimmunity to overt type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). Pediatr Diabetes 7(5):247–253. https://doi.org/10.1111/j.1399-5448.2006.00198.x
32. Vehik K, Boulware D, Killian M et al (2022) Rising hemoglobin A1c in the nondiabetic range predicts progression of type 1 diabetes as well as oral glucose tolerance tests. Diabetes Care 45(10):2342–2349. https://doi.org/10.2337/dc22-0828
33. Gallagher EJ, Le Roith D, Bloomgarden Z (2009) Review of hemoglobin A(1c) in the management of diabetes. J Diabetes 1(1):9–17. https://doi.org/10.1111/j.1753-0407.2009.00009.x
34. Evans-Molina C, Sims EK, DiMeglio LA et al (2018) β cell dysfunction exists more than 5 years before type 1 diabetes diagnosis. JCI Insight 3(15):e120877. https://doi.org/10.1172/jci.insight.120877
35. Sosenko JM, Skyler JS, Beam CA et al (2013) Acceleration of the loss of the first-phase insulin response during the progression to type 1 diabetes in diabetes prevention trial-type 1 participants. Diabetes 62(12):4179–4183. https://doi.org/10.2337/db13-0656
36. Weiss A, Zapardiel-Gonzalo J, Voss F et al (2022) Progression likelihood score identifies substages of presymptomatic type 1 diabetes in childhood public health screening. Diabetologia 65(12):2121–2131. https://doi.org/10.1007/s00125-022-05780-9
37. Pribitzer S, O'Rourke C, Ylescupidez A et al (2024) Beyond stages: predicting individual time dependent risk for type 1 diabetes. J Clin Endocrinol Metab 109(12):3211–3219. https://doi.org/10.1210/clinem/dgae292
38. Galderisi A, Sims EK, Evans-Molina C et al (2025) Trajectory of beta cell function and insulin clearance in stage 2 type 1 diabetes: natural history and response to teplizumab. Diabetologia 68(3):646–661. https://doi.org/10.1007/s00125-024-06323-0
39. Galderisi A, Carr ALJ, Martino M, Taylor P, Senior P, Dayan C (2023) Quantifying beta cell function in the preclinical stages of type 1 diabetes. Diabetologia 66(12):2189–2199. https://doi.org/10.1007/s00125-023-06011-5
40. Kahn SE, Prigeon RL, McCulloch DK et al (1993) Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 42(11):1663–1672. https://doi.org/10.2337/diab.42.11.1663
41. Bergman RN, Ader M, Huecking K, Van Citters G (2002) Accurate assessment of beta-cell function: the hyperbolic correction. Diabetes 51(Suppl 1):S212-220. https://doi.org/10.2337/diabetes.51.2007.s212
42. Ismail HM, Cuthbertson D, Galderisi A et al (2025) The disposition index in autoantibody-positive individuals at risk for type 1 diabetes. Diabetes 74(7):1196–1204. https://doi.org/10.2337/db24-1000
43. Russell WE, Bundy BN, Anderson MS et al (2023) Abatacept for delay of type 1 diabetes progression in stage 1 relatives at risk: a randomized, double-masked, controlled trial. Diabetes Care 46(5):1005–1013. https://doi.org/10.2337/dc22-2200
44. Herold KC, Gitelman SE, Masharani U et al (2005) A single course of anti-CD3 monoclonal antibody hOKT3gamma1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. Diabetes 54(6):1763–1769. https://doi.org/10.2337/diabetes.54.6.1763
45. Herold KC, Gitelman SE, Ehlers MR et al (2013) Teplizumab (anti-CD3 mAb) treatment preserves C-peptide responses in patients with new-onset type 1 diabetes in a randomized controlled trial: metabolic and immunologic features at baseline identify a subgroup of responders. Diabetes 62(11):3766–3774. https://doi.org/10.2337/db13-0345
46. Haller MJ, Schatz DA, Skyler JS et al (2018) Low-dose Anti-Thymocyte Globulin (ATG) preserves β-cell function and improves HbA1c in new-onset type 1 diabetes. Diabetes Care 41(9):1917–1925. https://doi.org/10.2337/dc18-0494
47. Jacobsen LM, Bundy BN, Greco MN et al (2020) Comparing beta cell preservation across clinical trials in recent-onset type 1 diabetes. Diabetes Technol Ther 22(12):948–953. https://doi.org/10.1089/dia.2020.0305
48. Keskinen P, Korhonen S, Kupila A et al (2002) First-phase insulin response in young healthy children at genetic and immunological risk for Type I diabetes. Diabetologia 45(12):1639–1648. https://doi.org/10.1007/s00125-002-0981-8
49. Balti EV, Vandemeulebroucke E, Weets I et al (2015) Hyperglycemic clamp and oral glucose tolerance test for 3-year prediction of clinical onset in persistently autoantibody-positive offspring and siblings of type 1 diabetic patients. J Clin Endocrinol Metab 100(2):551–560. https://doi.org/10.1210/jc.2014-2035
50. Vandemeulebroucke E, Keymeulen B, Decochez K et al (2010) Hyperglycaemic clamp test for diabetes risk assessment in IA-2-antibody-positive relatives of type 1 diabetic patients. Diabetologia 53(1):36–44. https://doi.org/10.1007/s00125-009-1569-3
51. Sims EK, Geyer SM, Long SA, Herold KC (2023) High proinsulin:C-peptide ratio identifies individuals with stage 2 type 1 diabetes at high risk for progression to clinical diagnosis and responses to teplizumab treatment. Diabetologia 66(12):2283–2291. https://doi.org/10.1007/s00125-023-06003-5
52. Truyen I, De Pauw P, Jørgensen PN et al (2005) Proinsulin levels and the proinsulin:c-peptide ratio complement autoantibody measurement for predicting type 1 diabetes. Diabetologia 48(11):2322–2329. https://doi.org/10.1007/s00125-005-1959-0
53. Dalem AV, Demeester S, Balti EV et al (2016) Prediction of impending type 1 diabetes through automated dual-label measurement of proinsulin:C-peptide ratio. Plos One 11(12):e0166702. https://doi.org/10.1371/journal.pone.0166702
54. Lam A, Oram RA, Forbes S et al (2022) Estimation of early graft function using the BETA-2 score following clinical islet transplantation. Transpl Int 35:10335. https://doi.org/10.3389/ti.2022.10335
55. Forbes S, Oram RA, Smith A et al (2016) Validation of the BETA-2 score: an improved tool to estimate beta cell function after clinical islet transplantation using a single fasting blood sample. Am J Transplant 16(9):2704–2713. https://doi.org/10.1111/ajt.13807
56. Taylor PN, Collins KS, Lam A et al (2023) C-peptide and metabolic outcomes in trials of disease modifying therapy in new-onset type 1 diabetes: an individual participant meta-analysis. Lancet Diabetes Endocrinol 11(12):915–925. https://doi.org/10.1016/S2213-8587(23)00267-X
57. So M, Vogrin S, Waibel M, Kay TWH, Wentworth JM (2025) β-cell function derived from routine clinical measures reports and predicts treatment response to immunotherapy in recent-onset type 1 diabetes. Diabetes Care 48(8):1370–1376. https://doi.org/10.2337/dc25-0565

58. Le Minh V, Harrison LC, Spelman T, Wentworth JM (2025) M120 risk score improves identification of children at high risk of developing clinical type 1 diabetes and reports short-term response to preventive immunotherapy. Diabetes Care 48(8):1352–1355. https://doi.org/10.2337/dc24-2794
59. Bundy BN, Krischer JP, Type 1 Diabetes TrialNet Study Group (2020) A quantitative measure of treatment response in recent-onset type 1 diabetes. Endocrinol Diabetes Metab 3(3):e00143. https://doi.org/10.1002/edm2.143
60. Sosenko JM, Krischer JP, Palmer JP et al (2008) A risk score for type 1 diabetes derived from autoantibody-positive participants in the diabetes prevention trial-type 1. Diabetes Care 31(3):528–533. https://doi.org/10.2337/dc07-1459
61. Nathan BM, Redondo MJ, Ismail H et al (2022) Index60 identifies individuals at appreciable risk for stage 3 among an autoantibody-positive population with normal 2-hour glucose levels: implications for current staging criteria of type 1 diabetes. Diabetes Care 45(2):311–318. https://doi.org/10.2337/dc21-0944
62. Sosenko JM, Skyler JS, Palmer JP, The Diabetes Type 1 TrialNet and Diabetes Prevention Trial-Type 1 Study Groups (2015) The development, validation, and utility of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS). Curr Diab Rep 15(8):49. https://doi.org/10.1007/s11892-015-0626-1
63. Sosenko JM, Skyler JS, DiMeglio LA et al (2014) A new approach for diagnosing type 1 diabetes in autoantibody-positive individuals based on prediction and natural history. Diabetes Care 38(2):271–276. https://doi.org/10.2337/dc14-1813
64. Swaby R, Narayan K, Scudder C et al (2025) Testing methods used to predict disease progression in children with early-stage type 1 diabetes: a systematic review and meta-analysis. Diabet Med 42(9):e70077. https://doi.org/10.1111/dme.70077
65. Cobelli C, Dalla Man C, Toffolo G, Basu R, Vella A, Rizza R (2014) The oral minimal model method. Diabetes 63(4):1203–1213. https://doi.org/10.2337/db13-1198
66. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA (2005) β-cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. J Clin Endocrinol Metab 90(1):493–500. https://doi.org/10.1210/jc.2004-1133
67. Galderisi A, Moran A, Evans-Molina C et al (2021) Early impairment of insulin sensitivity, β-cell responsiveness, and insulin clearance in youth with stage 1 type 1 diabetes. J Clin Endocrinol Metab 106(9):2660–2669. https://doi.org/10.1210/clinem/dgab344
68. Sims EK, Mirmira RG, Evans-Molina C (2020) The role of beta-cell dysfunction in early type 1 diabetes. Curr Opin Endocrinol Diabetes Obes 27(4):215–224. https://doi.org/10.1097/MED.0000000000000548
69. Sosenko JM, Skyler JS, Krischer JP et al (2010) Glucose excursions between states of glycemia with progression to type 1 diabetes in the diabetes prevention trial-type 1 (DPT-1). Diabetes 59(10):2386–2389. https://doi.org/10.2337/db10-0534
70. Jacobsen LM, Atkinson MA, Sosenko JM, Gitelman SE (2024) Time to reframe the disease staging system for type 1 diabetes. Lancet Diabetes Endocrinol 12(12):924–933. https://doi.org/10.1016/S2213-8587(24)00239-0
71. Sosenko JM, Skyler JS, Mahon J et al (2014) Use of the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) for improving the accuracy of the risk classification of type 1 diabetes. Diabetes Care 37(4):979–984. https://doi.org/10.2337/dc13-2359
72. DiMeglio LA, Evans-Molina C, Oram RA (2018) Type 1 diabetes. Lancet 391(10138):2449–2462. https://doi.org/10.1016/S0140-6736(18)31320-5
73. Karges B, Prinz N, Placzek K et al (2021) A comparison of familial and sporadic type 1 diabetes among young patients. Diabetes Care 44(5):1116–1124. https://doi.org/10.2337/dc20-1829
74. Driscoll KA, Tamura R, Johnson SB et al (2021) Adherence to oral glucose tolerance testing in children in stage 1 of type 1 diabetes: the TEDDY study. Pediatr Diabetes 22(2):360–368. https://doi.org/10.1111/pedi.13149
75. Haller MJ, Bell KJ, Besser REJ et al (2024) ISPAD clinical practice consensus guidelines 2024: screening, staging, and strategies to preserve beta-cell function in children and adolescents with type 1 diabetes. Horm Res Paediatr 97(6):529–545. https://doi.org/10.1159/000543035
76. Haynes A, Tully A, Smith GJ et al (2024) Early dysglycemia is detectable using continuous glucose monitoring in very young children at risk of type 1 diabetes. Diabetes Care 47(10):1750–1756. https://doi.org/10.2337/dc24-0540
77. Hoffmann L, Kohls M, Arnolds S et al (2025) EDENT1FI Master Protocol for screening of presymptomatic early-stage type 1 diabetes in children and adolescents. https://doi.org/10.1136/bmjopen-2024-088522
78. McQueen RB, Geno Rasmussen C, Waugh K et al (2020) Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. Diabetes Care 43(7):1496–1503. https://doi.org/10.2337/dc19-2003
79. Ziegler A-G, Kick K, Bonifacio E et al (2020) Yield of a public health screening of children for islet autoantibodies in Bavaria, Germany. JAMA 323(4):339–351. https://doi.org/10.1001/jama.2019.21565
80. Chen C, Luca S, Hansen A et al (2025) Protocol for the development of a core outcome set for type 1 diabetes risk screening. BMJ Open. https://doi.org/10.1136/bmjopen-2025-099537
81. Bell KJ, Brodie S, Couper JJ et al (2024) Protocol for the Australian type 1 diabetes national screening pilot: assessing the feasibility and acceptability of three general population screening models in children. Diabet Med 41(11):e15419. https://doi.org/10.1111/dme.15419
82. Mulvihill C, Brooks A, Basudev N, Lincoln P (2022) Continuous glucose monitoring for adults and children with diabetes: summary of updated NICE guidance. BMJ 379:o2418. https://doi.org/10.1136/bmj.o2418
83. Ng SM (2023) NICE and NHS England leads the way to improve diabetes care with access to continuous glucose monitoring for people with type 1 diabetes. BMC Medicine 21(1):295. https://doi.org/10.1186/s12916-023-03014-2
84. American Diabetes Association Professional Practice Committee (2024) 7. Diabetes technology: standards of care in diabetes—2025. Diabetes Care 48(Suppl 1):S146–S166. https://doi.org/10.2337/dc25-S007
85. Blonde L, Umpierrez GE, Reddy SS et al (2022) American association of clinical endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan-2022 update. Endocr Pract 28(10):923–1049. https://doi.org/10.1016/j.eprac.2022.08.002
86. Tauschmann M, Forlenza G, Hood K et al (2022) ISPAD clinical practice consensus guidelines 2022: diabetes technologies: glucose monitoring. Pediatr Diabetes 23(8):1390–1405. https://doi.org/10.1111/pedi.13451
87. Helminen O, Pokka T, Tossavainen P, Ilonen J, Knip M, Veijola R (2016) Continuous glucose monitoring and HbA1c in the evaluation of glucose metabolism in children at high risk for type 1 diabetes mellitus. Diabetes Res Clin Pract 120:89–96. https://doi.org/10.1016/j.diabres.2016.07.027
88. Steck AK, Dong F, Taki I, Hoffman M, Klingensmith GJ, Rewers MJ (2014) Early hyperglycemia detected by continuous glucose monitoring in children at risk for type 1 diabetes. Diabetes Care 37(7):2031–2033. https://doi.org/10.2337/dc13-2965
89. Van Dalem A, Demeester S, Balti EV et al (2015) Relationship between glycaemic variability and hyperglycaemic clamp-derived functional variables in (impending) type 1 diabetes.

Diabetologia 58(12):2753–2764. https://doi.org/10.1007/s00125-015-3761-y
90. Steck AK, Dong F, Taki I et al (2019) Continuous glucose monitoring predicts progression to diabetes in autoantibody positive children. J Clin Endocrinol Metab 104(8):3337–3344. https://doi.org/10.1210/jc.2018-02196
91. Steck AK, Dong F, Geno Rasmussen C et al (2022) CGM metrics predict imminent progression to type 1 diabetes: Autoimmunity Screening for Kids (ASK) study. Diabetes Care 45(2):365–371. https://doi.org/10.2337/dc21-0602
92. Wilson DM, Pietropaolo SL, Acevedo-Calado M et al (2023) CGM metrics identify dysglycemic states in participants from the TrialNet pathway to prevention study. Diabetes Care 46(3):526–534. https://doi.org/10.2337/dc22-1297
93. Huber E, Singh T, Bunk M et al (2025) Discrimination and precision of continuous glucose monitoring in staging children with presymptomatic type 1 diabetes. J Clin Endocrinol Metab 110(6):1624–1632. https://doi.org/10.1210/clinem/dgae691
94. Desouter AK, Keymeulen B, Van de Velde U et al (2025) Repeated OGTT versus continuous glucose monitoring for predicting development of stage 3 type 1 diabetes: a longitudinal analysis. Diabetes Care 48(4):528–536. https://doi.org/10.2337/dc24-2376
95. Ylescupidez A, Speake C, Pietropaolo SL et al (2023) OGTT metrics surpass continuous glucose monitoring data for T1D prediction in multiple-autoantibody-positive individuals. J Clin Endocrinol Metab 109(1):57–67. https://doi.org/10.1210/clinem/dgad472
96. Montaser E, Breton MD, Brown SA, DeBoer MD, Kovatchev B, Farhy LS (2023) Predicting immunological risk for stage 1 and stage 2 diabetes using a 1-week CGM home test, nocturnal glucose increments, and standardized liquid mixed meal breakfasts, with classification enhanced by machine learning. Diabetes Technol Ther 25(9):631–642. https://doi.org/10.1089/dia.2023.0064
97. Montaser E, Brown SA, DeBoer MD, Farhy LS (2024) Predicting the risk of developing type 1 diabetes using a one-week continuous glucose monitoring home test with classification enhanced by machine learning: an exploratory study. J Diabetes Sci Technol 18(2):257–265. https://doi.org/10.1177/19322968231209302
98. Montaser E, Farhy LS, Rich SS (2025) Enhancing type 1 diabetes immunological risk prediction with continuous glucose monitoring and genetic profiling. Diabetes Technol Ther 27(4):292–300. https://doi.org/10.1089/dia.2024.0496
99. Kontola H, Alanko I, Koskenniemi JJ et al (2022) Exploring minimally invasive approach to define stages of type 1 diabetes remotely. Diabetes Technol Ther 24(9):655–665. https://doi.org/10.1089/dia.2021.0554
100. Calhoun P, Spanbauer C, Steck AK et al (2025) Continuous glucose monitor metrics from five studies identify participants at risk for type 1 diabetes development. Diabetologia 68(5):930–939. https://doi.org/10.1007/s00125-025-06362-1
101. Besser REJ, Griffin KJ (2024) Transitioning to stage 3 type 1 diabetes: when to start insulin. Lancet Diabetes Endocrinol 12(10):692–694. https://doi.org/10.1016/S2213-8587(24)00238-9
102. Mathieu C, Wych J, Hendriks AEJ et al (2025) Minimum effective low dose of antithymocyte globulin in people aged 5–25 years with recent-onset stage 3 type 1 diabetes (MELD-ATG): a phase 2, multicentre, double-blind, randomised, placebo-controlled, adaptive dose-ranging trial. Lancet 406(10510):1375–1388. https://doi.org/10.1016/S0140-6736(25)01674-5
103. Shah VN, DuBose SN, Li Z et al (2019) Continuous glucose monitoring profiles in healthy nondiabetic participants: a multicenter prospective study. J Clin Endocrinol Metab 104(10):4356–4364. https://doi.org/10.1210/jc.2018-02763
104. Spartano NL, Sultana N, Lin H et al (2025) Defining continuous glucose monitor time in range in a large, community-based cohort without diabetes. J Clin Endocrinol Metab 110(4):1128–1134. https://doi.org/10.1210/clinem/dgae626
105. Köhlmoos A, Dittmar M (2025) Glycemic variability and control by CGM in healthy older and young adults and their relationship with diet. J Endocr Soc 9(7):bvaf081. https://doi.org/10.1210/jendso/bvaf081
106. Pazos-Couselo M, Portos-Regueiro C, González-Rodríguez M et al (2022) Aging of glucose profiles in an adult population without diabetes. Diabetes Res Clin Pract 188:109929. https://doi.org/10.1016/j.diabres.2022.109929
107. Shou J, Chen P-J, Xiao W-H (2020) Mechanism of increased risk of insulin resistance in aging skeletal muscle. Diabetol Metab Syndr 12(1):14. https://doi.org/10.1186/s13098-020-0523-x
108. Keshet A, Shilo S, Godneva A et al (2023) CGMap: characterizing continuous glucose monitor data in thousands of non-diabetic individuals. Cell Metab 35(5):758-769.e3. https://doi.org/10.1016/j.cmet.2023.04.002
109. Hirsch IB (2018) Introduction: history of glucose monitoring. In: Hirsch IB, Batteliino T, Peters AL, Chamberlain JJ, Aleppo G, Bergenstal RM (eds) Role of continuous glucose monitoring in diabetes treatment. American Diabetes Association, Arlington, VA, USA
110. Pleus S, Kamecke U, Waldenmaier D et al (2021) Time in specific glucose ranges, glucose management indicator, and glycemic variability: impact of Continuous Glucose Monitoring (CGM) system model and sensor on CGM metrics. J Diabetes Sci Technol 15(5):1104–1110. https://doi.org/10.1177/19322968209318251
111. Freckmann G, Pleus S, Schauer S et al (2021) Choice of continuous glucose monitoring systems may affect metrics: clinically relevant differences in times in ranges. Exp Clin Endocrinol Diabetes 130:343–350. https://doi.org/10.1055/a-1347-2550
112. Freckmann G, Wehrstedt S, Eichenlaub M et al (2025) A comparative analysis of glycemic metrics derived from three continuous glucose monitoring systems. Diabetes Care 48(7):1213–1217. https://doi.org/10.2337/dc25-0129
113. Kim SJ, Hirsch IB (2025) Intersystem accuracy in continuous glucose monitoring: when does this matter? Diabetes Care 48(7):1161–1163. https://doi.org/10.2337/dci25-0035
114. Waldenmaier D, Wehrstedt S, Eichenlaub M et al (2025) Response to comments on Freckmann et al. A comparative analysis of glycemic metrics derived from three continuous glucose monitoring systems. Diabetes Care 48(10):e128–e129. https://doi.org/10.2337/dci25-0071
115. Eichenlaub M, Waldenmaier D, Wehrstedt S et al (2025) Performance of three continuous glucose monitoring systems in adults with type 1 diabetes. J Diabetes Sci Technol. https://doi.org/10.1177/19322968251315459
116. Pleus S, Eichenlaub M, Eriksson Boija E et al (2024) The need for standardization of continuous glucose monitoring performance evaluation: an opinion by the international federation of clinical chemistry and laboratory medicine working group on continuous glucose monitoring. J Diabetes Sci Technol. https://doi.org/10.1177/19322968241296097
117. Pleus S, Eichenlaub M, Gerber T et al (2024) Improving the bias of comparator methods in analytical performance assessments through recalibration. J Diabetes Sci Technol 18(3):686–694. https://doi.org/10.1177/19322968221133107
118. Bailey TS, Klaff LJ, Wallace JF et al (2016) Fundamental importance of reference glucose analyzer accuracy for evaluating the performance of Blood Glucose Monitoring Systems (BGMSs).

J Diabetes Sci Technol 10(4):872–875. https://doi.org/10.1177/1932296816634356
119. Freckmann G, Pleus S, Eichenlaub M et al (2025) Recommendations on the collection of comparator measurement data in the performance evaluation of continuous glucose monitoring systems. J Diabetes Sci Technol 19(4):1072–1081. https://doi.org/10.1177/19322968251336221
120. Pemberton JS, Adolfsson P, Wilmot EG, Choudhary P, Moser O (2025) Urgent need for standardization in CGM performance assessment. Diabetes Care 48(10):e126–e127. https://doi.org/10.2337/dc25-1213
121. Johnson SB, Lynch KF, Roth R, Schatz D (2017) My child is islet autoantibody positive: impact on parental anxiety. Diabetes Care 40(9):1167–1172. https://doi.org/10.2337/dc17-0166
122. Johnson SB, Smith LB (2023) General population screening for islet autoantibodies: psychosocial challenges. Diabetes Care 46(12):2123–2125. https://doi.org/10.2337/dci23-0061
123. O'Donnell HK, Rasmussen CG, Dong F et al (2023) Anxiety and risk perception in parents of children identified by population screening as high risk for type 1 diabetes. Diabetes Care 46(12):2155–2161. https://doi.org/10.2337/dc23-0350
124. Roberts AG, Tully AS, Binkowski SK et al (2024) Parental experiences of using continuous glucose monitoring in their young children with early-stage type 1 diabetes: a qualitative interview study. Front Clin Diabetes Healthc 5. https://doi.org/10.3389/fcdhc.2024.1479948
125. Markowitz JT, Pratt K, Aggarwal J, Volkening LK, Laffel LMB (2012) Psychosocial correlates of continuous glucose monitoring use in youth and adults with type 1 diabetes and parents of youth. Diabetes Technol Ther 14(6):523–526. https://doi.org/10.1089/dia.2011.0201
126. Pickup JC, Ford Holloway M, Samsi K (2015) Real-time continuous glucose monitoring in type 1 diabetes: a qualitative framework analysis of patient narratives. Diabetes Care 38(4):544–550. https://doi.org/10.2337/dc14-1855
127. Tansey M, Laffel L, Cheng J et al (2011) Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes. Diabet Med 28(9):1118–1122. https://doi.org/10.1111/j.1464-5491.2011.03368.x
128. Ramchandani N, Arya S, Ten S, Bhandari S (2011) Real-life utilization of real-time continuous glucose monitoring: the complete picture. J Diabetes Sci Technol 5(4):860–870. https://doi.org/10.1177/193229681100500407
129. Patton SR, Clements MA (2016) Psychological reactions associated with continuous glucose monitoring in youth. J Diabetes Sci Technol 10(3):656–661. https://doi.org/10.1177/1932296816638109
130. Smith LB, Lynch KF, Baxter J et al (2014) Factors associated with maternal-reported actions to prevent type 1 diabetes in the first year of the TEDDY study. Diabetes Care 37(2):325–331. https://doi.org/10.2337/dc13-0449
131. Smith LB, Lynch KF, Driscoll KA, Johnson SB, TEDDY Study Group (2021) Parental monitoring for type 1 diabetes in genetically at-risk young children: the TEDDY study. Pediatr Diabetes 22(5):717–728. https://doi.org/10.1111/pedi.13173
132. Ahn D, Pettus J, Edelman S (2016) Unblinded CGM should replace blinded CGM in the clinical management of diabetes. J Diabetes Sci Technol 10(3):793–798. https://doi.org/10.1177/1932296816632241
133. Mazze RS, Strock E, Wesley D et al (2008) Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. Diabetes Technol Ther 10(3):149–159. https://doi.org/10.1089/dia.2007.0293
134. Xing D, Kollman C, Beck RW et al (2011) Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther 13(3):351–358. https://doi.org/10.1089/dia.2010.0156
135. Neylon OM, Baghurst PA, Cameron FJ (2014) The minimum duration of sensor data from which glycemic variability can be consistently assessed. J Diabetes Sci Technol 8(2):273–276. https://doi.org/10.1177/1932296813519011
136. Riddlesworth TD, Beck RW, Gal RL et al (2018) Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. Diabetes Technol Ther 20(4):314–316. https://doi.org/10.1089/dia.2017.0455
137. Danne T, Nimri R, Battelino T et al (2017) International consensus on use of continuous glucose monitoring. Diabetes Care 40(12):1631–1640. https://doi.org/10.2337/dc17-1600
138. Battelino T, Alexander CM, Amiel SA et al (2023) Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. Lancet Diabetes Endocrinol 11(1):42–57. https://doi.org/10.1016/S2213-8587(22)00319-9
139. Battelino T, Danne T, Bergenstal RM et al (2019) Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 42(8):1593–1603. https://doi.org/10.2337/dci19-0028
140. O'Rourke C, Ylescupidez A, Bahnson HT et al (2023) Risk modeling to reduce monitoring of an autoantibody-positive population to prevent DKA at type 1 diabetes diagnosis. J Clin Endocrinol Metab 108(3):688–696. https://doi.org/10.1210/clinem/dgac594
141. Sutton H, Boughton CK, Allen JM et al (2023) Variation in the reporting of glucose values during simultaneous glucose sensor wear. Practical Diabetes 40(6):12–16. https://doi.org/10.1002/pdi.2482
142. US Food and Drug Administration (2022) Medical devices; Clinical chemistry and clinical toxicology devices; classification of the Integrated continuous glucose monitoring system. Available from: https://www.federalregister.gov/documents/2022/02/18/2022-03504/medical-devices-clinical-chemistry-and-clinical-toxicology-devices-classification-of-the-integrated. Accessed 23 Sept 2025
143. Eichenlaub M, Waldenmaier D, Pleus S, Haug C, Brandt D, Freckmann G (2025) Compliance with FDA iCGM special controls is dependent on study design and procedures. J Diabetes Sci Technol. https://doi.org/10.1177/19322968251329879
144. Heinemann L (2021) Interferences with CGM systems: practical relevance? J Diabetes Sci Technol 16(2):271–274. https://doi.org/10.1177/19322968211065065
145. Holt E, Nguyen H, Bispham J, Liu J, Chapman K, Grady M (2024) Perceptions of continuous glucose monitoring systems in the T1D exchange diabetes registry: satisfaction, concerns, and areas for future improvement. Clin Diabetes 42(1):104–115. https://doi.org/10.2337/cd23-0005
146. Rhee CM, Gianchandani RY, Kerr D et al (2024) Consensus report on the use of continuous glucose monitoring in chronic kidney disease and diabetes. J Diabetes Sci Technol. https://doi.org/10.1177/19322968241292041
147. Davey RJ, Low C, Jones TW, Fournier PA (2010) Contribution of an intrinsic lag of continuous glucose monitoring systems to differences in measured and actual glucose concentrations changing at variable rates in vitro. J Diabetes Sci Technol 4(6):1393–1399. https://doi.org/10.1177/193229681000400614
148. Færch K, Amadid H, Bruhn L et al (2021) Discordance between glucose levels measured in interstitial fluid vs in venous plasma after oral glucose administration: a post-hoc analysis from the

randomised controlled PRE-D trial. Front Endocrinol 12. https://doi.org/10.3389/fendo.2021.753810
149. Jiao Y, Lin R, Hua X et al (2022) A systematic review: cost-effectiveness of continuous glucose monitoring compared to self-monitoring of blood glucose in type 1 diabetes. Endocrinol Diabetes Metab 5(6):e369. https://doi.org/10.1002/edm2.369
150. Huang ES, O'Grady M, Basu A et al (2010) The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes Care 33(6):1269–1274. https://doi.org/10.2337/dc09-2042
151. Clarke W, Kovatchev B (2009) Statistical tools to analyze continuous glucose monitor data. Diabetes Technol Ther 11(Suppl 1):S-45-S−54. https://doi.org/10.1089/dia.2008.0138
152. Klonoff DC, Bergenstal RM, Cengiz E et al (2025) CGM data analysis 2.0: functional data pattern recognition and artificial intelligence applications. J Diabetes Sci Technol. https://doi.org/10.1177/19322968251353228
153. Matabuena M, Petersen A, Vidal JC, Gude F (2021) Glucodensities: a new representation of glucose profiles using distributional data analysis. Stat Methods Med Res 30(6):1445–1464. https://doi.org/10.1177/0962280221998064
154. Cui EH, Goldfine AB, Quinlan M, James DA, Sverdlov O (2023) Investigating the value of glucodensity analysis of continuous glucose monitoring data in type 1 diabetes: an exploratory analysis. Front Clin Diabetes Healthc 4. https://doi.org/10.3389/fcdhc.2023.1244613
155. Metwally AA, Perelman D, Park H et al (2024) Prediction of metabolic subphenotypes of type 2 diabetes via continuous glucose monitoring and machine learning. Nat Biomed Eng. https://doi.org/10.1038/s41551-024-01311-6
156. Li L, Sun J, Ruan L, Song Q (2021) Time-series analysis of continuous glucose monitoring data to predict treatment efficacy in patients with T2DM. J Clin Endocrinol Metab 106(8):2187–2197. https://doi.org/10.1210/clinem/dgab356
157. Kim Y, Crackel R, Cho HS, Tu W, Wang Y (2025) Beyond time in range: hidden statistical challenges of continuous glucose monitoring data in diabetes drug development. J Diabetes Sci Technol. https://doi.org/10.1177/19322968251394046
158. Center for Drug Evaluation and Research (2024) Diabetes mellitus: efficacy endpoints for clinical trials investigating antidiabetic drugs and biological products. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diabetes-mellitus-efficacy-endpoints-clinical-trials-investigating-antidiabetic-drugs-and-biological. Accessed 23 Sep 2025
159. Van der Schueren B, Vrijlandt P, Thomson A, Janssen H, Dunder K (2024) New guideline of the European Medicines Agency (EMA) on the clinical investigation of medicinal products in the treatment and prevention of diabetes mellitus. Diabetologia 67(7):1159–1162. https://doi.org/10.1007/s00125-024-06162-z
160. Committee for Medicinal Products for Human Use (CHMP) (2023) Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus – Scientific guideline. Available from: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-or-prevention-diabetes-mellitus-scientific-guideline. Accessed 23 Sep 2025
161. Bakker E, Hendrikse NM, Ehmann F et al (2022) Biomarker qualification at the European medicines agency: a review of biomarker qualification procedures from 2008 to 2020. Clin Pharmacol Ther 112(1):69–80. https://doi.org/10.1002/cpt.2554
162. US Food and Drug Administration (2024) FDA clears first over-the-counter continuous glucose monitor. Available from: https://www.fda.gov/news-events/press-announcements/fda-clears-first-over-counter-continuous-glucose-monitor. Accessed 11 May 2025
163. Abbott (2024) Abbott receives U.S. FDA clearance for two new over-the-counter continuous glucose monitoring systems. Available from: https://abbott.mediaroom.com/2024-06-10-Abbott-Receives-U-S-FDA-Clearance-for-Two-New-Over-the-Counter-Continuous-Glucose-Monitoring-Systems. Accessed 3 Jul 2025
164. US Food and Drug Administration (2024) 510(k) Premarket notification. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K233861. Accessed 23 Sep 2025