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Beyond type 1 and type 2: the case for CGM-based glycemic phenotyping to guide diabetes therapy

Abstract

Diabetes therapy is still chosen largely by diagnostic label (type 1, type 2) and by a single summary number, HbA1c. Yet two people with the same label and the same HbA1c can have very different glucose profiles: one runs steadily high, another swings between postprandial peaks and nocturnal lows. Continuous glucose monitoring (CGM) now captures these patterns in fine detail, and CGM use is expanding rapidly, including in India. In this Perspective we argue that the glucose profile itself — not only the etiological category — should be tested as a guide to treatment selection. We outline five candidate glycaemic phenotypes that can plausibly be identified from 14 days of CGM data (stable hyperglycaemia, hypoglycaemia-prone, postprandial-dominant, dawn-phenomenon-dominant and high-variability) and propose a matched therapeutic logic for each. We then describe a two-stage study design to test the idea: data-driven derivation and validation of phenotypes, followed by a pragmatic, randomised trial comparing phenotype-directed therapy with guideline-based care. Finally, we discuss the open questions — phenotype stability, the risk of over-fitting, cost and access, and the place of this approach alongside existing data-driven subtyping — that such a programme must answer before CGM phenotyping can enter routine practice. We also group the challenges facing this approach into clinical and physiological, technical and algorithmic, and patient and systemic categories, and outline future research directions spanning multi-omics integration, phenotype-targeted trials and next-generation multi-analyte sensing.

Keywords: continuous glucose monitoring, glycaemic phenotype, glucose variability, precision medicine, time in range, type 2 diabetes, India

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Abbreviations: ADA, American diabetes association; AI, artificial intelligence; BMI, body mass index; CGM, continuous glucose monitoring; CONGA, continuous overlapping net glycaemic action; CV, coefficient of variation; GAD, glutamic acid decarboxylase; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin; HBGI, high blood glucose index; HOMA, homeostatic model assessment; LBGI, low blood glucose index; MAGE, mean amplitude of glycaemic excursions; OGTT, oral glucose tolerance test; SGLT-2, sodium–glucose cotransporter-2; TIR, time in range.

Introduction

An estimated 589 million adults were living with diabetes worldwide in 2024, a figure projected to reach 853 million by 2050.[1] India alone has an estimated 101 million people with diabetes.[2] Despite a broad and growing pharmacopoeia, a large share of people treated for diabetes do not reach glycaemic targets, and treatment intensification is often delayed for years.[3] Part of the problem lies in how we choose therapy. Current guidance organises treatment around the etiological category - type 1, type 2 or other specific types - and steps up therapy mainly on HbA1c, with comorbidity and perceived risk (cardiovascular, renal, weight) shaping drug choice.[4] These are sound principles, but they describe *who the patient is*, not *how their glucose behaves*. Within a single category, people differ widely in the timing, size and stability of their glucose excursions, and in how they respond to the same drug.[5,6]

Data-driven approaches have begun to challenge the classic taxonomy. Cluster analysis of routine clinical variables has identified reproducible subgroups of adult-onset diabetes with distinct risks of complications[5], and simple clinical features can predict differential response to drug classes.[6] Separately, CGM studies have shown that glucose dysregulation follows recognisable patterns ("glucotypes") that cut across conventional categories,[7] and that post-meal responses to identical foods vary sharply between individuals.[8]

What has not yet been tested is the obvious next step: using the CGM-derived glucose profile *directly* to choose therapy, and asking whether doing so improves outcomes compared with standard care. This Perspective sets out the case for that approach, proposes a working framework of candidate phenotypes, and outlines how it could be evaluated rigorously.

Objective

The main objective of this Perspective is to propose, and set out a pathway to test, the hypothesis that CGM-derived glycaemic phenotypes can guide the choice of glucose-lowering therapy more effectively than diagnostic category and HbA1c alone. Specifically, we aim to (i) describe a working set of candidate phenotypes with a matched therapeutic logic; (ii) outline a two-stage programme for their derivation, validation and randomised evaluation; (iii) examine the clinical, technical and systemic challenges that could limit the approach; and (iv) identify the research directions needed to bring it into routine practice, with particular attention to the Indian setting.

What CGM reveals that HbA1c misses

HbA1c reflects average glycaemia over roughly three months. It says nothing about when glucose is high, how fast it moves, or how often it falls dangerously low. Two people with an HbA1c of 8.0% (64 mmol/mol) may have entirely different problems: one with fasting hyperglycaemia and flat daytime curves, another with modest fasting values but repeated postprandial peaks above 250 mg/dL (13.9 mmol/L) and nocturnal lows.

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CGM fills this gap. International consensus now defines a standard set of CGM metrics — time in range (TIR, 70–180 mg/dL [3.9–10.0 mmol/L]), time above and below range, and the coefficient of variation (CV), with agreed targets.[9] TIR is associated with microvascular complications such as retinopathy[10] and correlates with, but is not interchangeable with, HbA1c.[11] Glucose fluctuations also matter in their own right: acute swings activate oxidative stress more than sustained hyperglycaemia,[12] and the dawn phenomenon alone can add meaningfully to overall glucose exposure in type 2 diabetes.[13]

Beyond the core metrics, a 14-day CGM trace yields many further descriptors: the mean amplitude of glycaemic excursions (MAGE), continuous overlapping net glycaemic action (CONGA), dawn-phenomenon magnitude, postprandial excursion size, nocturnal nadir, and risk indices such as the low and high blood glucose indices (LBGI, HBGI).[14–16] Together these describe *glucose behaviour,* a layer of information that sits between pathophysiology and clinical outcome, and that is directly modifiable by treatment choice. Existing data-driven subtyping has mostly used baseline clinical and biochemical variables (age at onset, BMI, HbA1c, HOMA indices, GAD antibodies).[5,17] These subgroups predict complications well but have so far had limited influence on day-to-day prescribing.[6,18] CGM-based phenotyping differs in two ways: the features are dynamic, and each phenotype maps more naturally onto a specific therapeutic lever.

A proposed framework: five candidate glycaemic phenotypes

From clinical experience and the CGM literature, we propose five candidate phenotypes as a starting hypothesis (Table 1). They are not meant as a fixed taxonomy. There are other possibilities based on ADA-recommended CGM metrics as suggested by Jiahuan Helen et al.,[19]: "hypoglycemia high-variability," "moderate-hypoglycemia moderate-variability," "well-controlled," "moderate-hyperglycemia moderate-variability," and "hyperglycemia low-variability". The actual number and boundaries of phenotypes should come from data (see next section), and individuals may show features of more than one. The value of the framework is that each phenotype points to a different primary therapeutic lever, largely regardless of whether the person has type 1 or type 2 diabetes.

The CV cut-off of 36% follows international consensus.[9] All other features are for illustration only; operational definitions would come from the derivation stage described below. Proposed therapies are drawn from currently licensed options and would be applied within existing safety guidance, including cardiorenal indications.[4]

How to test it: a proposed two-stage programme

The framework is a hypothesis. We propose testing it in two linked stages (Figure 1), each answering a distinct question.

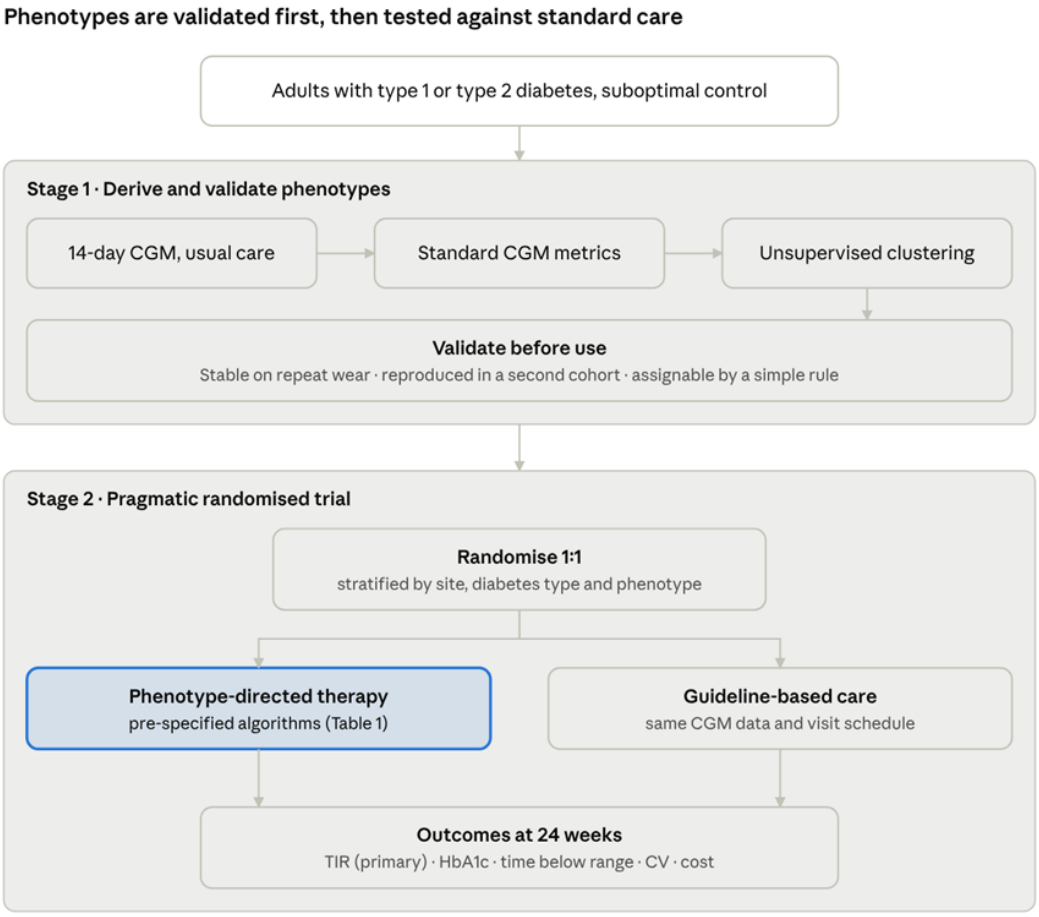


Figure 1 proposed two-stage programme.

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Figure 1 Proposed two-stage programme. Stage 1 derives and validates CGM phenotypes. Stage 2 randomises phenotyped participants to phenotype-directed therapy or guideline-based care, with the same CGM data and visit schedule in both arms.

Stage 1 - Do reproducible phenotypes exist? Adults with type 1 or type 2 diabetes and suboptimal control would wear a factory-calibrated CGM for 14 days under usual care, meeting the consensus data-sufficiency threshold of at least 70% sensor wear.[14] A pre-specified set of standard metrics would be computed using established methods.[14–16] Unsupervised clustering (for example, k-means or Gaussian mixture models after dimensionality reduction) would identify candidate phenotypes, with the number of clusters chosen by agreed internal-validity indices. We propose to conduct stage 1 with CGM data from 500 patients across 30 sites in India. Three tests are essential before any phenotype is used clinically:

I. **Stability within a person** - does a repeat 14-day CGM wear, weeks later and without a treatment change, assign the same phenotype?

II. **Reproducibility across cohorts** - do the phenotypes re-emerge in an independent validation cohort and across sites?

III. **Clinical interpretability** - can each cluster be described by a few metrics and assigned by a simple, transparent rule that a clinician could apply?

Stage 2 - Does phenotype-directed therapy improve outcomes? Participants would be randomised to phenotype-directed therapy, following pre-specified algorithms such as those in Table 1, or to guideline-based standard care.[4] Randomisation would be stratified by site, diabetes type and phenotype. A pragmatic, open-label design with blinded outcome assessment is realistic, since clinicians cannot be blinded to the strategy.

Table 1 Candidate CGM-derived glycaemic phenotypes and their proposed therapeutic emphasis

Phenotype	Distinguishing CGM features (illustrative)	Likely dominant driver	Proposed emphasis - type 2 diabetes	Proposed emphasis - type 1 diabetes
Stable hyperglycaemia	High mean glucose, high time above range, low CV, small excursions	Insufficient basal glucose lowering	Strengthen basal control: SGLT-2 inhibitor and/or basal insulin titrated to fasting target	Increase total daily dose; rebalance basal:bolus
Hypoglycaemia-prone	Elevated time below range and LBGI, frequent nocturnal lows, often alongside high peaks	Over-treatment, especially with insulin or sulfonylureas	De-escalate hypoglycaemia-causing agents; prefer glucose-dependent agents (e.g. GLP-1 receptor agonist); CGM low alerts	Automated insulin delivery where available; less aggressive correction factors
Postprandial-dominant	Near-target fasting glucose, large post-meal excursions, high MAGE	Inadequate prandial insulin response; meal composition	Prandial targeting: GLP-1 receptor agonist, □-glucosidase inhibitor, or pre-meal rapid-acting insulin; dietary review	Larger or earlier pre-meal bolus; revisit carbohydrate counting
Dawn-phenomenon-dominant	Rise of glucose between about 04:00 and 08:00 with otherwise moderate daytime values	Early-morning hepatic glucose output	Evening basal insulin timing or dose; agents that reduce fasting glucose	Pump: higher early-morning basal rate; injections: re-time or split basal dose
High variability	High CV (above 36%), frequent swings in both directions, inconsistent day-to-day pattern	Irregular meals, activity or dosing; complex regimens	Simplify regimen; structured self-management education; consistent meal pattern; closer remote follow-up	Structured education in dose adjustment; consider pump or automated insulin delivery

We suggest these elements:

I. **Primary outcome:** change in TIR over 24 weeks, measured by masked or blinded-analysis CGM. HbA1c would be a key secondary outcome, in line with consensus recommendations on CGM endpoints in clinical trials.[20]

II. **Secondary outcomes:** time below range (<70 and <54 mg/dL), time above range, CV, severe hypoglycaemia, body weight, treatment satisfaction, diabetes distress and cost.

III. **Effect heterogeneity:** pre-specified interaction tests by phenotype and diabetes type, to show *which* phenotypes benefit rather than reporting only an average effect.

IV. **Fidelity and safety:** monitoring of algorithm adherence, and an independent data-monitoring committee.

Sample size would be based on a minimal clinically important difference in TIR. A 5% absolute TIR gain (about 1 hour per day) is widely regarded as clinically meaningful.[9] Pilot data from Stage 1 would provide the variance estimates needed.

Challenges and open questions

Several uncertainties could undermine the approach, and a credible programme must address them openly. We group them into clinical and physiological challenges, technical and algorithmic limitations, and patient and systemic hurdles, followed by issues specific to trial design.

Clinical and physiological challenges

Lack of standardised diagnostic thresholds. International consensus defines targets for TIR, time below range and CV in people already diagnosed with diabetes,[9] but there are no agreed CGM thresholds for diagnosing dysglycaemia, for staging it, or for assigning a phenotype. Reference ranges in people without diabetes have only recently been described,[23] and proposed cut-offs for early type 1 diabetes, such as time above 140 mg/dL (7.8 mmol/L), remain research criteria rather than diagnostic standards.[24] Any phenotype boundary, for example the size of a dawn rise or postprandial excursion that qualifies as 'dominant', will therefore need to be defined empirically and agreed before it can be applied consistently across clinics.

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Reproducibility and generalisability. Glucose responses are noisy even under controlled conditions. In an inpatient feeding study, postprandial CGM responses to identical meals eaten about a week apart correlated only weakly within individuals,[25] and two different sensors worn simultaneously ranked the same meals differently.[26] Phenotypes built on short windows of postprandial data may therefore be less reproducible than they appear. Generalisability is a separate concern: most CGM phenotyping work comes from small, selected and largely Western cohorts, and may not transfer to populations with different body composition, diets and care pathways, including Indian patients.[17]

Phenotype stability. Glucose patterns shift with diet, illness, season, festivals and fasting, and with treatment itself. A phenotype that changes between two consecutive CGM wears is of little use for prescribing. Phenotyping may need to be repeated, and the trial algorithm should allow a person to be re-phenotyped as their profile changes.

Over-fitting and arbitrary clusters. Clustering algorithms always return clusters, even when none truly exist. Overlapping or continuous phenotypes are likely. External validation, stability testing and comparison with simpler rule-based classification (for example, thresholds on CV, dawn rise and postprandial excursion) are essential. If simple rules perform as well as machine learning, they should be preferred.

Confounding pathophysiology. Similar CGM traces can arise from different underlying defects. Gold-standard metabolic testing shows that early dysglycaemia reflects varying combinations of muscle insulin resistance, β-cell dysfunction, impaired incretin action and hepatic insulin resistance, often co-existing in the same person,[27] and inter-individual differences in postprandial response track insulin resistance and β-cell function as well as molecular signatures.[28] A postprandial-dominant profile could thus be driven by deficient insulin secretion in one person and by insulin resistance in another, with different implications for drug choice. CGM phenotypes describe glucose behaviour; on their own they do not identify mechanism.

Confounding by current therapy. A CGM trace reflects the disease *and* its present treatment. A hypoglycaemia-prone profile may simply be a sulfonylurea effect. Phenotypes should be interpreted alongside the current regimen, and the clustering stage may need to adjust for it.

Technical and algorithmic limitations

Sensor artefacts and interfering substances. CGM measures interstitial rather than plasma glucose, with a physiological lag, and readings can be distorted by compression during sleep, early-wear instability and signal dropout. Some electrochemical sensors are affected by commonly used substances, including paracetamol (acetaminophen), high-dose ascorbic acid and hydroxyurea, to a degree that differs between manufacturers and device generations.[29,30] Because different sensors can yield discordant postprandial profiles in the same person,[26] phenotype assignment may be partly device-dependent. Derivation studies should record sensor type and concomitant medication, apply pre-specified artefact-detection rules, and test whether phenotypes remain stable across devices.

The need for advanced multi-omics integration. Glucose dynamics are the end-product of genetic, metabolic, microbial and behavioural inputs. Recent deep-phenotyping work has linked individual postprandial responses to lipidomic, metabolomic and gut-microbiome signatures,[28] and earlier work showed that microbiome and clinical features together predict personalised glycaemic responses.[8] Clustering on CGM metrics alone ignores this information; integrating it will require larger datasets, harmonised laboratory methods and analytical approaches that can handle high-dimensional data without over-fitting.

An incomplete picture of whole-body metabolism. Glucose is only one metabolic signal. CGM does not capture ketones, lipids, lactate or amino acids, and it does not measure insulin secretion or sensitivity directly. Euglycaemic ketoacidosis with SGLT-2 inhibitors illustrates how a reassuring glucose trace can hide a dangerous metabolic state.[31] Phenotypes based on glucose alone are therefore a partial description of metabolism and should be interpreted alongside clinical and biochemical data.

Trial design and positioning

Is the effect due to phenotyping or to closer attention? Intensive CGM review in one arm could improve outcomes regardless of phenotype matching. The comparator should therefore receive the same CGM data and visit schedule, so that the trial isolates the value of the *treatment-selection rule* rather than of more contact.

Relationship to existing subtyping. CGM phenotypes and clinical clusters[5,17,21] are complementary, not competing. A combined model, in which clinical clusters inform long-term risk and CGM phenotypes inform the next treatment step, may prove most useful. Precedents from monogenic diabetes show that matching treatment to mechanism can change practice.[22]

Patient and systemic hurdles

High discontinuation rates. Many people stop using CGM after initiation, because of cost, skin reactions, alarm fatigue, the burden of wearing a device, or a sense that the data are not acted upon.[30] In the MOBILE extension, adults with type 2 diabetes who stopped CGM after eight months lost about half of their initial gain in TIR.[32] For phenotyping, attrition matters in two ways: incomplete wear can fall below the 70% data-sufficiency threshold,[14] and selective drop-out can bias which phenotypes are captured.

Literacy and numeracy barriers. Interpreting an ambulatory glucose profile requires both health literacy and numeracy. Lower diabetes-related numeracy is independently associated with poorer glycaemic control,[33] and these skills vary widely across age, education and language groups in India. Phenotype reports should therefore be designed primarily for the clinician, with simple, pictorial and vernacular summaries for patients.

Cost, equity and affordability. CGM is still not universally reimbursed. A short, intermittent phenotyping wear (for example 14 days once or twice a year) is far cheaper than continuous use and could be evaluated for cost-effectiveness within the trial. In India most CGM costs are still borne out of pocket, and Asia-Pacific consensus recommendations have identified cost and limited access as key barriers to adoption in the region.[34] Without deliberate attention to equity, phenotype-directed care could widen rather than narrow existing gaps. Pragmatic trials should therefore include public-sector and non-metropolitan sites, report outcomes by socioeconomic group, and generate the cost-effectiveness data that payers need for decisions.[30]

Why India, and how it could be implemented

India combines a very large diabetes population[2] with distinctive glucose physiology and diet. Asian Indian people tend to develop diabetes at a younger age and lower BMI. Data-driven subgroups in Indian cohorts differ in their distribution from European ones.[17]

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Carbohydrate-rich staple diets and frequent religious or cultural fasting are also likely to produce strong postprandial and variability-driven patterns. Phenotypes derived only from Western cohorts may not transfer, so Indian derivation data are valuable in their own right.

Implementation is also becoming more feasible. Factory-calibrated sensors are now commercially available in India at falling cost, and smartphone-based data upload allows remote review. Phenotype assignment could be automated within electronic health records or chronic-care platforms, returning a phenotype label and a suggested treatment focus to the clinician. Any such tool would itself need validation and, where it informs treatment decisions, appropriate regulatory oversight. The clinician would always keep the final decision, informed by comorbidities, cost and patient preference.

Future research directions

Moving CGM phenotyping from hypothesis to practice will require coordinated advances in three areas: computational, clinical and biotechnological.

Multi-omics and data-driven integration

Decoupling pathophysiology through 'virtual OGTTs'. Machine-learning models applied to the shape of the glucose curve recorded by CGM during an at-home oral glucose tolerance test (OGTT) can predict gold-standard measures of muscle insulin resistance and β-cell function with good discrimination.[27] Such virtual OGTTs, or standardised meal challenges captured by CGM, could add a mechanistic layer to phenotypes derived from free-living data and help separate profiles that look alike but have different causes. Validation in larger and more diverse cohorts, including South Asian populations, is a priority.

Metabolomic and microbiome mapping. Linking CGM phenotypes to metabolomic, lipidomic and microbiome profiles[8,28] could reveal the biology underlying each phenotype, identify circulating markers that predict drug response, and point to dietary or microbiome-targeted interventions. Indian cohorts, with their distinctive diets and gut ecology, could contribute substantially to this effort.

Longitudinal digital phenotyping. Rather than a single 14-day snapshot, repeated CGM wears combined with data from activity trackers, sleep monitoring, meal logs and electronic health records could track how a person's phenotype evolves with time, treatment and life events. A generative foundation model trained on more than 10 million CGM measurements already outperforms standard CGM metrics in forecasting glycaemic parameters and long-term outcomes,[35] and similar models could be adapted to flag phenotype transitions that warrant a change in therapy.

Clinical validation and trial infrastructure

Predictive validation against hard endpoints. TIR is associated with retinopathy and with all-cause and cardiovascular mortality,[10,36] but whether CGM phenotypes add prognostic information beyond TIR and HbA1c is unknown. Long-term cohorts that link baseline phenotype to retinopathy, nephropathy, cardiovascular events and death are needed, ideally built into registries embedded in routine care.

Phenotype-targeted randomised controlled trials. The TriMaster crossover trial showed that simple clinical features can identify which drug class gives an individual the greatest HbA1c reduction.[37] Analogous phenotype-stratified trials, for example testing whether people with a postprandial-dominant profile respond better to a GLP-1 receptor agonist than to basal insulin intensification, would directly test the therapeutic logic in Table 1. Multi-site networks with shared CGM protocols, central analysis and adaptive designs would make such trials feasible and efficient.

Early screening in niche populations. CGM may detect dysglycaemia before conventional tests. In islet autoantibody-positive children, spending more than 10% of time above 140 mg/dL identified a high risk of progression to clinical type 1 diabetes within a year,[38] and consensus guidance now includes CGM in the monitoring of pre-stage 3 type 1 diabetes.[24] Similar approaches could be explored in other high-risk groups, such as women with previous gestational diabetes, young adults with a strong family history, people with prediabetes, and lean Asian Indian individuals in whom dysglycaemia appears at lower BMI.

Next-generation sensor technology and healthcare delivery

Multi-analyte continuous biosensing. Combined glucose–ketone sensors are now entering clinical use, and international expert recommendations on continuous ketone monitoring have been published.[31] Future devices that also measure lactate, insulin or other analytes could extend phenotyping beyond glucose, for example by identifying people on SGLT-2 inhibitors who are at risk of ketosis, or by adding insulin dynamics to distinguish secretion-driven from resistance-driven phenotypes.

Mitigating psychosocial and technical attrition with generative AI. Large language models can compute standard CGM metrics and draft narrative summaries of 14 days of CGM data, although with errors that still require clinician oversight,[39] and retrieval-grounded conversational agents have been evaluated against clinician-authored responses as adjuncts for CGM review and patient education.[40] Delivered in local languages through messaging platforms already widely used in India, such tools could explain phenotype reports, answer questions, troubleshoot sensor problems and sustain engagement, helping to reduce discontinuation and the literacy barriers described above. Their safety, accuracy and effect on persistence must be tested prospectively, and they should support rather than replace clinical decisions.

Conclusion

CGM has given clinicians a detailed view of glucose behaviour, yet treatment choice still rests mostly on diagnostic label and HbA1c. We propose that CGM-derived glycaemic phenotypes, stable hyperglycaemia, hypoglycaemia-prone, postprandial-dominant, dawn-phenomenon-dominant and high-variability, offer a practical and testable basis for choosing therapy. The idea is simple, but it has not been rigorously evaluated. A two-stage programme, robust derivation and validation of phenotypes, followed by a pragmatic randomised trial against guideline-based care, would show whether this is a genuine step toward precision diabetes care or merely a more elaborate description of what clinicians already see. Progress will depend on addressing the clinical, technical and systemic challenges outlined above, and on parallel advances in multi-omics integration, trial infrastructure and sensor technology. We invite collaboration from clinicians, trialists and data scientists to carry it out.

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Conflict of interest

The authors declare that there is no conflict of interest.

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