



## Redefining Prediabetes Through Cardiometabolic Digital Phenotyping: From Signals to Clinical Decision-Making

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### Abstract

Prediabetes is defined when the fasting blood glucose test result is between 100 and 125 mg/dL, an impaired glucose tolerance test result between 140 and 199 mg/dL after 2 hours on a 75 g oral glucose tolerance test, or a HbA1c level between 5.7% and 6.4%. Prediabetes prevalence is increasing with the rising obesity, physical inactivity and aging population: in 2021, the global prevalence of prediabetes is 9.1% (464 million) for impaired glucose tolerance and 5.8% (298 million) for impaired FBS; in 2045, it will be 10.0% (638 million) and 6.5% (414 million). This condition is highly heterogeneous that can lead to insulin resistance, beta cell dysfunction and inflammation, loss of incretins and higher prevalence of chronic renal failure, subclinical cardiovascular autonomic neuropathy and endothelial dysfunction and atherosclerosis among high-risk subtypes. In this narrative review, our aim is to investigate whether the inclusion of cardiometabolic digital phenotyping along with CGM using wearable technologies, biosensors, and artificial intelligence/machine learning (AI/ML), DTs, and risk stratification could be useful for the early detection of metabolic disease. Mesh terms such as prediabetes, CGM, prediabetes and wearables, prediabetes and AI/ML were searched in English and full-text literature (from 2015 to 2026); literature that was not peer-reviewed or non-human were not included. Results showed that CGM was able to parameterize TIR (time in range (70-180mg/dl for prediabetes), glucose variability (d-GMPD, SDGMPD) and to estimate HbA1c, glucose variability and make short time predictions. While DT approaches can benefit anthropometric and cardiometabolic

markers and facilitate anticipatory care, their effects vary, and there is limited external validation, short-term evidence, bias, interoperability issues, and lack of cost-effectiveness data, and digitally connected cohorts may lead to inequities. In summary, CGM, wearable devices, AI/ML and DT technologies possess the capability of revolutionizing the understanding of prediabetes as an evolving cardiometabolic disease and preventive modality for cardio protection, however, the measurement of multidimensional, standardized, multi-center clinical trials, model interpretability, and generalizability, as well as fair implementation of the technology, are required to achieve this potential.

**Keywords:** Prediabetes, Impaired Glucose Tolerance (IGT), Impaired Fasting Glucose (IFG), Type 2 Diabetes Mellitus (T2DM), Digital Phenotyping, Digital Biomarkers, Digital Health Technologies.

## Background

As defined by the American Prediabetes Association, prediabetes is an intermediary state preceding diabetes where the blood sugar levels are elevated above the normal values (<100mg/dL fasting) yet remain lower than the diabetic diagnostic threshold (>126mg/dL). Therefore, the blood sugar levels in prediabetic individuals' range between 100 and 125mg/dL [1]. Additionally, the percentage of hemoglobin bound to sugar, Hemoglobin A1C (HbA1c), ranges from 5.7 to 6.4%. Testing 2 hours after 75g of glucose within the parameters of an Oral Glucose Tolerance Test (OGTT) results in impaired glucose tolerance, with blood sugar levels in the range of 140-199mg/dL. The prevalence of prediabetes is increasing in parallel to rising obesity related to food habits, sedentary lifestyles and the aging populations [1]. According to PMID: 37196350, the global prevalence of impaired glucose tolerance (IGT) in 2021 was 9.1% (464 million) and is expected to increase to 10.0% (638 million) in 2045. Meanwhile, the prevalence of impaired fasting glucose (IFG) was 5.8% (298 million) in 2021 and is projected to increase to 6.5% (414 million) by 2045. Notably, the current prevalence of IGT and IFT is in high-income countries. However, by 2045, low-income countries are anticipated to have the largest relative growth in IGT and IFT. This highlights disparities in current detection and prevention strategies [2].

Patho-physiologically, prediabetes manifests due to contributions of insulin resistance, beta cell dysfunction, incretin deficiency, unrestrained hepatic glucose production and low-grade inflammation. These mechanisms collectively contribute to the progression to type 2 diabetes mellitus (T2DM). Prediabetes is associated with endothelial dysfunction and atherosclerosis, and therefore increased risk of cardiovascular diseases (CVD) [2]. In a phenotype-based cluster KORA F4/FF4 cohort study, it was revealed that the prevalence of chronic kidney diseases (CKD) was higher in the high-risk clusters having prediabetes. Parallely, a trend of higher inflammatory load was found amongst a high-risk group, correspondingly increasing the cardiometabolic risk profile, thereby underscoring the heterogeneity of disease progression. Additionally, prediabetes is associated with the manifestation of cardiovascular autonomic neuropathy (CAN), a microvascular complication leading to the dysfunction

of the cardiovascular autonomic nervous system [3]. Complications may begin prior to the onset of symptomatic diabetes, thus challenging the accepted paradigms.

### Challenges and Limitations in Current Glycemic Assessment

The current diagnostic tests rely on biochemical measurements, including blood tests and urine analysis. Blood testing is utilized for obtaining measurements necessary for fasting plasma glucose (measurement of glucose levels after fasting overnight), OGTT (response to a standard glucose load), HBA1C (average blood sugar levels in the preceding three months) and average blood sugar (A1C) measurement [3]. While clinically established, these traditional investigations are limited in time, providing static, time-dependent insights into glucose levels in patients. However, glycemic levels are homeostatically variable and are subject to the influence of exogenous and endogenous factors such as diet, physical activity, circadian rhythms and stress. Traditional episodic measurements fail to detect variability and early deviations [4]. The mismatch between disease variability and current methodology results in delayed detection, often when the patient is symptomatic with significant impairments in quality of life. Moreover, the patient must refer themselves to a medical establishment for testing, which may pose geographic, socioeconomic and healthcare system constraints, further inhibiting early identification.

Blood testing is intrusive and invasive; as a result, reduced patient compliance must be expected. OGTT is costly and time-consuming, limiting its implementation in health care on a scale [4]. Even though self-monitoring glucose meters are widely used by diabetic patients, they also involve invasive fingertip blood sampling, reintroducing a barrier to frequent measurement, thereby reducing data reliability and impairing the modification of treatment plans. Urine analysis can be used in the event of type 1 diabetes (T1DM). However, it lacks sensitivity during the early stages of the disease, and its use in prediabetes detection is limited. Collectively, current static investigative methods are inadequate in capturing early and fluctuating metabolic dysglycemia. The need for continuous, minimally invasive paradigms for early detection and prevention of disease is paramount [5].

Table1: Advantages of digital phenotyping over traditional diagnostic methods.

Aspect	Traditional methods (FPG, OGTT, HbA1c)	Digital phenotyping approaches
Data type	Static, one-time	Continuous, real time
Sensitivity	Constrained for early dysglycemia	Detection of subtle metabolic changes with time

Behavioural integration	Absent	integrated
Predictive capability	Limited	High through machine learning models
Personalization	Low	High (AI driven insights)

### Emerging role of digital health technologies

Digital technologies offer a potential solution to the limitations of conventional diagnostics. Digital phenotyping involves the use of non-intrusive biometric sensors or wearables which can generate digital biomarkers to continuously monitor physiological parameters related to glycemic metrics in real time [5]. Current continuous glucose monitoring (CGM) methods utilize a small biosensor inserted under the skin. CGM measures time in range (TIR), which is the time duration for which our blood sugar levels remain within a target range. For prediabetics, it is currently 70 to 180mg/dl. CGM testing can be used to identify prediabetes very early on, allowing for early intervention and prevention of disease progression in patients who are at risk for diabetic complications [5]. Subcutaneous insertion of sensors may, however, still lead to reduced patient compliance.

Non-invasive CGM methods involving body compatible wearables such as patches, wristbands and temporary tattoos attempt to combat the limitations of standard sensors by monitoring glucose levels in external body fluids such as tears, sweat, and saliva, limiting contact with blood and thereby reducing the chances of sensitization in the immune system. However, they present several shortcomings related to accuracy, calibration and physiological variability [6]. The utilization of machine learning (ML), deep learning (DL) and artificial intelligence (AI) allows for the efficient analysis of complex, multidimensional data obtained from the sensors. Particularly, ML in CGM-based data collection has led to accurate and safe prediction of glucose values for up to 60 minutes in prediabetics and T2DM individuals. The prediction model can be used to enhance the function of insulin delivery systems used in personalized treatment to further better management in patients [6]. Concerns exist over data bias and the generalizability of the model, posing challenges to clinical use. A proof-of-concept study published in 2021 was able to ascertain that HbA1c and glucose variability could be estimated to a high accuracy using noninvasive wrist worn wearables. [6,7]. It was shown that to estimate HbA1c, several sensors were used to collect data on skin temperature, electrodermal activity, heart rate and accelerometry, the cumulative of which gave information on the HbA1c levels.

Digital twin (DT) technology involves the use of real time physiological, behavioral and clinical data to build dynamic virtual models of individuals. It can be used to model disease progression and the efficacy of treatment methods [7]. In abnormal adiposity chronic disorder which can be associated with hyperglycemia, DT precision treatment programmers were able to produce significant mean BMI reductions. Additionally, using DT, the onset of CKD and ophthalmic complications was predicted successfully in patients with T2DM, as cited by [7]. Further, DT can be used to predict CVDs occurring

as a complication of diabetes and simulate its treatment in a clinical setting, allowing clinicians to better understand pathologies and anticipate challenges faced during treatment. Thereby improving clinical results. It is, however, limited by several factors, namely, ethical considerations, data privacy concerns and complexity of integration [7].

Table 2: Technology used in cardiometabolic phenotyping of prediabetes.

Technology used	Measuring parameter	Clinical usage
Continuous glucose monitoring (CGM) based phenotyping, CGMformer, ultrahuman M1	Glucose variability, Glycemic excursions	Identification of subclinical abnormalities and early detection of dysglycemia
multimodal wearables electrochemical sensors	Physical activity, heart rate, sleep, glucose trends	constant and real-life metabolic monitoring
HbA1c monitoring wearables	Variability indices and glycemic surrogates	Patient friendly monitoring
AI driven simulation models	Behavioural and integrated metabolic data	Risk prediction which are highly personalised to each individual
CGM and machine learning (ML) frameworks, AI models	Phenotype clustering and pattern recognition	Identifying metabolic subphenotypes

Wearables are non-intrusive, readily accessible and widely used by the general population. Thereby, the technology can be utilized universally for glycemic monitoring, bypassing geographic and socioeconomic barriers, enhancing its reach and efficacy [8]. Despite the advantages associated with the novel diagnostic methods, several critical gaps remain. The long-term accuracy and efficacy of these methods are yet to be established. Furthermore, there is a lack of standardized guidelines to clinically integrate multimodal data. Differences in the adoption of these technologies may lead to inequalities in detection and management [8].

#### Multimodal Cardiometabolic Signal Integration in Digital Phenotyping

Digital phenotyping encompasses the continuous and dynamic quantification of an individual's observable phenotypes using CGM, wearables, biosensors, smartphones and other relevant devices. Glucose metabolism is tightly interconnected with cardiovascular function, autonomic regulation and behavioral factors forming a complex cardiometabolic network. This integration is at the core of digital phenotyping [9,10]. Metabolic responses to exogenous and endogenous stimuli lead to the fluctuations of glucose levels, parallel to which changes in autonomic nervous regulation can be seen. They manifest physiologically as variations in heart rate, temperature and energy levels, which are measurable signals detected by investigative procedures. Using our understanding of association, variation in signals from the norm can be used to indicate early glycemic dysfunction that would usually be undetected by conventional investigations until much later in the stage of disease. Once progressed to T2DM, the disease becomes chronic and lifelong. The treatment required is far more invasive, and related complications may arise. Thus, the importance of early detection is apparent [9,10].

Emerging studies have demonstrated that incorporating dynamic CGM data with the physiological lifestyle parameters of the subject vastly facilitates early detection and management of disease via personalized intervention plans [10]. Therefore, digital phenotyping introduces a minimally invasive approach of dynamically measuring metabolic biomarkers contributing towards enhanced risk prediction, guided clinical decision making and mitigatory measures that may potentially improve patient outcomes. However, this integrative multimodal approach remains within early developmental stages. It faces several challenges, such as signal noise, phenotypic expression variability among individuals and limited validation. Additionally, the ability of cardiometabolic biomarkers to indicate the glycemic status amongst a generalized population has not been attested and remains a subject of ongoing debate [9,10].

## Study Objectives

Within this review, we aim to evaluate the role of CGM, wearables and digital phenotyping in gathering data regarding cardiometabolic biomarkers and redefining prediabetes as dynamic cardiometabolic conditions. More importantly, we will pay attention to how these metabolic signals, along with the integration of AI and ML, lead to data driven early detection, risk stratification and personalized clinical decision making in dysglycemia. By using current resources available to us, we will analyze the limitations of these potential diagnostic paradigms and assess whether a shift towards dynamic data driven models can feasibly improve the identification and management of prediabetes.

## Methodology

### Study Design

This narrative review was performed to understand the role of cardiometabolic digital phenotyping in early diagnosis of prediabetes and its impact on clinical decision-making. The choice of narrative approach was predetermined by the emerging, heterogeneous, and interdisciplinary nature of the

existing literature, combining clinical medicine, digital health technologies, and artificial intelligence. To find relevant publications written in 2015-2026, a thorough literature search was conducted using PubMed and Google Scholar. Reference lists of selected articles were also screened manually (snowballing technique) to increase the coverage.

### Search Strategy

The search strategy comprised of the combination of Medical Subject Headings (MeSH) and free-text words, i.e.: prediabetes, impaired glucose tolerance, cardiometabolic health, digital phenotyping, wearables, continuous glucose monitoring, biosensors, artificial intelligence, machine learning, and clinical decision making. The search was refined with the help of Boolean operators ( AND, OR). An exemplary search query was the following:

(prediabetes) OR (IMG) AND (digital phenotyping) OR (wearables) OR (continuous glucose monitoring) OR (biosensors) AND (artificial intelligence) OR (machine learning) OR (clinical decision making).

### Study Selection

Abstracts and titles of the successful retrieved records were first vetted to evaluate the relevance. The full-text review was done on articles that satisfied the inclusion criteria. The authors independently selected the studies, and all differences were sorted out through discussions and consensus.

### Inclusion and Exclusion Criteria

Included studies that: human studies, printed in English and provided full-text availability, concentrated on prediabetes, cardiometabolic monitoring or digital phenotyping.

Excluded studies that: preclinical or animal studies, not peer-reviewed (e.g. preprints) and only contained abstracts, editorials, conference abstracts, dissertations or book chapters.

### Data Sources and Evidence Prioritization

Preference was given to peer-reviewed papers, such as observational studies, cohort studies, and reviews. The systematic reviews and meta-analyses are considered to be higher levels of evidence, but narrative and exploratory studies were also incorporated because of the dynamism of digital phenotyping and its use in prediabetes. Particular focus was given to the keyword 'Prediabetic' to prevent the overlap of the literature on the established diabetic conditions.

The principal observations were organized narratively under three main domains: (1) Limitations of the current prediabetes models, (2) Cardiometabolic digital phenotyping, and (3) Clinical implications.

## Discussion

### Clinical Outcomes and Cardiometabolic Enhancements

Recently, several studies have shown digital twin (DT)-based interventions as complementary approaches to enhance cardiometabolic health in people with type 2 diabetes mellitus (T2D). Based on the evidence of observational studies, pilot interventions and, relatively, a few RCTs, DT-based approaches have been proven to be effective for anthropometric outcomes such as body weight, BMI, and VAS [11]. These alterations are of clinical significance because they have been linked to improved insulin sensitivity and decreased risk for cardiovascular disease. In addition to what is already shown, the most often reported improvements with glycemic control include a reduction in HbA1c, an increase in glycemic variability (GV), and time-in-range (TIR). Nonetheless, there was a wide range of impact across all studies, with RCTs generating somewhat more modest and heterogeneous effects than observational or single-arm studies alone. This would suggest the modest contribution of enhanced patient engagement, behavioral incentives, and improvement in monitoring to patient benefit beyond what DT alone can provide [12]. Many studies propose substantial reductions in blood pressure, lipid profiles and hepatic markers as well as glycemic control. However, these results have been derived from few patients with short duration of treatment plus, limitations and not been completed but, the overall effect is positive. Moreover, the quality of evidence is unclear (moderate to low) and there are no causal relationships to explain nor conclusions to be drawn [11,12].

### Personalization Through Digital Phenotyping and Data Integration

One of the main features of DT systems is the ability to combine high-frequency complex multimodal data into dynamic individualized models. Data can be continuous glucose monitoring (CGM), diet, exercise, sleep, medications and behaviors. These systems represent a person's metabolic and behavioral profile in a way that is continuously updated, using digital phenotyping. Analysis with machine learning reveals large inter-individual variability of metabolic response particularly postprandial glucose excursion and of response to lifestyle interventions [13]. The differences in the outcomes showed the necessity of personalized strategies for the treatment of type 2 diabetes and the potential for individualized interventions. Also, bias often occurs due to sensor inaccuracies, missing data or insufficient information and inconsistent participation by users. Furthermore, most of these datasets reflect digitally connected populations and generalization to larger patient populations whose digital connection is limited [13].

### Tackling Heterogeneity, Multisystem Disease Burden

T2D has come to be viewed as a heterogeneous and multisystem disorder, featuring a continuum of insulin resistance, malfunction of  $\beta$ -cells, chronic inflammation, and autonomic dysfunction. This heterogeneity leads to a variety of clinical phenotypes and disease trajectories. To classify specific

metabolic subtypes of T2D and to identify which have specific risk and treatment response, recent clustering and machine learning methods have been introduced. DT approaches try to tackle heterogeneity by continuously studying the physiological and behavioral traits, which evolve phenotyping and adapt the therapy. Several of these sub-group classifications, however, are statistical, pattern recognition, and do not involve a mechanistic pathway. This improves predictive stratification but makes things less predictable in real life and decreases clinician trust in real life [14].

### Predictive Analytics and Early Risk Identification

New predictive models have been added to DT systems, including supervised machine learning, time-series analysis, and probabilistic forecasting, for the identification of early metabolic deterioration, even before the onset of the acute clinical stages [14,15]. Changes in glucose dynamics (greater nocturnal glucose variability, reduced glucose return-to-baseline after meals, or circadian changes) in the subclinical phenotype may be the first stages of disease progression. It is a paradigm shift from reactive care towards anticipatory and preventative diabetes care [15]. For instance, early detection of impaired metabolic control on the one hand enables even more intensive treatment with an emphasis on lifestyle modification, with an aim of reducing the chances for later development of microvascular or macrovascular complications. Yet this predictive ability is incredibly brittle and relies on the diversity of your model set and what variables you pick, or what level of external validation, etc. The majority of the existing models tend to be derived from homogeneous sets of cohorts and are not particularly generalized across ethnic, SES, and clinical subgroups [15]. Overfitting remains a challenge, especially in applications based on deep learning, which requires high-dimensional input data. In addition, most such studies have internal validation measures, with few prospective external validations, which hamper their translation readiness.

### Role of Wearables and Remote Monitoring

DT systems are built on top of wearable devices, the basic elements for data collection. In free-living environments, to represent the metabolic response in an environment that may not be captured by traditional clinic-based assessment, continuous glucose monitors (CGMs), accelerometers, smartwatches and future biosensors are used to provide real-time physiological monitoring [16]. These technologies contribute high-resolution temporal data to the understanding of metabolic regulation, intra- and inter-day variability. Longitudinal information, from a systems biology perspective, allows us to model feedback among behavior, physiology and response to pharmacological challenges at a larger scale. At the same time, however, there are serious long-term barriers to putting such systems in place [16]. As the time goes on, the adherence of these types of devices tends to wane due to fatigue, discomfort and perceived burden. In addition, technical limitations, i.e. sensor drift, errors in calibration and loss of data generate measurement uncertainty. Nevertheless, this is a constraint that should be resolved, particularly in settings where healthcare is limited, such as remote areas. This is a challenge for integration with clinical workflows because of the lack of inter-device and inter-platform interoperability [16].

## Implications for Precision Medicine and Public Health

DT systems are in close alignment with the principles of precision medicine, where therapeutic decision making is performed on an individual basis based on dynamic physiological feedback. This allows for the customization of pharmacological and lifestyle interventions to a unique metabolic profile [17]. When combined at a population level, aggregated DT data could be used to identify groups at higher risk, disease trends and opportunities for interventions. Unfortunately, the existing data sets are biased in favor of populations that are digitally literate and have a higher socioeconomic status, presenting strong selection bias. This has implications for equity and generalizability, because less-represented populations could have uneven advantages when it comes to innovations in DT-driven healthcare. In such instances, there needs to be a disparity that is faced with fair deployment [17].

## Limitations and Challenges

While there have been rapid advances in recent years, there is still limited evidence supporting DT systems for T2D. The majority of studies are observational, pilot or short-term interventional; there is a relatively limited number of high-quality RCTs. Some interest limitations are small sample sizes, short follow-up periods, different study designs of the intervention, and different definitions of outcomes. These factors may contribute to low comparability of studies and to lowered overall evidence [18]. Selection bias, performance bias (due to increased monitoring), and attrition bias are among these biases that can often occur. In addition, this could be publication bias with over representation of positive results. The long-term effects such as microvascular and macrovascular complications have not been well studied [18].

Table3: Challenges and limitations of digital phenotyping.

Challenge	Implication
Data overload; large volumes of continuous data	Requirement of advanced analytics
Standardization issues; lack of uniform CGM metrics	Limitation in comparison between studies
Accessibility; cost and availability of devices	Inequitable access in healthcare system
Clinical integration; difficulty in incorporating towards workflow	Slow adaptability in practice
Algorithm bias; ML models are trained on a limited population	Difficulty in generalization

## Technical and Implementation Barriers

Deployment of DT systems - DT systems face various technological issues for implementation, such as device non-interoperability, fragmented data systems, and limited integration with electronic health records. The collection of health data across the spectrum presents significant privacy, security, and ethical governance issues under regulation [19]. Building an effective enforcement framework across health care systems will need far more work. There is also an economic limitation on their use. There are barriers to implementation even in resource-constrained settings: High investment in infrastructure, unclear reimbursement pathways, and a lack of proof of cost effectiveness are important [19].

## Future Directions and Clinical Translation

The T2D strategies in the digital twin are a relatively new paradigm and the first attempt to integrate real-time surveillance, predictive modelling and individual analysis in one strategy to manage disease. Some initial evidence of glycemic control, cardiometabolic risk modulation, and early risk identification is available, but in many cases this evidence is from relatively diverse and early studies and has limited potential causal inference [20]. DT systems may provide a better-integrated and more theoretically complete model of treatment options compared with standard care and CGM-only techniques, but the incremental clinical benefit of DT systems is unknown as there is limited head-to-head randomized evidence. Future progress will be based on large multi-center RCTs with standardized methods. The latter will need more external validation, multi-omics data and models with explainable AI. Lacking these advances, DT systems are likely to remain in the translational or experimental stage, not fully integrated into clinical practice [20].

## Conclusion

In the past, prediabetes was diagnosed based on static thresholds such as fasting blood sugar and HbA1c levels. Also, it has been the standard protocol for treatments for many years without being able to capture the complex biological diversity of this disease. Recent studies in cardiometabolic digital phenotyping have identified that prediabetes represents a biological diversity of different metabolic pathways that carry varying risks for heart disease and diabetes. To understand this complexity, continuous glucose monitoring (CGM) is an important criterion which is not as same as regular laboratory testing because it provides details of glucose level in 24 hours to find the pattern of glucose variability, and postprandial spikes taken at a single point unable to discern. While some people are insulin resistant others show early beta-cell dysfunction. These differences are clinically important since they suggest that preventive strategies should not be the same for every patient. In reality two people with the same HbA1c levels could need rather different clinical treatment.

However, it's not just glucose. Phenotypic variation occurs early, with the prospective cohorts KORA showing different inflammatory, dyslipidemia and organ-specific vulnerabilities, including subclinical cardiovascular autonomic neuropathy which evolves to increase cardiovascular risk further in the long term. Now, wearable sensors allow for non-invasive, continuous monitoring of HRV, activity levels,

and sleep architecture in addition to glycemia, thus expanding the cardiometabolic assessment paradigm beyond glycemia. Artificial intelligence, combined with multimodal wearable data, is used to create dynamic, individual metabolic phenotypes representative of ambulatory physiology. While these developments are still mainly in the exploratory stage, digital twin systems improve on this by simulating the responses to interventions. These changes point to a shift in control of prediabetes toward effective prevention. However, there are still major limitations, such as limited population representativeness, lack of standardized CGM measurements, developing regulatory frameworks for AI tools, and unequal access to technology. Future work in translating digital phenotyping into mainstream use must emphasize methodological rigor, generalizability, fair dissemination, and clinical validation.

In conclusion, cardiometabolic digital phenotyping redefines the notion of prediabetes from a mere glycemic cut-off to a dynamic interaction of active pathophysiological processes that can be targeted with tailored treatments. The integration of CGM, wearables, artificial intelligence and digital twins allow for real-time personalization of clinical care, turning prediabetes from a diagnostic crossroads into a pivotal window of opportunity for cardio protection.

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#### References

1. Metwally AA, Park H, Wu Y, McLaughlin T, Snyder MP. Use of continuous glucose monitoring with machine learning to identify metabolic subphenotypes and inform precision lifestyle changes. *J Diabetes Sci Technol.* 2026;20(3):673-683. doi:10.1177/19322968261431860.
2. Seyedi SA, González-Rivas JP, Mellacheruvu P, Mellacheruvu A, Aledavood SP, Esteghamati A, Mechanick JI. Cardiometabolic risk reduction with digital twinning in patients with type 2 diabetes. *Explor Med.* 2025;6:1001242. doi:10.1186/s40842-025-00242-8.
3. Dey AK, Sharma A, Kumar N. Impact of artificial intelligence and digital twin technology on cardiovascular disease diagnosis and management: challenges and future directions. *World Acad Sci J.* 2025. doi:10.3892/wasj.2025.363.

- 4.Rathmann W, Kuss O, Peters A, Meisinger C, Thorand B. Phenotype-based clusters, inflammation and cardiometabolic complications in older people before the diagnosis of type 2 diabetes: KORA F4/FF4 cohort study. *Cardiovasc Diabetol.* 2025;24:117. doi:10.1186/s12933-025-02617-8.
- 5.ElSayed NA, Vigers T, O'Brien T, et al. Integration of artificial intelligence and wearable technology in the management of diabetes and prediabetes. *NPJ Digit Med.* 2025;8:96. doi:10.1038/s41746-025-02036-9.
- 6.Wang Y, Liu X, Chen J, Zhang H. Non-invasive wearable electrochemical sensors for continuous glucose monitoring. *Electrochem Commun.* 2025;168:107894. doi:10.1016/j.elecom.2025.107894.
- 7.Perelman D, Snyder MP, Palma JA, et al. Multimodal digital phenotyping of diet, physical activity, and glycemia in Hispanic/Latino adults with or at risk of type 2 diabetes. *NPJ Digit Med.* 2023;6:214. doi:10.1038/s41746-023-00985-7.
- 8.Kapoor N, Sinha B, Kalra S, et al. Metabolic health tracking using Ultrahuman M1 continuous glucose monitoring platform in non- and pre-diabetic Indians: a multi-armed observational study. *Sci Rep.* 2024;14:56933. doi:10.1038/s41598-024-56933-2.
- 9.Reddy RK, Pooni R, Zaharieva DP, Senf B, El Youssef J, Dassau E, et al. Non-invasive wearables for remote monitoring of HbA1c and glucose variability: proof of concept. *BMJ Open Diabetes Res Care.* 2021;9:e002027. doi:10.1136/bmjdr-2020-002027.
- 10.Bergental RM, Beck RW, Close KL. Continuous glucose monitoring for prediabetes: what are the best metrics? *J Diabetes Sci Technol.* 2024. doi:10.1177/19322968241242487.
- 11.Zhang Y, Li X, Chen W. Continuous glucose monitoring combined with artificial intelligence: redefining the pathway for prediabetes management. *Front Endocrinol (Lausanne).* 2025;16:1571362. doi:10.3389/fendo.2025.1571362.
- 12.Spallone V, Ziegler D, Freeman R, Bernardi L. Cardiovascular autonomic neuropathy in diabetes: an update with a focus on management. *Diabetologia.* 2024;67:1234-1249. doi:10.1007/s00125-024-06242-0.
- 13.Li J, Zhao H, Wang P, et al. CGMformer: a novel deep-learning model promising for early detection of prediabetes to effectively prevent type 2 diabetes. *Natl Sci Rev.* 2025. doi:10.1093/nsr/nwaf188.
- 14.Vogels N, van der Velden RMJ, Boer JM, et al. Machine learning-based glucose prediction with use of continuous glucose and physical activity monitoring data: the Maastricht Study. *PLoS One.* 2021;16(6):e0253125. doi:10.1371/journal.pone.0253125.
- 15.Alshahrani A, Alenazi A, Alghamdi S. Applications of artificial intelligence and machine learning in prediabetes: a scoping review. *J Diabetes Sci Technol.* 2025. doi:10.1177/19322968251351995.

16. Fernández-Real JM, Ortega E, Ricart W, et al. Prediabetes detection in unconstrained conditions using wearable sensors. *Nutr Metab Cardiovasc Dis.* 2024. doi:10.1016/j.nutos.2024.09.013.
17. Pedroso AF, Khera R. Leveraging AI-enhanced digital health with consumer devices for scalable cardiovascular screening, prediction, and monitoring. *NPJ Cardiovasc Health.* 2025;2(1):34. doi:10.1038/s44325-025-00071-9.
18. Sameh A, Rostami M, Oussalah M. Digital phenotypes and digital biomarkers for health and diseases: a systematic review of machine learning approaches utilizing passive non-invasive signals collected via wearable devices and smartphones. *Artif Intell Rev.* 2025;58:66. doi:10.1007/s10462-024-11009-5.
19. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med.* 2019;25(1):44-56. doi:10.1038/s41591-018-0300-7.
20. Dunn J, Runge R, Snyder M. Wearables and the medical revolution. *Per Med.* 2018;15(5):429-448. doi:10.2217/pme-2018-0044.