

# Precision Medicine in Type 2 Diabetes Mellitus: Advances in Continuous Assessment, Subclassification, Personalized Therapies, and Disease Remission: A Comprehensive Review.

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## ABSTRACT

Precision medicine in type 2 diabetes mellitus (T2DM) shifts from uniform treatment to individualized strategies addressing genetic, metabolic, environmental, and clinical heterogeneity. Key pillars include continuous glucose monitoring (CGM) for dynamic glycemetic insights, subtype stratification (e.g., severe insulin-resistant diabetes [SIRD], severe insulin-deficient diabetes [SIDD]), pharmacogenomics-guided therapy, and interventions enabling remission. CGM improves time in range, reduces variability, and supports tailored adjustments beyond HbA1c limitations. Clustering identifies differential complication risks and drug responses, favoring SGLT2 inhibitors in SIRD or GLP-4 receptor agonists in SIDD. Remission sustained normoglycemia without medication

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## INTRODUCTION

Precision medicine in type 2 diabetes mellitus (T2DM) represents a transformative shift from conventional, population-based treatment paradigms toward individualized care strategies that account for genetic, environmental, behavioral, and metabolic heterogeneity. This approach is increasingly supported by advances in continuous disease assessment technologies, personalized therapeutic interventions, and emerging evidence of disease reversal potential. The integration of these elements enables clinicians to move beyond symptom management and target the underlying pathophysiological mechanisms driving T2DM in specific patient subgroups.

A cornerstone of precision medicine in T2DM is, which provides high-resolution, real-time data on glycemetic patterns, including time-in-range (TIR), glucose variability, and postprandial excursions. Unlike traditional

is achievable via intensive lifestyle changes, bariatric surgery, or digital tools, particularly early in disease course. Emerging machine learning, multi-omics, and digital twins enhance prediction and personalization. Challenges include model reliability, implementation barriers, and equity. Precision approaches promise predictive, preventive, personalized care, potentially transforming T2DM management toward reversal in select patients.

**Keywords:** Precision medicine; Type 2 diabetes mellitus; Continuous glucose monitoring; Diabetes subtypes; Disease remission; Pharmacogenomics; Artificial intelligence; SGLT2 inhibitors; GLP-1 receptor agonists.

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phenomenon can be identified and managed with adjusted insulin regimens or timing of medications. Studies have demonstrated that CGM use leads to improved glycemic outcomes across diverse T2DM populations, particularly when combined with structured lifestyle interventions and digital health platforms (Son et al., 2025). These insights allow for more precise titration of glucose-lowering agents and facilitate early detection of treatment failure or adverse effects.

Personalized therapies in T2DM are grounded in the recognition of distinct endotypes and clinical phenotypes. Research has identified several clusters of T2DM, such as severe insulin-resistant diabetes (SIRD), severe insulin-deficient diabetes (SIDD), and mild obesity-related diabetes (MOD), each associated with different risks for complications and differential responses to treatment (Bonfond & Froguel, 2021). For example, individuals in the SIRD cluster exhibit marked insulin resistance and are at higher risk for diabetic kidney disease, making them ideal candidates for sodium-glucose cotransporter-2 inhibitors (SGLT2i), which confer renal and cardiovascular protection independent of glycemic control. Conversely, those in the SIDD cluster may benefit more from glucagon-like peptide-1 receptor agonists (GLP-1 RAs) due to residual beta-cell function that can be augmented pharmacologically (Wang et al., 2025). Pharmacogenomic studies further refine this approach by identifying genetic variants such as those in **TCF7L2** or **KCNJ11** that influence drug response, enabling genotype-guided selection of sulfonylureas or other agents (Venkatachalapathy et al., 2021).

The concept of disease reversal in T2DM challenges the long-held belief that it is inevitably progressive. Remission, defined as sustained normoglycemia without pharmacological intervention, has been achieved through intensive lifestyle modification, bariatric surgery, and very-low-calorie diets. A retrospective study found that a multi-interventional approach combining customized nutrition, fitness programming, and behavioral support led to significant reductions in HbA1c, fasting glucose, and body weight, with some participants achieving medication-free remission (Mehra, 2022). Similarly, evidence suggests that early, aggressive intervention during the prediabetic or early diabetic phase can preserve beta-cell function and reverse glucolipotoxicity, thereby halting disease progression (Chang, 2023). Digital health tools, artificial intelligence, and metabolomic profiling enhance the feasibility of such strategies by identifying optimal candidates and personalizing intervention intensity.

Despite its promise, precision diabetology faces significant challenges. Methodological limitations in developing prediction models particularly small sample sizes and overfitting can undermine the reliability of risk stratification algorithms (Riley et al., 2021). Moreover, while there is strong evidence of treatment heterogeneity, robust clinical predictors to guide individualized therapy remain limited, raising questions about generalizability and implementation in routine practice (Kuss et al., 2023). Ethical considerations also arise regarding access disparities, data privacy, and the potential medicalization of risk states like prediabetes.

Nevertheless, the trajectory of research supports a future where precision medicine becomes central to T2DM management. Integration of multi-omics data including genomics, epigenetics, transcriptomics, and microbiome analysis holds promise for uncovering novel biomarkers and therapeutic targets (Tian et al., 2025; Tian et al., 2025). Artificial intelligence and machine learning models trained on electronic health records and CGM data are already demonstrating utility in predicting hypoglycemic events, optimizing insulin dosing, and subclassifying patients for targeted prevention (Edgar, 2025). As these technologies mature, they will enable

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HbA1c measurements, which offer only an average estimate over weeks, CGM reveals dynamic fluctuations that are critical for tailoring therapy. For instance, patients with predominant nocturnal hypoglycemia or dawn

proactive rather than reactive care, shifting the focus from managing chronic hyperglycemia to preventing its onset and reversing its course.

Furthermore, precision medicine in T2DM leverages continuous disease assessment, molecular stratification, and individualized interventions to improve outcomes and, in select cases, achieve remission. While not yet ready for universal application, ongoing research and technological innovation are rapidly advancing the field toward a new standard of care that is predictive, preventive, personalized, and participatory.

Precision medicine in type 2 diabetes (T2D) management represents a transformative shift from the traditional, generalized approach to one that is deeply individualized, leveraging continuous disease assessment and personalized therapies to optimize outcomes. This paradigm recognizes T2D not as a monolithic disease but as a heterogeneous condition with diverse underlying pathophysiological mechanisms, including insulin resistance,  $\beta$ -cell dysfunction, obesity, inflammation, and genetic predisposition (Milla-Amekor & Ewusie, 2023; Javed et al., 2024). The goal of precision diabetology is to match the right intervention be it lifestyle modification, pharmacotherapy, or advanced technology to the right patient at the right time, thereby improving glycemic control, reducing complications, and potentially achieving remission.

A cornerstone of this approach is continuous disease assessment, primarily through Continuous Glucose Monitoring (CGM). Unlike intermittent finger-stick glucose measurements, CGM provides a dynamic, high-resolution view of an individual's glucose fluctuations throughout the day and night, capturing critical metrics such as Time in Range (TIR), Glycemic Variability (GV), and hypoglycemic exposure (Ajjan et al., 2024). This rich data stream allows clinicians to move beyond relying solely on HbA1c, which is a static average and can mask significant glucose instability. For instance, two patients with identical HbA1c levels may have vastly different TIRs, indicating very different risks for complications. Studies have shown that CGM use in noninsulin-treated T2D patients leads to improved glycemic control, reduced HbA1c, and enhanced selfmanagement skills, particularly when integrated into telemedicine platforms (Oriot et al., 2024; Tan et al., 2024; Ajjan et al., 2024). Furthermore, CGM data can be used to triage patients based on risk severity, enabling more efficient allocation of healthcare resources. While its adoption has been slower in T2D compared to type 1 diabetes, expanding CGM access to broader T2D populations, especially those on basal insulin or with comorbidities like psychiatric illness or cancer, is increasingly supported by evidence (Ajjan et al., 2024).

Personalized therapies are built upon the foundation of this continuous assessment and a deeper understanding of patient heterogeneity. Stratification of T2D into distinct subtypes, such as Severe Insulin-Resistant Diabetes (SIRD) or Mild Age-Related Diabetes (MARD), has revealed that these clusters have different risks for complications and respond differently to treatments (Misra et al., 2023; Wei & Colón-Franco, 2021). For example, individuals with SIRD, characterized by profound insulin resistance and high BMI, are at a significantly greater risk for diabetic kidney disease and thus benefit most from organ-protective agents like SGLT2 inhibitors (Franks & Sargent, 2024). In contrast, patients with severe insulin-deficient diabetes may require earlier initiation of insulin therapy. The TriMaster study exemplifies this stratified approach, demonstrating that clinical characteristics like BMI and kidney function can predict differential responses to specific drugs, such as thiazolidinediones versus DPP-4 inhibitors, allowing for more informed second-line treatment selection (Shields et al., 2022). Beyond pharmacogenomics, personalized nutrition and exercise regimens are critical. Evidence supports that low-calorie or low-carbohydrate diets are effective for remission, but their success is highly dependent on individual adherence and metabolic context (Arias-Marroquín et al., 2024; Mehra, 2022). A personalized multi-interventional approach combining customized nutrition, progressive fitness, and lifestyle modification has been shown to significantly reduce HbA1c, fasting blood sugar, and weight (Mehra, 2022). Machine learning is poised to further enhance personalization by integrating complex datasets including genomics, epigenetics, gut microbiota, and real-time CGM data to generate optimized drug mix and dose recommendations, as demonstrated by systems like AIDA (Ghosh et al., 2025; Nambiar et al., 2024).

The potential for diabetes reversal is perhaps the most compelling outcome of precision medicine. Remission, defined as achieving normoglycemia without pharmacological therapy for at least one year, is now recognized as a feasible target, particularly for patients with shorter disease duration and preserved  $\beta$ -cell function (Chang, 2023; Kanorskii, 2022). Interventions such as intensive lifestyle programs, bariatric surgery, and digital twin-enabled precision nutrition have all demonstrated the ability to induce remission by addressing the root causes of hyperglycemia (Shamanna et al., 2021; Kanorskii, 2022). Bariatric surgery, for instance, induces

remission not just through weight loss but also by profoundly altering gut hormone secretion, leading to increased GLP-1 production, which enhances insulin sensitivity and secretion (Kanorskii, 2022). Digital twin technology uses a virtual model of a patient's metabolism to simulate and optimize interventions before they are applied in the real world, defining stages of reversal to provide a more nuanced view than a simple binary outcome (Shamanna et al., 2021). The likelihood of remission can be quantified using predictive models that incorporate factors like age, BMI, C-peptide levels, and duration of diabetes, providing a powerful tool for setting realistic goals and guiding therapeutic intensity (Kalra et al., 2021).

In conclusion, precision medicine is redefining the trajectory of T2D management. By embracing continuous assessment with tools like CGM, stratifying patients based on their unique pathophysiology, and tailoring multifaceted interventions, the field is moving towards a future where optimal glycemic control and even disease remission are achievable for many. This approach requires a unified electronic medical record linking patient profiles to treatment plans, the integration of machine learning for decision support, and a focus on high-value care activities like telemedicine and improved self-management (Ajjan et al., 2024). While challenges remain in implementation and accessibility, the evidence base continues to grow, signaling a new era of hope and efficacy in the fight against type 2 diabetes.

## MATERIALS AND METHODS

This comprehensive review synthesizes current evidence on precision medicine in type 2 diabetes mellitus (T2DM), focusing on continuous disease assessment, subclassification, personalized therapies, and disease remission. The approach combines a structured literature search with narrative synthesis to provide an up-to-date overview of advances, challenges, and future directions.

### Literature Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar (January 2010–December 2025), plus reference lists and consensus reports. Iterative updates included 2025–2026 publications. Additional sources included reference lists of key articles, recent consensus reports (e.g., from the American Diabetes Association and European Association for the Study of Diabetes), and preprint servers for emerging publications. The search was not limited to systematic reviews or randomized trials but prioritized high-impact original research, meta-analyses, narrative reviews, and clinical studies relevant to continuous glucose monitoring (CGM), diabetes clustering/subclassification, pharmacogenomics, remission interventions, machine learning/multi-omics integration, and personalized management in T2DM.

Searches were updated iteratively during manuscript preparation to incorporate the most recent publications (e.g., 2025 studies on CGM expansion, AI applications, and GLP-1/SGLT2 mechanisms).

### Search Terms and Eligibility Criteria

Search terms were developed using a combination of Medical Subject Headings (MeSH) and free-text keywords, combined with Boolean operators (AND/OR). Core search strings included:

- ("type 2 diabetes" OR "type 2 diabetes mellitus" OR T2DM OR "non-insulin dependent diabetes") AND ("precision medicine" OR "personalized medicine" OR "precision diabetology" OR "stratified medicine" OR "subclassification" OR "clustering" OR "endotypes" OR "phenotypes") AND ("continuous glucose monitoring" OR CGM OR "time in range" OR TIR OR "glycemic variability" OR "remission" OR "reversal" OR "disease reversal" OR "pharmacogenomics" OR "SGLT2 inhibitors" OR "GLP-1 receptor agonists" OR "machine learning" OR "artificial intelligence" OR "multi-omics" OR "digital twin")

Additional filters were applied for specific subtopics (e.g., "severe insulin-resistant diabetes" OR SIRD; "severe insulin-deficient diabetes" OR SIDD; "bariatric surgery" AND remission).

Eligibility criteria for inclusion were:

- Publications in English.

- Peer-reviewed original research, systematic reviews, meta-analyses, narrative reviews, consensus statements, or clinical studies involving human participants with T2DM (or prediabetes where relevant to prevention/remission).
- Focus on precision approaches, including CGM for assessment, subtype stratification, personalized pharmacotherapy/lifestyle interventions, remission achievement, or emerging technologies (e.g., AI, multi-omics).
- Exclusion of: animal-only studies, type 1 diabetes-exclusive papers, monogenic diabetes without T2DM relevance, editorials without data synthesis, or low-quality case reports.

Titles and abstracts were screened for relevance, followed by full-text review to confirm alignment with the review's scope.

**Study Selection Process:** Approximately 450 records identified after duplicates removed. Titles/abstracts screened; ~180 full texts assessed. Final inclusion: ~60 high-relevance sources (original research, meta-analyses, reviews, consensus statements) focused on precision approaches in T2DM. Exclusions: animal studies, type 1 diabetes-exclusive, low-quality reports. No formal PRISMA flow diagram generated (narrative review), but selection prioritized recency, impact, and methodological strength.

### Quality Assessment

As this is a narrative/comprehensive review rather than a formal meta-analysis, formal quantitative quality scoring (e.g., using tools like AMSTAR-2 for reviews or Cochrane Risk of Bias for trials) was not uniformly applied to all sources. Instead, a qualitative appraisal was performed to prioritize high-quality evidence based on established criteria:

- Study design hierarchy (e.g., randomized controlled trials, large cohort studies, and meta-analyses ranked higher than case series or expert opinion).
- Reproducibility and validation of findings (e.g., preference for externally validated clustering models or remission predictors across populations).
- Sample size, follow-up duration, and adjustment for confounders in observational/interventional studies.
- Alignment with emerging reporting standards for precision medicine research, such as the BePRECISE checklist (where applicable to clinical relevance, equity, and methodological transparency).
- Recency and impact (e.g., publications from high-impact journals or those cited in recent consensus reports).

Studies with major methodological limitations (e.g., small sample sizes with overfitting risks in prediction models, lack of external validation) were noted as such in the synthesis, with emphasis placed on robust, replicated evidence.

### Data Synthesis

Data were synthesized narratively to integrate findings across themes: continuous assessment via CGM, subtype stratification and personalized pharmacotherapy, remission potential, emerging technologies, and challenges/future directions. Key evidence was grouped thematically rather than meta-analyzed due to heterogeneity in study designs, populations, interventions, and outcomes (e.g., TIR improvements, HbA1c reductions, remission rates).

### Synthesis prioritized:

- Consistent patterns across high-quality sources (e.g., CGM benefits in TIR and HbA1c; differential drug responses in SIRD vs. SIDD clusters).

- Mechanistic insights and clinical implications.
- Identification of gaps (e.g., implementation barriers, equity issues).
- Critical discussion of limitations in the evidence base.

**Continuous Disease Assessment: The Foundation of Precision Approaches** Continuous glucose monitoring (CGM) provides real-time TIR (70–180 mg/dL), glycemic variability (GV), and patterns missed by HbA1c, improving control in non-insulin T2DM when integrated with education/telemedicine. Evidence supports expanded use for risk triage and proactive titration. In T2DM, including non-insulin-treated patients, CGM use improves HbA1c, TIR, self-management, and risk stratification, particularly when paired with telemedicine or structured education. Expanding access to broader T2DM populations (e.g., basal insulin users or those with comorbidities) is supported by evidence showing reduced glucose instability and better resource allocation. CGM enables proactive therapy titration and early detection of treatment failure. CGM

**Stratification and Personalized Pharmacotherapy:** Clustering identifies endotypes with differential risks/responses: SIRD (high insulin resistance, kidney/CV risk → SGLT2i preferred); SIDD (beta-cell failure → GLP-1 RAs/insulin). TriMaster and pharmacogenomics refine choices.

- Severe insulin-resistant diabetes (SIRD): High insulin resistance, elevated BMI, increased diabetic kidney disease/cardiovascular risk → preferential benefit from SGLT2 inhibitors for organ protection.
- Severe insulin-deficient diabetes (SIDD): Profound beta-cell failure → earlier insulin or GLP-1 receptor agonists (GLP-1 RAs) to augment residual function.
- Mild obesity-related (MOD) or age-related (MARD) diabetes: Lower complication risks, different priorities.

Clinical tools like BMI and kidney function predict responses (e.g., TriMaster study: thiazolidinediones vs. DPP4 inhibitors). Pharmacogenomics refines selection (e.g., TCF7L2/KCNJ11 variants influencing sulfonylurea efficacy). Personalized nutrition/exercise, aided by machine learning integrating genomics, microbiome, and CGM data, optimizes adherence and outcomes.

**Critical note:** Ahlqvist-derived clustering is reproducible in multiple cohorts but shows variability in non-European populations and over time; external validation remains limited, with risks of overfitting in smaller models.

- 5. Potential for Disease Remission and Reversal:** Remission (HbA1c <6.5% without therapy  $\geq$ 3–12 months) is feasible early in disease. Intensive lifestyle: ~46% in DiRECT (vs 4% control); multi-interventional approaches reduce HbA1c/weight significantly. Bariatric surgery: 18–50% long-term remission (higher with RYGB ~57–67% at 1 year vs medical/lifestyle). Digital twins/personalized models predict likelihood. Predictive models (age, BMI, duration, biomarkers) guide candidate selection and intensity, addressing glucolipotoxicity early to halt progression.
- 6. Emerging Technologies and Multi-Omics Integration:** Machine learning on electronic records, CGM, and multi-omics (genomics, epigenetics, transcriptomics, microbiome) predict hypoglycemia, optimize dosing, subclassify patients, and recommend drug combinations. These tools enable proactive care, shifting from reactive hyperglycemia management to prevention and reversal.
- 7. Challenges and Future Directions:** Limitations include small-sample prediction models prone to overfitting, sparse robust predictors for routine use, treatment heterogeneity evidence gaps, implementation in diverse settings, access inequities, data privacy, and ethical concerns (e.g., prediabetes medicalization). Future progress requires larger datasets, standardized multi-omics, validated machine learning, unified records, and equitable CGM/telemedicine access. Reporting guidelines like BePRECISE may enhance rigor in precision diabetes research.

## CONCLUSION

Precision medicine advances T2DM management via CGM, stratification, personalized therapies, and remission strategies, with CGM HbA1c reductions ~0.2–0.3%, reproducible subtypes, and remission rates 46–61% (lifestyle) or higher (surgery).

This review adds value by integrating the latest 2025–2026 evidence (e.g., expanded CGM roles, AI/digital twins), emphasizing remission feasibility, and addressing implementation/equity in low-resource contexts differentiating it from prior narrative reviews focused on Western/high-income settings.

### Summary Table of Key Studies:

Theme	Reference	Design/Sample	Major Findings	Limitations
CGM	Ajjan et al. (2024); Son et al. (2025)	Reviews/RCTs	Improved TIR/HbA1c; better in non-insulin T2DM	High; consistent but adoption barriers
Subclassification	Misra et al. (2023); Ahlqvist (2018 replicated)	Systematic review/cohorts	SIRD: SGLT2i benefit; SIDD: GLP-1/insulin; variable reproducibility	Moderate-high; needs more external validation
Personalized Therapy	Shields et al. (TriMaster, 2022)	RCT	BMI/kidney predict drug response	High; clinical utility demonstrated
Remission (Lifestyle)	DiRECT (Lean et al.); Mehra (2022)	RCT/retrospective	46–61% remission with intensive intervention	High; early disease best
Remission (Surgery)	Courcoulas et al. (2024)	Long-term RCT	18% at 7 years, 12.7% at 12 years vs medical	High; superior to medical but access issues
AI/multi-omics	Ghosh et al. (2025); Nambiar (2024)	Narrative/ML studies	Predictive dosing/subclassification	Emerging; overfitting risks

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**Competing interests:** Authors have declared that no competing interests exist.

Dear Editor,

We are pleased to submit our original manuscript entitled "**Precision Medicine in Type 2 Diabetes Mellitus: Advances in Continuous Assessment, Subclassification, Personalized Therapies, and Disease Remission: A Comprehensive Review**" for consideration as a review article in the *International Journal of Research and Scientific Innovation (IJRSI)*.

This comprehensive review synthesizes recent advances (up to 2025–2026) in precision diabetology, focusing on continuous glucose monitoring (CGM), diabetes subtype stratification (e.g., SIRD, SIDD), pharmacogenomics-guided therapies (including SGLT2 inhibitors and GLP-1 receptor agonists), and

evidencebased strategies for achieving disease remission through lifestyle, surgical, and digital interventions. It also discusses emerging roles of machine learning, multi-omics, and digital twins, while addressing implementation challenges and equity issues.

The manuscript is original, has not been published elsewhere, and is not under consideration by any other journal. All authors have contributed significantly, read and approved the final version, and declare no competing interests. This work received no specific funding, and ethical approval/consent was not applicable as it is a review article.

We believe this review aligns well with IJRSI's multidisciplinary scope, particularly in advancing knowledge on chronic disease management, health innovation, and personalized approaches to global health challenges like type 2 diabetes mellitus.

Thank you for considering our submission. We look forward to your feedback and are happy to provide any additional information or revisions as needed.

Sincerely,

Dr. Mohammad Ali Asraf Suhag

Corresponding Author

On behalf of all authors.

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