



Precision Medicine in Diabetes: Rethinking a Heterogeneous Disease

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INTRODUCTION

Diabetes mellitus remains one of the most significant global health challenges, currently affecting more than half a billion individuals worldwide.¹ Traditionally, diabetes has been classified into type 1 (autoimmune, insulin-deficient) and type 2 diabetes (T2D) (insulin-resistant, lifestyle-associated).² However, clinical and epidemiological evidence increasingly demonstrates that this binary classification fails to reflect the true heterogeneity of the disease.^{2,3} Patients differ in their underlying pathophysiology, risk of complications, and therapeutic responses. In this context, precision medicine—tailoring diagnosis, risk prediction, and therapy to the individual—offers a transformative framework for diabetes care.^{4,5} Emerging research, including cluster-based stratification of T2D, the recognition of lean diabetes phenotypes in South Asians with predominantly insulin secretory defects and advances in genetic diagnosis of monogenic forms such as maturity-onset diabetes of the young (MODY), demonstrates how precision diabetes is gradually moving from theory into clinical practice.^{6–8} In Asian Indians, visceral fat—rather than subcutaneous fat—showed a progressive increase with worsening glucose tolerance and is strongly associated with insulin resistance.⁹ Genetic studies in the same population demonstrated that several *ADIPOQ* gene variants are significantly associated with T2D, obesity, and hypoadiponectinemia, highlighting the dual impact of both visceral adiposity and adiponectin pathway genetics on diabetes susceptibility in South Indians.¹⁰

Recent international consensus highlights that precision medicine is a natural evolution of evidence-based diabetes care, aiming to reduce errors and optimize outcomes by explicitly accounting for disease heterogeneity.¹¹ However, significant gaps persist in generating clinically translatable evidence, particularly in non-European ancestry populations which underscores the urgent need for more inclusive research.

BEYOND ONE-SIZE-FITS-ALL: SUBGROUPS OF TYPE 2 DIABETES

T2D is not a single disease but a spectrum. Data-driven cluster analyses, first developed in Scandinavian populations¹² and later validated in Asian Indian cohorts,⁶ have identified at least four reproducible subgroups in Indians:

- Severe insulin-deficient diabetes (SIDD).
- Insulin-resistant obese diabetes (IROD).
- Combined insulin-resistant and deficient diabetes (CIRDD).
- Mild age-related diabetes (MARD).

These clusters differ in glycemic progression, complication profiles, and treatment needs. For example, SIDD patients—often lean with poor beta-cell function—are at high risk for retinopathy and may require early insulin, while IROD patients have an elevated risk of nephropathy and cardiovascular disease and may benefit from insulin therapy. This approach challenges current guidelines, which rely primarily on duration of diabetes, HbA1c, and age of onset of diabetes. Instead, precision subtyping enables proactive, individualized monitoring and therapy.

LEAN DIABETES: A FEATURE OF TYPE 2 DIABETES IN INDIANS

Perhaps the most striking evidence of T2D heterogeneity comes from lean diabetes in India.^{13,14} A recent large-scale study demonstrated that lean T2D (BMI <18.5 kg/m²) accounts for ~1.5% of clinic-based T2D cases in India,⁸ but these patients carry disproportionately higher complication rates compared with overweight/obese peers.

Unlike classical T2D, lean diabetes is characterized by severe beta-cell dysfunction with relatively preserved insulin sensitivity.⁸ This phenotype overlaps partially with malnutrition-related diabetes (MRDM) described decades ago, but the lack of a specific marker for MRDM makes it difficult to diagnose.¹⁵ A recent commentary on the

epidemic of cardiometabolic disorders in South Asia has emphasized that lean diabetes is not only common but is accompanied by distinct metabolic traits such as excess ectopic fat deposition, smaller adipocytes, and adverse lipid profiles, which significantly increase cardiometabolic risk despite normal or low BMI.¹⁶ The recognition of lean diabetes raises several precision-medicine questions: Should treatment be intensified earlier with insulin? Can biomarkers of beta-cell reserve (e.g., C-peptide, proinsulin-to-insulin ratios) help refine the diagnosis? Importantly, it highlights the fact that ethnicity-specific phenotypes must be incorporated into future classification systems, particularly in low- and middle-income countries (LMICs) where lean diabetes is more common.

MONOGENIC DIABETES: A PROTOTYPE FOR PRECISION CARE

Monogenic diabetes (particularly MODY) and neonatal diabetes represent the precision medicine paradigm.^{17,18} Identification of genetic mutations in MODY has immediate therapeutic and prognostic implications:

- HNF1A-MODY and HNF4A-MODY → respond significantly to sulfonylureas
- GCK-MODY → usually requires no pharmacological therapy
- Neonatal diabetes → neonates diagnosed below 6 months of age with KCNJ11 or ABCC8 mutations respond to sulfonylureas, and insulin can often be stopped completely.

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Without genetic testing, many MODY cases are misclassified as type 1 or T2D, leading to unnecessary insulin use. The clinical overlap between MODY and T2D emphasizes the need for genetic testing in targeted subgroups (young-onset, lean, antibody-negative patients). This is particularly crucial in LMICs, where clinical heterogeneity is high and low-cost genetic panels are becoming more feasible.^{19,20} Rare monogenic forms of diabetes clearly illustrate the promise of precision medicine, as the nature of the genetic defect can be directly linked to targeted therapy.^{21–24}

INTEGRATING BIOMARKERS AND DIGITAL HEALTH

While genetics and clustering represent precision tools, other emerging domains hold promise:

- Biomarkers: Proteins such as fetuin-A, adiponectin, and inflammatory markers may stratify insulin resistance, beta-cell stress, and risk of complications. Studies have reported that fetuin-A differs across gestational diabetes phenotypes and correlates with HOMA-IR.²⁵
- Digital health and artificial intelligence (AI): Retinal imaging combined with AI-based grading not only aids complication screening but may also serve as a proxy for systemic risk stratification.^{26,27} Diabetic retinopathy (DR), a leading microvascular complication and the fifth most common cause of blindness worldwide, underscores the urgent need for scalable screening approaches.²⁸ Annual retinal assessment is recommended, but the massive volume of individuals requiring review poses a significant global challenge.^{29,30} AI-driven deep learning tools have emerged as promising solutions, capable of analyzing large numbers of retinal images and automating DR diagnosis.³¹ However, building such robust AI models requires access to large, diverse, high-quality retinal image databases with standardized annotations from trained ophthalmic professionals. Recognizing this need, recent efforts in India have initiated the creation of a large-scale multicenter Retinal Image Database, designed to support the development of cost-effective and scalable AI diagnostic tools for DR.³² This initiative exemplifies how digital health innovations can strengthen precision diabetes care by enabling both early detection of complications and system-level risk stratification, particularly in resource-constrained LMIC settings. The DIANA

(Diabetes Novel Subgroup Assessment) tool, developed in Asian Indians, uses machine learning to classify patients into four distinct T2D endotypes and predict the risk of retinopathy (78.4%) and nephropathy (89.6%) with high accuracy.³³

- Omics approaches: Transcriptomics, proteomics, and metabolomics could eventually refine subgrouping, although accessibility and affordability remain limited in LMICs.³⁴

CHALLENGES IN IMPLEMENTING PRECISION MEDICINE

Despite clear scientific rationale, several barriers remain:

- Cost and accessibility: Genetic tests, biomarker assays, and advanced imaging are not universally available and are expensive.
- Validation across ethnicities: Most clustering studies originate from Europe; applying them directly to South Asian or African populations may be misleading without validation.
- Clinical translation gap: Clinicians still lack decision-support tools to incorporate precision subtyping into routine care.
- Equity: Precision medicine must not exacerbate health disparities by allowing only those who can afford them to receive more expensive tests or medications.

THE LOW- AND MIDDLE-INCOME COUNTRIES PERSPECTIVE

For LMICs, where the diabetes burden is greatest, scalable and affordable precision strategies are needed. Examples include:

- Using simple clinical clustering algorithms [age, BMI, homeostatic model assessment of beta-cell function (HOMA-β), homeostatic model assessment of insulin resistance (HOMA-IR)] instead of omics-heavy approaches.
- Deploying portable fundus (retinal) imaging for early detection of high-risk phenotypes.
- Building local biobanks and data repositories to study population-specific diabetes subtypes.
- Developing tiered genetic testing (low-cost panels for MODY, targeted sequencing for atypical cases of diabetes).
- Such pragmatic approaches can ensure that precision medicine is not a luxury but a reality even in less-resourced settings.

CONCLUSION

Diabetes is not a single disease but a spectrum of disorders with overlapping and distinct mechanisms. Precision medicine—through cluster-based phenotyping, identification of lean diabetes, and genetic diagnosis of

MODY and neonatal diabetes—offers a roadmap to individualized care. While high-income countries can lead with omics and advanced diagnostics, LMICs must adopt scalable models of precision care that leverage clinical algorithms, digital health, and selected biomarkers.

The future of diabetes care will be defined not by a one-size-fits-all approach, but by nuanced strategies that respect biological diversity, ethnicity-specific patterns, and socioeconomic realities. Precision medicine is not a distant dream—it is already emerging, but the challenge is to integrate it equitably into everyday practice, especially in developing countries.

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