

# Subclassification of Type 2 Diabetes Paves the Way for Personalized Outcome Prediction and Patient Management

Ruhan Wei and Jessica M. Colón-Franco\*

In the United States, 34 million people are diagnosed with diabetes, accounting for 10.5% of the population, at a significant annual cost exceeding \$300 billion. Diabetes is mostly classified as type 1 or type 2, based on the presence of pancreatic islet  $\beta$ -cells autoantibodies and young age at diagnosis in the former. Other minor diabetes types are the latent autoimmune disease of the adult and rare monogenic types, including maturity-onset diabetes and neonatal diabetes. These classifications result in 75%–85% of patients with diabetes categorized as type 2, although the subgroup is highly heterozygous in etiology, clinical characteristics, progression, and risk of complications. A recently published article in *Diabetes* by Ahlqvist et al. (1) described an alternative approach to subcategorizing diabetes.

The proposed data-driven model uses 6 commonly measured clinical parameters: glutamate decarboxylase autoantibodies, body mass index, glycosylated hemoglobin, age at diabetes onset,  $\beta$ -cell function, insulin resistance estimated from fasting glucose, and C-peptide. Five clusters with unique clinical characteristics, disease progression, and outcomes were generated using data from newly diagnosed adult patients with diabetes. The subtype severe autoimmune diabetes consists of patients with type 1 diabetes and latent autoimmune disease of the adult who are positive for glutamate decarboxylase autoantibodies, characterized by low insulin secretion and poor metabolic control. Type 2 diabetes was further stratified into severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes, and mild age-related diabetes. The newly proposed system offers advantages over the traditional standard of care by subcategorizing patients with their clinical characteristics and risk stratification for diabetes-related outcomes, providing personalized medicine opportunities and tailored treatment plans. Patients with severe autoimmune diabetes or severe insulin-deficient diabetes, for example, had the highest

glycosylated hemoglobin results and progressed the most in response to insulin treatment. Diabetic retinopathy and neuropathy were most prevalent in those with severe insulin-deficient diabetes, which was not restored with traditional glycemic control goals. Patients with severe insulin-resistant diabetes have a higher chance of developing diabetic kidney disease and nonalcoholic fatty liver disease. In principle, these clinical differences suggest a need for special pharmacological treatment, frequent monitoring, and prompt intervention in patients who are more prone to a specific complication. The model was initially derived from thousands of newly diagnosed patients in the Swedish ANDIS (All New Diabetics in Scania) diabetes cohort but was tested and replicated in Chinese, Indian, non-Hispanic White, and non-Hispanic Black populations, suggesting applicability beyond European populations. It is unclear if patient classification differs at presentation and during the progression of the disease and if the clusters themselves represent distinct groups or different stages in the disease spectrum.

This new cluster-defined system challenges the way we classify diabetes, which has not been updated in decades, and could promote appropriate clinical and financial resource allocation in managing patients with diabetes. Such a change in the diagnosis and prognosis paradigm is promising but requires careful evaluation before clinical adoption. Questions around feasibility, applicability across populations, and validation in randomized clinical trials—particularly those evaluating therapeutic interventions—will need to be addressed further in prospective studies.

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Department of Pathology and Laboratory Medicine, Cleveland Clinic, Cleveland, OH, USA.  
\*Address correspondence to this author at: Department of Laboratory Medicine, Cleveland Clinic, 10300 Carnegie Ave., Cleveland, OH 44195, USA. Fax 216-555-5555; e-mail COLONJ3@ccf.org.

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