Dr. Josep Franch Nadal.
Primary Care Physician, EAP Raval Sud, Barcelona, Catalonia, Spain.
Fundación redGDPS.

Present and Future of Precision Medicine in Type 2 Diabetes:

Where We Are and Where We're Heading

Since ancient times, the natural tendency of medical professionals who care for patients has been to base their actions on experience. They have made decisions according to previous outcomes and adapted them to the times in which they lived. Clearly, Galen could not request an X-ray, and currently, leeches should not be applied. However, we also know that experience alone cannot resolve all problems, which is why new ideas and techniques have had to be experimented with, with varying results.

The evolution of medicine has been closely linked to the evolution of technology. Currently, we have machines capable of learning faster than humans, making fewer mistakes, reaching complex diagnoses, predicting the future course of disease, the effectiveness of treatment, and ultimately making decisions that greatly help patients.

The traditional approach to diabetes disease involves a diagnosis based on blood glucose cut-off points, followed by treatment aimed at reducing blood glucose to the lowest possible values (without causing hypoglycemia) to prevent the onset of disease-specific complications. To this end, different pharmacological families have been used, each playing a role in the different pathophysiological mechanisms that may be involved in the disease. In recent decades, there has been a significant reevaluation of the urgent need for a healthy lifestyle and the patient's involvement in managing their disease.

But currently, we have the feeling that we have reached a glass ceiling that prevents further progress in the fight against diabetes. This is where new thinking, driven by technology, has emerged. Specifically, I believe the paradigm shift occurred when the focus moved away from glycemia as the central element of the process. Instead, the real objective became preventing complications and improving the patients' quality of life.

This approach involves many factors beyond glycemia, which vary for each patient and at different stages of the disease's progression. This shift gave birth to Precision Personalized Medicine (PPM), specifically as applied to diabetes mellitus (DM).

Perhaps the first major conceptual breakthrough came from the Scandinavian group led by Emma Ahlqvist (1). They moved away from basing the diagnosis of T2DM on a single glycemia cutoff point and instead asked critical questions: What will happen to the patients? What is the prognosis for someone newly diagnosed with diabetes? Will all patients have the same disease progression? Will they respond similarly to treatment?

This group leveraged advances in artificial intelligence (AI) and machine learning. Using clustering techniques, they identified six key predictive variables at diabetes onset that would shape each patient's future trajectory. These variables include HbA1c levels, age at onset, body mass index (obesity), the presence of antibodies, beta-cell insulin secretion, and peripheral insulin resistance (the latter two derived from C-peptide levels). With these variables, they established five distinct patient groups with varying disease progressions, complication risks, treatment responses, and overall prognoses. This classification allowed for the tailoring of preventive and therapeutic measures specific to each individual.

T2DM was previously considered a catch-all category for all forms of diabetes that could not be classified into specific types. However, it is now understood that T2DM includes 5 distinct patterns: diabetes strongly associated with immunity, corresponding to classical T1DM; diabetes linked to severe insulin secretion deficiency; diabetes related to insulin resistance; diabetes associated with obesity; and diabetes influenced by age. Each of these patterns requires a tailored approach to minimize the disease's impact efficiently and effectively.

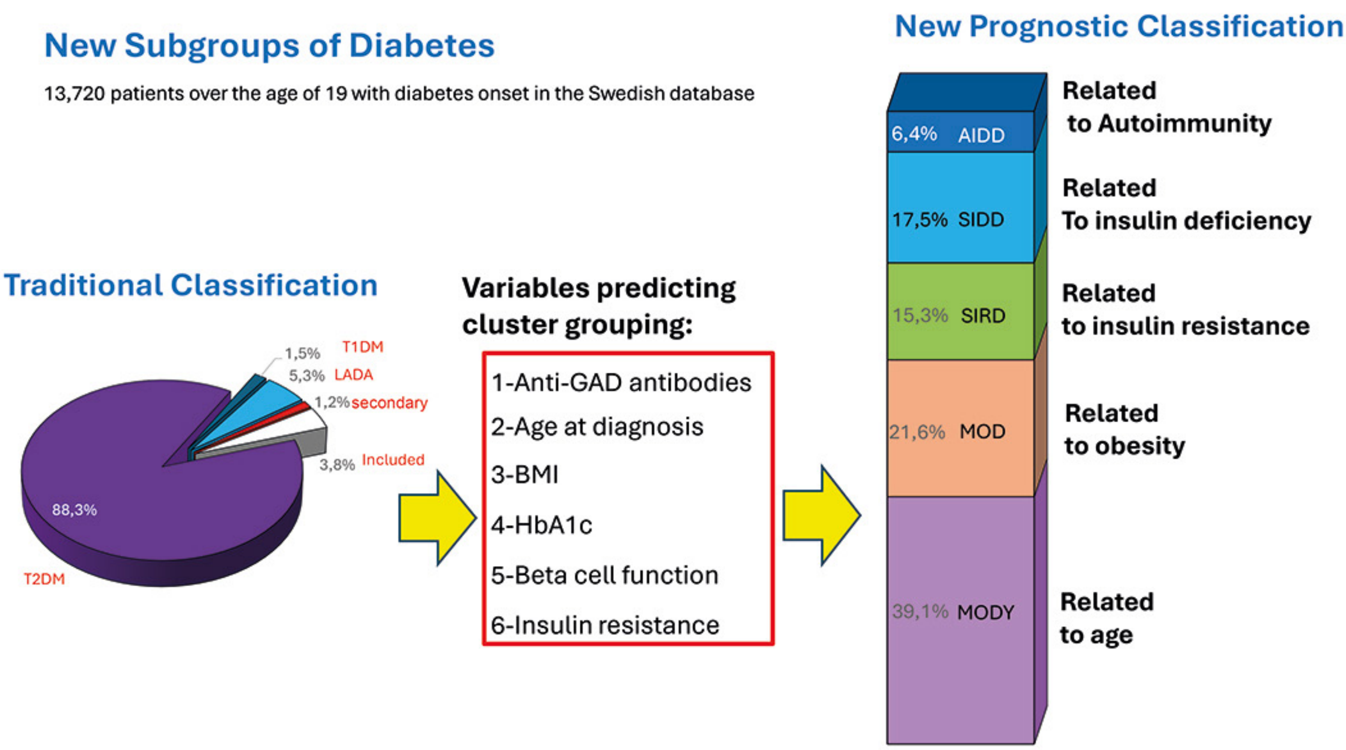
Building on this phenotypic classification, numerous complementary studies have emerged. For instance, it is now evident that the creation of these groups varies across ethnicities and may change over time, (2) highlighting the importance of using locally relevant data to make optimal decisions.

Furthermore, the genotype plays a significant role in modulating prognosis based on phenotypes and helps elucidate the mechanisms underlying these outcomes (3). Recent research has also demonstrated varying efficacy and tolerability of pharmacological treatments depending on the phenotype and genotype of patients with DM.

A paradigm shift is underway in how we study and understand the disease and biology in general. Advances in omics sciences, epigenetics, and microbiota research are shedding light on the causes and individual variations in many biological processes. Simultaneously, the addition of billions of clinical data points from healthcare centers worldwide, combined with technological advances in machine learning, enables the analysis of vast datasets to extract valuable insights into the progression of diabetes. »

PRECISION PERSONALIZED MEDICINE (PPM) NOT ONLY HAS THE POTENTIAL TO IMPROVE HEALTH OUTCOMES FOR PEOPLE WITH DIABETES, BUT IT COULD ALSO HAVE A SIGNIFICANT IMPACT ON REDUCING HEALTH CARE COSTS

"IF YOU WANT DIFFERENT RESULTS, DO NOT ALWAYS DO THE SAME THING." ALBERT EINSTEIN



Ahlqvist E et al. Lancet Diabetes Endocrinol 2018; 6: 361–69. Ahlqvist E et al. Diabetes 2020;69:2086-2093.

All of this leads us to reconsider the nature of diabetes as a disease. Leading scientific societies have issued consensus statements and specific documents reflecting on this topic. They analyze the different areas where PPM could be useful and establish recommendations based on this approach (4).

In our region, PPM has enabled the identification of 7 different trajectories in the progression of diabetes based on widely used clinical variables. This allows us to predict, for example, whether a person is more likely to develop chronic kidney disease and should therefore undergo diagnostic tests for this condition more frequently. It also justifies the use of preventive measures, including pharmacological ones (5).

Recently in Spain, a study called the Copernican study has been launched, aiming to change the paradigm of diabetes management from the onset of the disease. Its purpose is to identify distinct clusters from the beginning, based on different prognoses, the occurrence of complications, and varied responses to therapeutic options. Another study, part of the IMPACT strategy of the Ministry of Health, also seeks to identify genomic alterations, particularly in extreme patient groups at the onset of diabetes. Once these and similar studies are completed, we will have a much more precise profile of people with diabetes in our region. This will allow us to better predict their prognosis and apply preventive and therapeutic measures with greater effectiveness and lower risk.

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Another significant advancement of AI in the field of medicine and diabetes is the use of large databases (Big Data) (6) and synthetic databases. Much of the scientific evidence we currently have comes from clinical trial results, which often

» have highly restricted entry conditions. While the internal validity of these results is indisputable, their applicability (external validity) is usually very limited because most patients would not meet the inclusion criteria for the trials. For these patients, we apply the conclusions of studies in which they could not have participated. This is especially true for certain groups of patients, such as the elderly or those with associated comorbidities (e.g., mental illness or chronic kidney disease).

To determine how to act for this large group of patients, we rely on the experience provided by extensive databases that contain vast numbers of unrestricted patients observed over long periods of time. These datasets enable us to understand what has happened and predict what might occur in patients with very similar characteristics. Such data can be used to develop personalized risk models, identify new therapeutic targets, and guide preventive and therapeutic actions.

Sometimes, using Big Data, simulations of patients are conducted, creating databases of non-existent patients (Synthetic Databases) (7) that do not exist but behave like real ones. This approach, in addition to preserving confidential data, allows us to perform different analyses based on the simulations, minimizing the risks associated with working with real data.

A more specific example would be working with so-called “digital twins” or “artificial patients,” which are imaginary clones of real patients (8). With them, we can test different therapeutic options, both pharmacological and lifestyle-related, without risking real patients’ safety.

These technologies are already being applied today.

It is important to emphasize that PPM not only has the potential to improve health outcomes for people with DM but could also have a significant impact on reducing health care costs. By focusing on the most effective interventions for each patient, PPM could help reduce the use of unnecessary drugs and hospitalizations.

The future of PPM applied to diabetes is very promising. Both conceptually and technologically, we are on a new and extraordinarily exciting path. However, it is important to note that PPM is not a one-size-fits-all solution for all the problems of diabetes. Another aspect to consider will be the development and implementation plan for PPM in different health care systems and the challenges this entails. A balanced approach is needed, combining PPM with traditional methods to ensure that all people with DM have access to the highest quality care possible. D

CONCLUSIONS

- PPM has the potential to transform the management of DM by providing more precise and effective strategies for diagnosis, treatment, and prevention.
- However, it is important to address the challenges and obstacles in implementing PPM, as well as the ethical and social considerations related to its use.
- Ongoing research and collaboration between scientists, healthcare professionals, patients, and policymakers will be essential to ensure that PPM is used responsibly and equitably, improving the health of individuals with DM and providing them with the best possible care at every stage.

REFERENCES

1. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018; 6(5): 361-369
2. Udler MS, McCarthy MI, Florez JC, et al. Genetic Risk Scores for Diabetes Diagnosis and Precision Medicine. Endocr Rev 2019; 40(6): 1500-1520
3. Herder C, Roden M.: A novel diabetes typology: towards precision diabetology from pathogenesis to treatment. Diabetologia 2022; 65 (11): 1770-1781.
4. Chung WK, Erion K, Florez JC, et al. Precision Medicine in Diabetes: A Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2020; 43 (7): 1617-1635.
5. Manzini E, Vlacho B, Franch-Nadal J, et al.: Longitudinal deep learning clustering of Type 2 Diabetes Mellitus trajectories using routinely collected health records. J Biomed Inform [Internet]. 2022; 104218. https://linkinghub.elsevier.com/retrieve/pii/S1532046422002234
6. de Mauro A, Greco M, Grimaldi M. What is big data? A consensual definition and a review of key research topics. In: AIP Conference Proceedings. American Institute of Physics Inc.; 2015. p. 97-104.
7. Stolfi P, Valentini I, Palumbo MC, et al.: Potential predictors of type-2 diabetes risk: machine learning, synthetic data and wearable health devices. BMC Bioinformatics. 2020; 21(Suppl 17): 508. doi: 10.1186/s12859-020-03763-4.
8. Shamanna P, Saboo B, Damodharan S, et al.: Reducing HbA1c in Type 2 Diabetes Using Digital Twin Technology-Enabled Precision Nutrition: A Retrospective Analysis. Diabetes Therapy. 2020; 11 (11): 2703-2714
9. Drucker, DJ; Hollander, P.: Precision medicine in diabetes—a perspective on the future. Nature Medicine, 2021; 27 (10): 1183- 1193 https://www.nature.com/articles/s41574-022-00799-9