



Precision Medicine in Diabetes: From Genetic Risk to Real-World Implementation

Author: Bertie Pearcey, EMJ, London, UK

Citation: EMJ Diabet. 2025;13[1]:30-34.
<https://doi.org/10.33590/emjdiabet/FXCO4643>



AT A LIVELY and data-packed session titled 'Clinical Applications of Precision Medicine in Diabetes', delivered during the European Association for the Study of Diabetes (EASD) Annual Meeting 2025, held in Vienna, Austria, from 15th–19th September 2025, leading researchers discussed the tangible and emerging strategies to implement precision medicine in diabetes care. The session, moderated by Jordi Merino, University of Copenhagen, Denmark, highlighted not only the clinical potential of genetic and biomarker-driven treatment, but also the growing imperative to bridge the gap between research and real-world care.

FROM CONCEPT TO CLINIC: DELIVERING PRACTICAL PRECISION MEDICINE

Kicking off the session, Ewan Pearson, University of Dundee, UK, took the audience on a compelling 'whistle-stop tour' of what he termed practical precision medicine for Type 2 diabetes (T2D). He emphasised that, while the evidence base for targeted care is growing, the key challenge lies in implementation.

Pearson began with monogenic diabetes, a field that exemplifies the promise and pitfalls of precision medicine. While the clinical benefits of identifying monogenic forms of diabetes have been known for over 2 decades, large-scale data show that diagnoses are still frequently missed. In Scotland, for example, up to two-thirds of monogenic diabetes cases may go unrecognised.¹

In response, Pearson and colleagues developed iDiabetes,² a clinical decision-support platform designed to embed precision care into routine practice. The system automates steps like

the measurement of C-peptide and autoantibodies, critical tests often overlooked in primary care, and integrates them with algorithmic models to identify likely cases of monogenic and Type 1 diabetes.

Moving to treatment decisions in T2D, Pearson critiqued current guidelines, stating that, while comprehensive, they can lack translation to a heterogeneous population. He argued that precision tools could help identify which patients are most likely to benefit from particular drug classes, not just on the basis of clinical characteristics, but also through biomarkers and polygenic risk scores (PRS).

Genetic Risk Scores: Refining Cardiovascular Stratification

One striking example involved the use of a coronary artery disease PRS in middle-aged men with T2D.³ Pearson showed how genetic risk could reclassify some individuals from low to high cardiovascular risk, potentially altering treatment decisions. In particular, patients with low clinical risk but high genetic risk might otherwise be

missed under conventional stratification. These risk scores, now implemented within the iDiabetes framework, offer an added layer of individualisation.

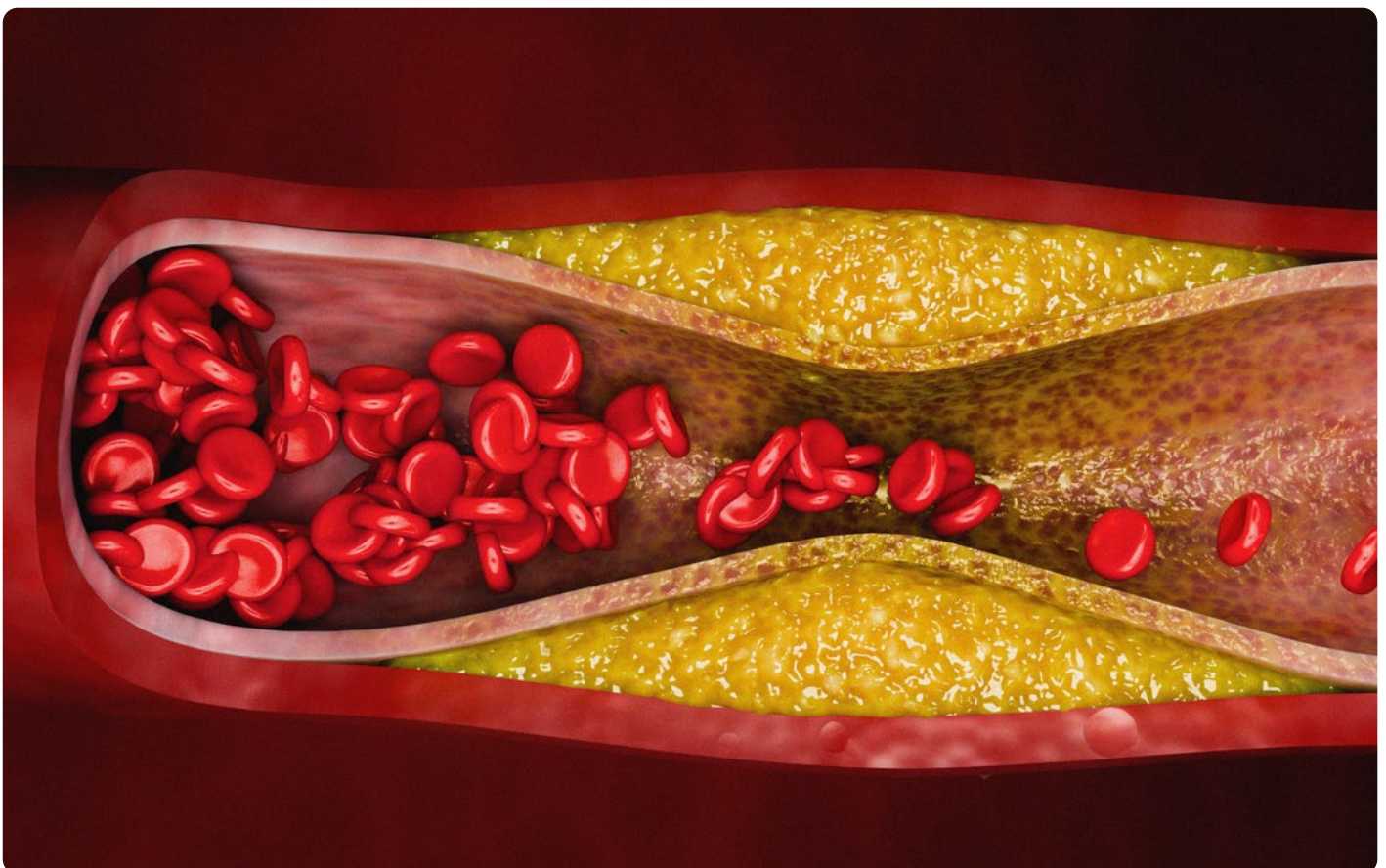
Next, Pearson described the Exeter 5-drug model,⁴ which uses nine routine clinical features, such as age, BMI, HbA1c, and lipid levels, to predict the likely glycaemic response to five commonly used glucose-lowering medications. The model highlights substantial inter-individual variation in drug response. Notably, it reveals a sex-based divergence: women tend to respond better to glucagon-like peptide-1 receptor agonists, while men respond more favourably to sodium-glucose co-transporter-2 inhibitors and sulfonylureas.⁵

“Genetic risk could reclassify some individuals from low to high cardiovascular risk, potentially altering treatment decisions”

“When we look at the data, around one in five people are not on their best drug,” said Pearson, highlighting the clinical relevance of these findings. Through the iDiabetes platform, the model has been deployed to help clinicians select the most effective therapy, with HbA1c reduction as the guiding outcome.

Pharmacogenetics: Variants That Matter in Routine Prescribing

Pearson also presented emerging evidence from pharmacogenetic studies linking genetic variants to cardiometabolic outcomes in commonly prescribed drugs. For example, people with loss-of-function variants in cytochrome P450 2C19 (CYP2C19), responsible for activating clopidogrel, have an increased risk of recurrent cardiovascular events. Despite guidelines recommending genotype-guided clopidogrel use, uptake remains limited.^{6,7} Similar findings were presented for digoxin and metformin: variants in *ABCB1* and *CUBN*, respectively, were associated with increased hospitalisation risk and



B12 deficiency in metformin users. While these pharmacogenetic markers are not yet implemented in iDiabetes, Pearson suggested that they represent a clear opportunity to refine prescribing practices.

The final part of Pearson's talk focused on closing the implementation gap. In Scotland, where a unified diabetes registry covers the entire population, Pearson's team is now conducting a cluster-randomised trial

involving over 10,000 patients. General practitioner practices are assigned to either usual care, iDiabetes guideline support, or iDiabetes Plus, which integrates additional genetic and biomarker data. The platform has achieved UK Conformity Assessed certification as a medical device and returns clinical recommendations within 2 weeks of sample collection. The team aims to recruit 20,000 patients by mid-2026, with results expected within the year.



“Even in cases with apparently straightforward monogenic mutations, outcomes may be influenced by polygenic background and environmental exposures”

OLIGOGENIC DIABETES: GENETIC COMPLEXITY BEYOND MONOGENIC AND POLYGENIC MODELS

Amélie Bonnefond, National Centre for Precision Medicine in Diabetes, Lille, France, offered a molecular deep dive into the genetics of T2D, focusing on the emerging concept of oligogenic diabetes. While most T2D cases are polygenic, with small contributions from many common variants, Bonnefond highlighted that some patients may carry rare variants with moderate-to-strong effects that do not meet the threshold for monogenic disease.

She contrasted monogenic and polygenic diabetes, noting that monogenic forms often involve genes crucial to β -cell development or insulin secretion. Importantly, some monogenic mutations are actionable: for example, patients with *GCK* mutations often require no treatment, while those with *GATA4* or *GATA6* mutations warrant cardiac evaluation due to associated defects.⁸

Opioid Receptors and Pancreatic β -Cells

One of the most intriguing parts of her presentation focused on the *OPRD1* gene as a novel example of oligogenic contribution to T2D. Rare gain-of-function variants in *OPRD1* were associated with increased diabetes risk but decreased adiposity, mirroring the metabolic effects of chronic opium use. Conversely, loss-of-function variants reduced diabetes risk but increased adiposity.⁹

Bonnefond's team showed that *OPRD1* is expressed in human pancreatic β -cells and that its antagonism, using the compound naltrindole, enhances insulin secretion *in vitro*. They further traced the endogenous ligand for *OPRD1* to β -endorphin, a cleavage product of the prohormone pro-opiomelanocortin, which is itself upregulated by agents that increase cyclic adenosine monophosphate.

In ongoing mouse studies, animals engineered to express human *OPRD1* in β -cells showed increased glycaemia, supporting the pathogenic role of *OPRD1*

gain-of-function mutations (unpublished data). This finding opens the door to new therapeutic targets: delta-opioid receptor antagonists, perhaps modified to avoid crossing the blood–brain barrier, could be used to enhance insulin secretion in a subset of patients with genetically elevated *OPRD1* activity.



RWD offers valuable insights, particularly when linked with genomic and exposomic data



Bonnefond concluded by highlighting the complexity of genetic interactions in diabetes. Even in cases with apparently straightforward monogenic mutations, outcomes may be influenced by polygenic background and environmental exposures. A study of over 500,000 people showed that carriers of *GCK* mutations still develop diabetes-related complications, highlighting the need for a more nuanced model that integrates monogenic, oligogenic, and polygenic contributions.¹⁰

REAL-WORLD DATA: A CRUCIAL PILLAR IN PRECISION MEDICINE

Chirag Patel, Harvard Medical School, Boston, Massachusetts, USA, closed the session with a broader view on how real-world data (RWD) can be used to drive precision medicine. He defined RWD as observational, non-randomised data drawn from sources such as medical records, biobanks, registries, and digital health tools. While often underappreciated compared to RCTs, RWD offers valuable insights, particularly when linked with genomic and exposomic data.

One challenge with RWD, he noted, is the potential for “vibration of effects,” which is finding contradictory results depending on how data are modelled. To address this, researchers must be cautious with confounding data and apply robust designs, such as trial emulation or Mendelian randomisation.

Patel presented unpublished data exploring how environmental exposures influence phenotypic outcomes in diabetes and related diseases. In one large-scale study, 619 exposures, including heavy metals, hydrocarbons, and diet, were associated with thousands of biomarkers. Although single exposures explained a small fraction of variance (approximately 0.5%), combining 20 exposures increased explained variance to 3.5%, approaching that of genome-wide PRSs.

Proteomics analyses revealed proteins, such as leptin and growth differentiation factor 15 (GDF15), that were tightly linked to both genetic and environmental exposures. These findings were then cross validated in RCTs such as the HERITAGE study¹¹ (exercise training) and the STEP trials^{12,13} (semaglutide), showing convergence between RWD and experimental interventions.

Looking forward, Patel envisions a future where integrated, multi-modal data, including continuous glucose monitoring, dietary logs, and genomics, will enable clinicians to capture both acute and chronic responses to therapy and environment. RWD, he stressed, must be part of an integrated whole to deliver truly actionable insights.

CONCLUSION

As the field of diabetes care moves toward precision medicine, this session made one point abundantly clear: progress depends not just on the discovery of genetic variants and predictive models, but on the ability to bring these tools into routine practice. Whether through decision-support systems, the molecular dissection of rare variants, or the integration of RWD, the future of personalised diabetes care is being built, one patient, one data point, and one clinical decision at a time.

References

1. Pang L et al. Improvements in awareness and testing have led to a threefold increase over 10 years in the identification of monogenic diabetes in the U.K. *Diabetes Care*. 2022;45(3):642-9.
2. iDiabetes. Home. 2025. Available at: <https://www.idiabetes.org.uk/>. Last accessed: 13 October 2025.
3. Riveros-McKay F et al. Integrated polygenic tool substantially enhances coronary artery disease prediction. *Circ Genom Precis Med*. 2021;14(2):e003304.
4. Dennis JM et al. A five-drug class model using routinely available clinical features to optimise prescribing in type 2 diabetes: a prediction model development and validation study. *Lancet*. 2025;405(10480):701-14.
5. Cardoso P et al. Phenotype-based targeted treatment of SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes. *Diabetologia*. 2024;67(5):822-36.
6. Itkonen MK et al. Clopidogrel increases dasabuvir exposure with or without ritonavir, and ritonavir inhibits the bioactivation of clopidogrel. *Clin Pharmacol Ther*. 2019;105(1):219-28.
7. Bedair KF. Pharmacogenetics at scale in real-world bioresources: CYP2C19 and clopidogrel outcomes in UK Biobank. *Pharmacogenet Genomics*. 2024;34(3):73-82.
8. Bonnefond A, Semple RK. Achievements, prospects and challenges in precision care for monogenic insulin-deficient and insulin-resistant diabetes. *Diabetologia*. 2022;65(11):1782-95.
9. Meulebrouck S et al. Functional genetics reveals the contribution of delta opioid receptor to type 2 diabetes and beta-cell function. *Nat Commun*. 2024;15(1):6627.
10. Barrett KMS et al. Underestimated risk of secondary complications in pathogenic and glucose-elevating GCK variant carriers with type 2 diabetes. *Commun Med (Lond)*. 2024;4(1):239.
11. Sarzynski MA et al. The HERITAGE family study: a review of the effects of exercise training on cardiometabolic health, with insights into molecular transducers. *Med Sci Sports Exerc*. 2022;54(5S):S1-43.
12. Wilding JPH et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002.
13. Davies M et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971-84.