Evolving Landscapes in Diabetes Genetics

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MORE THAN two decades after the completion of the Human Genome Project, a fundamental question remains: how far have genetic discoveries brought us towards precision medicine?

At the European Association for the Study of Diabetes (EASD) 2026 Annual Meeting in Milan, the Study Group for the Genetics of Diabetes (SGGD), an EASD reference group established approximately 20 years ago to foster international collaboration in diabetes genetics, brought together four leading researchers for its symposium, 'Evolving Landscapes in Diabetes Genetics'. The discussions explored the achievements of genomic research and the challenges of translating biological discoveries into meaningful improvements in clinical care.

HAS GENOMICS DELIVERED ON ITS PROMISE?

Opening the symposium, José Florez, Harvard Medical School, Boston, Massachusetts; Massachusetts General Hospital, Boston, USA, drew parallels between the genomic revolution and transformative moments in medical history, including the introduction of anaesthesia and insulin. Just as these breakthroughs fundamentally altered patient outcomes, the Human Genome Project promised to reshape our understanding and treatment of human disease. But has genomics delivered?

> **The symposium highlighted both the achievements of genomic medicine and the challenges that remain**

Florez argued that the answer is unequivocally yes, although its success extends well beyond applications already established in clinical practice. Genomic research has transformed our understanding of gene regulation, 3D genome organisation, and cellular diversity, while generating powerful technologies and resources, from genome-wide association studies and sequencing to genome editing and functional genomics.

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These advances have enabled researchers to move beyond identifying disease-associated variants towards understanding molecular mechanisms, uncovering biological pathways, and identifying potential therapeutic targets.[1]

Yet scientific progress does not automatically translate into clinical benefit. Florez emphasised the importance of distinguishing between research aimed at mechanistic discovery and research intended to inform clinical decisions. The latter demands rigorous validation, reproducibility, cost-effectiveness, and evidence of improved health outcomes.

Looking ahead, he highlighted the opportunities offered by integrating genomics with proteomics, epigenomics, and other molecular measurements, alongside electronic health records, population biobanks, and AI. His vision was one in which genetic information, potentially available from birth, could inform healthcare throughout life. Realising this ambition, however, will require multidisciplinary collaboration, equitable implementation, and a clear understanding of where genomic information genuinely adds clinical value.[1]

FROM GENE DISCOVERY TO CLINICAL DIAGNOSIS

If Florez's presentation established the broader achievements of genomics, Elisa de Franco, University of Exeter, UK, provided a compelling example of its clinical impact. Focusing on pancreatic agenesis, a rare developmental disorder causing neonatal diabetes and pancreatic exocrine insufficiency, she discussed findings from a 21-year international cohort study involving 129 affected individuals.[2] Comprehensive genetic testing identified the underlying molecular cause in 98% of probands, demonstrating how decades of gene discovery have transformed the diagnosis of an exceptionally rare condition.

The findings also highlighted the importance of looking beyond protein-coding regions. Variants affecting the distal enhancer of *PTF1A* accounted for a substantial proportion of cases, illustrating how clinically relevant genetic defects may be missed by conventional exome sequencing.

Approximately one-third of probands had not been recognised as having pancreatic agenesis when initially referred for genetic



testing. Identifying a pathogenic variant can therefore do more than confirm a suspected diagnosis: it can prompt investigations for previously unrecognised pancreatic exocrine insufficiency, guide appropriate treatment, and inform genetic counselling.[2]

This illustrates an important distinction in precision medicine. The clinical value of genetics is not necessarily confined to identifying targeted therapies. Establishing the correct molecular diagnosis can itself change clinical management. In rare, monogenic conditions, genomic medicine has already moved beyond promise to practice.

RETHINKING DIABETES HETEROGENEITY

Translating genetic discoveries into clinical care becomes considerably more challenging in common, heterogeneous forms of diabetes. Robert Wagner, Heinrich Heine University, Düsseldorf; German Diabetes Center, Düsseldorf, Germany, approached this challenge from a clinical perspective, questioning whether conventional diagnostic measurements adequately capture the biological diversity underlying diabetes.

> **Diabetes genetics has evolved beyond identifying susceptibility variants to fundamentally reshaping our understanding of disease mechanisms**

Phenotype-based clustering has represented an important step towards recognising this heterogeneity, identifying diabetes subgroups characterised by differences in insulin secretion, insulin resistance, and clinical presentation. However, Wagner highlighted several limitations: cluster assignments may change over time; individuals do not always fit neatly into discrete categories; and reducing continuous biological variation to predefined groups can obscure clinically relevant information. Crucially, whether these classifications improve treatment outcomes remains uncertain.[3]

Genetics offers a complementary perspective. Unlike clinical phenotypes, which evolve with disease progression and environmental exposures, inherited genetic susceptibility provides a relatively stable reference point. Pathway-specific genetic risk scores may help distinguish different mechanisms contributing to diabetes and its complications. However, Wagner cautioned against assuming that different clinical phenotypes necessarily represent distinct diseases. They may instead reflect different stages of a shared biological process, as illustrated by heterogeneity in adult-onset Type 1 diabetes.[3]

The challenge is therefore not simply to develop increasingly sophisticated classification systems, but to determine whether they can improve prevention, guide therapeutic decisions, and ultimately benefit patients.

UNCOVERING THE BIOLOGY OF BODY COMPOSITION

A related challenge arises in obesity genetics, where BMI has long served as the principal phenotype for genetic discovery. Ruth Loos, University of Copenhagen, Denmark, highlighted how reliance on BMI can obscure important biological differences.

Moving towards more refined measures, including body fat percentage, fat-free mass, and fat distribution, offers opportunities to uncover genetic influences that may remain hidden in conventional BMI-based analyses. Such approaches can provide a more detailed understanding of the biological pathways contributing to variation in body composition and metabolic susceptibility.[4]

Importantly, Loos emphasised the potential of genetically informed approaches to move beyond conventional definitions of obesity towards more biologically meaningful characterisation. Rather than treating obesity as a single homogeneous phenotype, understanding its underlying genetic architecture may help distinguish different biological processes contributing to excess adiposity and metabolic dysfunction. She also highlighted the opportunities

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for therapeutic discovery, particularly the identification of genetic targets that could inform strategies to reduce adiposity while preserving lean mass.[4]

The broader message closely echoed Wagner's discussion of diabetes heterogeneity. Conventional clinical measurements remain useful, but they do not necessarily reveal the biology underlying disease. More precise phenotyping, combined with genetic information, may provide a foundation for more targeted approaches to prevention and treatment.

FROM BIOLOGICAL INSIGHT TO CLINICAL IMPACT

Together, the four presentations illustrated how diabetes genetics has evolved beyond identifying susceptibility variants to fundamentally reshaping our understanding of disease mechanisms, heterogeneity, and therapeutic opportunities. From the remarkable diagnostic success in pancreatic agenesis to the emerging potential of genetically informed approaches to diabetes classification and body composition, the symposium highlighted both the achievements of genomic medicine and the challenges that remain.

Returning to the question posed at the beginning of the symposium: has genomics delivered on its promise? Perhaps not in quite the way originally anticipated. Rather than immediately revolutionising clinical practice, its greatest contribution has been to transform our understanding of human biology, revealing complexities that conventional clinical measurements and disease classifications often fail to capture. These discoveries are already translating into meaningful clinical benefits, and most importantly, laying the foundations for more precise approaches to prevention and treatment.



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