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EDITORIAL

Pinpointing precision medicine for diabetes mellitus

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As the medical field has embraced the omics era, and big data have provided novel insights into pathophysiology and disease progression, the term precision medicine has been coined to capture the promise of tailoring prevention, diagnosis and treatment such that each patient receives optimal therapy. It is a movement from one-size-fits-all to personalised therapy. The diabetes community has long recognised that diabetes, a state where glucose levels are elevated, encompasses a vast number of different subcategories, with divergent routes to manifestation, far more diverse than classification into simply type 1 and type 2 diabetes. For this special issue, we have commissioned 16 reviews on precision medicine as it pertains to diabetes mellitus; the authors set out the hopes and challenges of realising precision medicine in the management of diabetes.

Precision diagnostics of diabetes includes the phenotypic and genetic classification of diabetes. Deutsch et al [1] outline two complementary approaches: a phenotypic strategy utilising clinical variables such as autoantibodies, BMI and HbA_{1c}, and a genetics-based strategy, considering single-gene mutations, as well as genetic variants and polygenic scores. These approaches uncover clusters of individuals with distinct clinical phenotypes and pave the way for a more precise classification of disease development, progression and treatment. Following on from this, Herder and Roden [2] discuss how stratified subgroups associate with different trajectories in disease progression and onset of diabetes-related complications. They further explore how prevention and treatment approaches can be tailored for precision diabetology. Next, Bonnefond and Semple [3] exemplify how precision care is applied to monogenic insulin-deficient and insulin-resistant diabetes, disorders which have a less complex genetic basis and may serve as proof of concept.

Precision medicine also has the potential to be harnessed for precision prevention. To this end, Nicholas Wareham [4] outlines how the very general advice currently given to individuals at high risk of developing type 2 diabetes should be modified and describes different ways in which prevention of type 2 diabetes could become more personalised. Given that different individuals have divergent responses to prevention interventions, Sørensen et al [5] discuss the role of gene–environment interactions in type 2 diabetes prevention and indicate their implications for precision prevention. Much of prevention is already personalised to some degree, and there is a challenge in striking a balanced approach that also tackles type 2 diabetes as a large public health problem. Gestational diabetes remains the most common endocrinopathy in pregnancy. It not only increases the risk of complications during pregnancy and birth but also the long-term risk of developing type 2 diabetes and cardiovascular disease in both mother and offspring. Sparks and Ghildayal et al [6] review commonly implemented preventive strategies and highlight factors that aid in precision prescription of lifestyle interventions to prevent gestational diabetes.

Precision treatment, often relying on precision diagnostics, has the potential to offer direct clinical benefits to patients and to be more cost-efficient for society as time and resources are not wasted on less efficacious treatments. In the case of monogenic diabetes, as represented by *HNF1A*-MODY, Bonner and Saponaro [7] relate how carriers with different mutations in the *HNF1A* gene may respond to different therapies. In contrast, the promise of pharmacological precision medicine for type 2 diabetes remains largely unrealised, as detailed by Florez and Pearson [8]. This reflects, in part, the very heterogeneous nature of type 2 diabetes, and that pharmacological therapies are typically selected based on comorbidities, cost or side effects, rather than on the specific pathophysiology underlying disease in the individual patient; a goal of precision diabetes medicine. In a similar vein, Jordi Merino [9] tackles the area of precision nutrition in diabetes, discussing how differences arising from genetics, gut microbiome and other clinical and lifestyle characteristics are likely to impact

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an individual's response to a given diet. Charlotte Ling [10] goes on to provide an overview of the emerging field of pharmacoepigenetics in type 2 diabetes. Although still a relatively unexplored area, epigenetic enzymes have been noted to be dysregulated in tissues from individuals with type 2 diabetes, suggesting a potential for epigenetic therapies in the treatment of diabetes.

Also for type 1 diabetes, precision medicine promises to improve clinical management. While efforts to improve classification of different forms of type 2 diabetes are progressing, up to one in three adults with type 1 diabetes are still initially misdiagnosed as having type 2 diabetes. Carr et al [11] outline that while devices, insulin formulation and delivery systems have all improved clinical management of type 1 diabetes, there is still a need for more research into the variable pathogenesis in type 1 diabetes. Such understanding could lead to improved disease-modifying treatments and strategies for prevention, or even reversal of type 1 diabetes pathogenesis

At diagnosis, individuals with diabetes frequently exhibit one or more additional diagnoses. This highlights both a challenge in disease management as well as the need for precision medicine beyond diabetes mellitus. Understanding an individual's risk of developing diabetes-related complications would allow clinicians to optimise therapies for each patient. Precision diabetes prognostics aims at early identification of individuals who are at increased risk of particular complications. In their review, Schiborn and Schulze [12] shed light on the methodological challenges inherent in the development and validation of prognostic models, and they discuss how studies are needed to determine the clinical benefit of current strategies.

The explosive development of wearable devices and direct tracking has uncovered new possibilities in home monitoring. Hermanns and colleagues [13] review the state-of-the-art of precision monitoring in diabetes, discussing not only the role of devices but also the interplay between behaviour, mental health and blood glucose. Since associations between glycaemic outcomes, behaviour and mental health are idiosyncratic, these have implications for the therapeutic management of diabetes. Precision monitoring can inform precision diagnostics and precision therapeutics in diabetes. Kremers et al [14] further discuss the role of mental health disorders in precision medicine for diabetes and postulate that addressing mental disorders as a facet of precision diabetes medicine could have considerable value for routine diabetes care; however, there are still considerable gaps in knowledge and several challenges to be met to realise this.

The Precision Diabetes Medicine collection concludes with two reviews offering different perspectives on the field. Arleen Tuchman [15] discusses how precision diabetes medicine may be instrumental in reducing health disparities. To realise this, precision diabetes medicine must expand the current focus on biomarkers to include studies of the social determinants of health, such as food security, affordable housing and access to healthcare of high quality. Finally, Simon Griffin [16] poses the question of whether we are ready to harness the promise of precision diabetes medicine to change the clinical management or outcome for the majority of individuals with type 2 diabetes. At present, cost-effective behavioural interventions, such as exercise and healthy diet, are effective in reducing risk of type 2 diabetes (and a number of other diseases), regardless of the underlying genetic predisposition.

Precision medicine holds promise to deliver correct and effective treatment to improve health, as outlined in this special issue of *Diabetologia*. It is, to a great extent, driven by the expansion of knowledge about disease mechanisms, emanating from novel technologies and large-scale studies in biomedicine. Many of the concepts in precision medicine originate in the cancer field, where there is a wide appreciation that specific mutations respond differentially to therapy. Despite this insight, even the cancer field is only beginning to deliver on the promise of precision medicine [17]. Additional challenges exist for a heterogeneous disease such as diabetes mellitus, with a multifactorial aetiology, which from a genetic perspective is mostly polygenic in nature. It is wise and important to temper some of the enthusiasm spurred by the development of novel, and often expensive, technologies with the realisation that for a large number of people with diabetes, small improvements in the delivery of present-day standard diabetes care will also have a significant impact on health. Indeed, we have some way to go before diabetes patients globally receive the standard best-practise care that they deserve for this devasting disease.

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