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EDITORIAL

Precision diabetes: a realistic outlook on a promising approach

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Precision medicine, the tailoring of healthcare based on an individual's genetics, lifestyle and environment, is not a new concept. Throughout the history of medicine, clinicians have called on available resources to determine the optimum treatment for patients. A common example is the selection of specific blood types for blood transfusions on the basis of the recipient's blood group, a procedure that became routine following the discovery of human blood groups by Karl Landsteiner in 1901 [1]. Glasses are another example: lenses have been tailored to an individual's visual ability since circa 1284 [2]. By adopting a precision medicine approach, healthcare is made more effective, safer and more cost-efficient.

Years ago, diabetes physicians perhaps believed that they were practising precision medicine: young people had 'insulin-dependent' diabetes and needed insulin, while older people had 'non-insulin-dependent' diabetes, managed with lifestyle measures, metformin and/or sulfonylureas. It was Robert Tattersall's description in 1974 of three families with what we now recognise as Maturity Onset Diabetes of Youth (MODY) [3] that first focused our minds on the heterogeneity of clinical phenotypes, particularly in type 2 diabetes, and in the variation in response to treatment. The true age of precision medicine in diabetes was born.

Since that first clinical description of a subtype of diabetes, advances in technologies in genetics, molecular biomarkers and 'omics' have revealed much about the pathophysiology and natural history of diabetes and individual responses to glucose-lowering therapies. This work has required a change of attitude and approach by investigators; collaboration between many groups of investigators, sometimes on a global scale, has been necessary to build cohorts sufficiently large to be robustly informative. Collaboration across disciplines has also been necessary, involving clinician investigators for detailed clinical phenotyping, geneticists, molecular biologists, and latterly informatics experts able to handle huge databases integrating a wealth of information from different sources. A high level of resources has been, and continues to be, channelled into this work: early in 2016 the UK government's 'Innovate UK' initiative began funding the Precision Medicine Catapult, which 'aims to make the UK a world centre for precision medicine' [4]. Also in 2016, the NIH announced a $55 million award to help launch The Precision Medicine Initiative's 'All of Us Research Program', a programme with the ultimate goal of 'bringing precision medicine to all areas of health and healthcare on a large scale' [5–7].

What has all this effort meant for the person with diabetes and healthcare professionals? For the vast majority, the honest answer is very little. Life in the diabetes clinic is much the same as it was 30 years ago. We still work to the general principle that most young people have type 1 diabetes, albeit keeping an eye out for the rarer individuals with MODY. We now have many more classes of glucose-lowering agents and are aware that individuals respond differently in terms of glucose-lowering and weight effects. However, we cannot predict who will benefit most from which type of agent. Thus, treatment algorithms for type 2 diabetes usually suggest a 'try it and see' approach to second- , third- and fourth-line glucose-lowering agents. In most cases we are a long way from the position of some cancer treatments, where genetic analysis defines the necessary therapy and predicts response

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(e.g. good efficacy of vemurafenib in individuals with the *BRAF* V600E mutation [8]). However, the work so far in diabetes has not been in vain: we have learned a great deal about the pathophysiology, molecular biology and genetics of diabetes and this knowledge is opening up novel therapies. Precision medicine is important and offers much hope for the future in diabetes. Thus I am delighted to publish a series of articles in this issue of *Diabetologia* which details the progress that has been made so far with 'precision diabetes', acknowledges the difficulties and barriers of this approach and describes the exciting promise of what is to come.

To commence the series, Hattersley and Patel [9] describe the established success of precision medicine in monogenic diabetes. They discuss how the genetic diagnosis of neonatal diabetes and MODY aids the selection of specific treatment for these conditions and helps to predict clinical features and clinical course. They explain why precision medicine is so applicable to monogenic diabetes but also describe the challenges faced when trying to implement this approach into routine clinical care. Using this experience, Hattersley and Patel propose ways to overcome some of the difficulties that may occur when attempting to apply precision medicine to type 2 diabetes.

Obesity, with its genetic and environmental factors, is a major driver in the development of type 2 diabetes. In his review [10], Giles Yeo describes how rare genetic disorders that result in severe obesity (specifically those that cause disruption of the leptin–melanocortin pathway) may be used to provide insight into common obesity, and how this information may influence its treatment and management. He concludes that newly developed research tools can be used to acquire knowledge that may enable efficient implementation of a precision medicine approach for the management of common obesity, and thus of some types of diabetes.

Franks and Poveda [11] discuss how lifestyle interventions, effective first-line therapy for the treatment of type 2 diabetes, may be tailored to an individual. They explain how an individual's genotype, plus biomarker stratification, could potentially be used to predict their response to deleterious lifestyle factors that can lead to diabetes and, conversely, how these factors can be used to predict an individual's response to lifestyle interventions.

Rather than focusing on one specific driver for diabetes, Mark McCarthy [12] proposes a new model for precision medicine in diabetes that takes into account a plethora of risk factors. McCarthy describes how the prevailing diagnostic model for diabetes (the 'pigeonhole model', which places individuals into specific diagnostic categories) fails to account for the influence of multiple independent genetic and non-genetic factors on diabetes risk. Instead, he suggests an alternative 'palette model', which acknowledges type 2 diabetes as a multisystem disease. This model accounts for the magnitude of effect of different factors on diabetes risk, identifies those who are affected by multiple concomitant pathophysiological processes from those for whom diabetes has resulted from one predominant component pathway, and recognises the ability of therapeutic agents to beneficially affect diabetes risk and progression.

In his review [13], Jose Florez explains how pharmacogenetics may be used as a discovery tool to elucidate new drug targets, uncover pathophysiology, unravel disease heterogeneity and identify specific genes that contribute in a major way to disease risk. Florez details examples of these advances, including stratification for treatment of monogenic and polygenic diabetes (e.g. sulfonylureas in individuals with *ABCC8* and/or *KCNJ11* mutations), the impact of genetic variants (*SLC22A1*, *SLC47A1*, *ATM* and *SLC2A2*) on response to metformin and, finally, how variations in the response to glucose-lowering therapy are shedding light on the functionality of the *TCF7L2* risk genotype in diabetes.

The ideas described in this precision medicine series open up a new horizon in diabetes care: the ability to predict the impact of a noxious environmental insult on an individual; much improved identification of those at high risk of diabetes and of progressing to insulin-requiring diabetes; and the possibility of offering tailored lifestyle and pharmacological advice depending on a person's gene/biomarker profile, to name but a few. Precision medicine has already improved our knowledge and understanding of diabetes and has directly benefited a small number of individuals. An enormous amount of work remains necessary for further progress, but the foundations are well-laid, technology advances rapidly and collaborations across research disciplines are strong. The authors in this series outline individual barriers to success in their own areas but the weakest link, as is so often the case, is the translation of important advances in precision medicine into routine clinical care. Despite the excitement around the discovery of MODY genes, readily available screening and diagnostic tests, and a clear demonstration of the need for individualised management, diagnostic rates are very variable, at least across the UK. As a first step in the new world of precision medicine, diabetes clinicians must make routine use of the tools they currently have available (autoantibody and C-peptide measurements, perhaps, for all individuals, genetic testing for a few) to make a much more definitive diagnosis. This is the essential first step in positioning us to take advantage of all that precision medicine will offer in the future.

I hope that you enjoy reading this precision medicine review series, but ultimately I hope that it inspires further developments to make the application of this promising approach a reality for all aspects of diabetes care.

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