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Harnessing heterogeneity in type 2 diabetes mellitus

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Abstract

Personalized, or precision, medicine in type 2 diabetes mellitus is becoming a reality with new insights into the contributions of subgroup analyses. The roadmap to future implementation must take into account individual and subgroup variability in genetic architecture, environment, clinical measures, lifestyle, cost-effectiveness and treatment burden.

Edwin Gale once said that type 2 diabetes mellitus (T2DM) should instead be called ‘idiopathic hyperglycaemia’ for all the insight that the term T2DM allows. Gale foresaw precision medicine in T2DM as an emerging approach based on the integration of genetics, biomarkers, cluster analyses, physiology, the microbiome, behavioural medicine, wearable devices, economics and simple clinical measures[1]. Several articles have since made the point that heterogeneity of T2DM matters for understanding the natural history of disease, development of complications and identification of the most effective treatments[2,3].

In 2019, several key studies have helped improve T2DM diagnostics and aided in the development of the additional research necessary to support precision therapeutics. For example, John Dennis and colleagues[4] examined previous results of cluster analyses in T2DM[5,6], with or without a genetic basis, which revealed five subgroups of T2DM that differed in disease progression and complication risk. The analysis conducted by Dennis and colleagues included data on age at diagnosis, renal function, initial HbA_{1c} levels and sex. The authors used clinical measures to identify that the five clusters of T2DM not only recapitulated, but could be interpreted as an improvement over, the previously reported cluster analysis and could aid in the selection of targeted therapy. The contention, therefore, is that cluster analyses, augmented with genetic studies, might yield mechanistic insight into specific disease pathways and outcomes that underlie patient subgroups. Dennis and colleagues posit that precision medicine in T2DM can also be advanced by using specific phenotypic measures to predict specific treatment outcomes, rather than by assigning patients to subgroups[4]. However, the authors acknowledge that before precision medicine in T2DM can be implemented, an analysis of key clinical features not included in the original analysis, such as lifestyle factors, biomarkers, current treatments and treatment costs, will also be needed.

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Competing interests

The author declares no competing interests.

Oana Zeharia and colleagues[7] evaluated the utility of comprehensive phenotyping in redemonstrating the utility of these clusters at diagnosis and during 5 years of follow-up in the German Diabetes Study. The investigators evaluated insulin sensitivity, hepatocellular lipid content (fatty liver), hepatic fibrosis and neuropathy in patients with newly diagnosed type 1 diabetes mellitus or T2DM using functional and clinical criteria. It is important to note that studies on newly diagnosed patients can allow for aetiological conclusions, as opposed to studies that include patients with long-standing T2DM, whose phenotypic characterization will be modified by the diabetic state and metabolic burden of disease. Zeharia and colleagues[7] were able to identify specific phenotypic clusters that result in different disease complications. These results underline the need for metabolic phenotyping. They also demonstrate the utility of screening for anti-islet antibodies in all patients thought to have T2DM or perhaps even any presentation of T2DM at any age. With the increasing incidence of autoimmune diabetes mellitus in many populations regardless of BMI, this is an important addition to the definition of which set of phenotyping measures can have the greatest yield in terms of both the effect on clinical aspects of T2DM and the cost-effectiveness of interventions.

Part of the future of precision medicine in T2DM is the integrated use of omics and wearable devices. A small scale (n = 109) but extremely in-depth study examined omics and wearable devices, along with changes in metabolome, microbiome, physiology and behaviour[8]. The cohort was enriched for individuals with prediabetes but also included some patients with T2DM. Participants were assessed for the presence of disease pathways associated with T2DM or cardiometabolic disease at least quarterly for up to 8 years (median was 2.8 years). The authors noted 67 clinically actionable results from their data[8]. Based on their findings, the team were able to develop prediction models for insulin resistance that were equivalent to the usual more burdensome clamp studies for insulin dynamics. Beyond that, the early return of results to participants contributed to the majority of participants implementing diet and exercise changes. While an example of an extremely time-consuming and elaborate protocol, this study shows that giving people with T2DM, or those who are at risk of developing T2DM, their own interpretable data can result in lifestyle modification in the context of precision medicine.

Another study (n = 2,820) investigated how a long-term cardiovascular risk study could also inform choices for personalized medicine[9]. Using simple clinical variables including sex, urinary levels of microalbumin and/or creatinine and BMI, the authors were able to first identify a cohort with marked insulin resistance and showed that this group responded better to treatment that addressed insulin resistance (PPARγ agonist) than to a drug that increases insulin secretion (sulfonylurea). While most diabetologists would find this hardly surprising, the factors used in the study can be readily used to predict which individuals with T2DM would have improved outcomes, that is, better protection from cardiovascular disease, with the choice of treatment informed by simple clinical measures rather than by an algorithm. As straightforward as this might seem, studies such as this are needed to help inform further progress for precision medicine in T2DM.

Precision medicine in T2DM needs to be patient centred, yet few studies have addressed this issue directly. Sung Eun Choi and colleagues[10] developed and tested a model for second-line

therapy for T2DM that incorporated treatment options, individual patient risk factors and patient treatment preferences for specific treatments. The investigators conducted a meta-analysis consisting of ~220,000 individuals in 301 randomized trials to evaluate treatment efficacy, severity of off-target effects, risk of complications of T2DM and treatment preferences as simple (and as profound) as avoiding daily finger stick blood glucose measurements. The team then used the model to examine results expressed as quality-adjusted life-years (QALYs) from the US National Health and Nutrition Examination Survey 2003–2014. The actual QALYs resulting from the most advantageous treatment switch in patients who were at highest risk of microvascular disease was modest.

The study did, however, help validate an important principle for precision medicine in T2DM. The overall message is that precision medicine is not only about biomarkers, omics or invasive studies. Rather, by combining those studies, often using simple clinical measures, with treatment effect size estimates, individualized risk calculations and, importantly, patient preferences, can optimize personalized treatment selection for best outcomes.

We are only at the beginning of understanding how the aforementioned approaches, combined with key physiological, omic, behavioural and cost analyses, can be applied to precision medicine and help unravel the perplexing heterogeneity of T2DM. The studies reviewed here suggest that combining readily available omic data that is augmented with simple clinical measures with a patient-centred approach will foster individualized strategies for prevention and treatment of T2DM in all its heterogeneity.

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Key advances

- Subgroup analyses have divided patients with type 2 diabetes mellitus (T2DM) into at least five clusters that differ with regard to genetics, insulin secretion, disease progression and disease complications[4,7].
- Specific phenotypic measures of readily measured continuous clinical features can help predict specific outcomes such as fatty liver disease or neuropathy[4].
- Autoimmunity screening might be beneficial in all patients with T2DM[7].
- Deep longitudinal omics profiling can lead to prediction models of insulin resistance with increased acceptance of diet and exercise changes in research participants[8].
- Individuals with biomarkers of insulin resistance can benefit from targeted treatments with PPAR γ agonists as opposed to sulfonylureas to address cardiovascular protection[9].
- Models based on multi-criteria decision analyses that include disease outcomes, patient preferences and medication characteristics can improve personalized treatments[10].

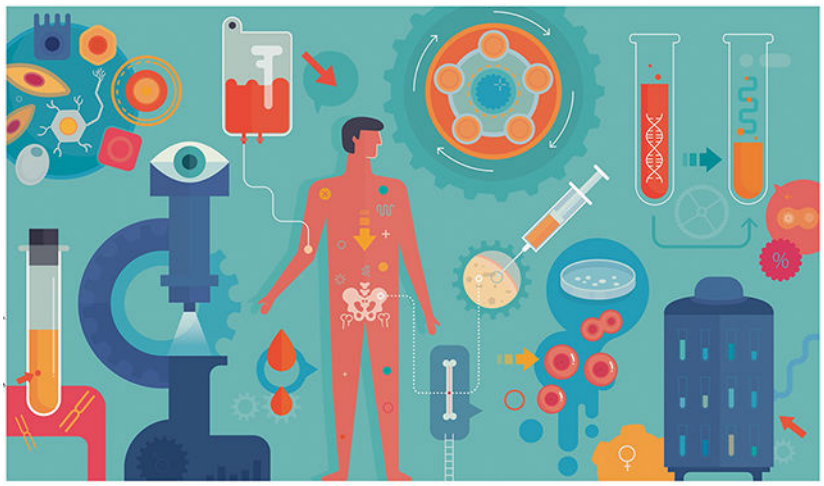

Fig 1.