Personalized medicine in Type 2 diabetes: what does the future hold?

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Practice Points

- Type 2 diabetes is a heterogeneous clinical syndrome with differing rates of progression and complications.
- Patients with Type 2 diabetes vary in their concurrent comorbid conditions, competing risks and personal preferences.
- The robust evidence base for diabetes management applies to populations rather than to individuals.
- Individualized treatment plans offer the potential to subtantially improve care, but there is currently insufficient evidence to guide *a priori* personalization of diabetes management.
- Personalized medicine will require further advances in measuring individual risk, accurately assessing patient preferences, understanding genetic base for disease and quantitatively predicting responses to different therapeutic options.

SUMMARY The management of patients with Type 2 diabetes is based on a remarkably robust evidence base. Large clinical trials and lengthy observational cohort studies have clearly established the importance of glycemic, blood pressure and lipid level control. Indeed, most elements of guideline-based diabetes care can be supported by clinical research evidence. While such studies are critical for establishing treatment recommendations, the evidence derived from clinical trial participants applies to populations of patients rather than to the individual sitting before the clinician. An important next step in diabetes care would be to develop and implement a framework for personalizing care. In this article, we highlight the major reasons for personalization and discuss what the future of personalized diabetes care may hold.

For most people, personalized medicine connotes the use of individual genetic information, proteomic profiling or systems biology to choose the optimal drug or treatment course for an individual [1]. While this ideal has been realized in several notable conditions (including some genetic forms of diabetes), genetic risk models have barely proven more effective than traditional clinical risk factors in predicting diabetes [2]. As the basic science underlying genomic and systems biology advances, combining these new data with the better use of available clinical factors and patient preferences offers the promise of delivering personalized medicine in the broadest and most effective sense.

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Why personalize diabetes care?

The American Diabetes Association publishes annually updated practice recommendations that reflect expert consensus on the evidence from clinical research studies related to Type 2 diabetes management [3] and periodically offers guidelines for medication choices for Type 2 diabetes [4]. Recommendations such as these form the basis for treatment guidelines that are adopted by physicians and healthcare networks. The goals outlined in such policies are increasingly used as standards for quality measurement and clinical performance review [101]. This approach to standardizing diabetes management has resulted in substantial improvement in overall diabetes care and is associated with a marked relative reduction in morbidity and mortality among patients with Type 2 diabetes [5,6].

Despite this clear progress in risk factor assessment and control, diabetes remains the leading cause of preventable blindness and nontraumatic amputations in the USA [102]. Patients with diabetes die on average 6 years earlier than patients without diabetes, and myocardial infarction and end-stage renal disease remain significant risks [7].

Reasons for continued morbidity and mortality in diabetes can be divided into two general categories: suboptimal application of evidence-based therapies (e.g., due to lack of medication intensification by physicians or insufficient lifestyle changes or medication adherence by patients) or inadequate efficacies of current therapies when optimally applied. There is reason for optimism due to the fact that advances in personalized medicine, as defined below, can address barriers in both these categories and may lead to the next major advances in our approach to diabetes control.

Limitations of guideline-driven care

While evidence-based guidelines have been critical to improving the overall quality of diabetes care, there are a number of key limitations that suggest improved tools for individualizing care may be needed.

■ Generalizability of clinical evidence

Evidence for guiding diabetes care is based on clinical trial populations rather than individuals. It is challenging to apply population-based criteria to specific patients because clinical trial participants are typically younger, have fewer comorbid conditions and may have different behavioral profiles given their willingness to participate in research studies. Even among patients who would have met eligibility criteria for the main clinical trials underlying the diabetes evidence base, there is no certainty that treating a specific individual will necessarily prevent an outcome. This is the difference between population-level risk and patient-level outcomes. For example, lowering low-density lipoprotein cholesterol levels below 100 mg/dl in patients with diabetes who are at high risk for cardiovascular events is expected to reduce the absolute risk of such events from 11 to 9% [8]. While clearly beneficial from a population perspective, there were 89 out of 100 patients in the control arm who did not experience cardiovascular disease events (i.e., were given unnecessary treatment) and there were nine patients in the treatment arm who still experienced cardiovascular disease events (i.e., were given futile treatment).

Uncritical application of metric-based guidelines may lead to unintended outcomes, such as excessive drug costs, polypharmacy and drug-related adverse events [9]. In theory, advances that would enable clinicians to identify which individuals would actually benefit from treatment would result in more efficient and effective care. In one recent analysis that modeled hypertension treatment according to individualized guidelines, for example, individualized care increased the quality and reduced cost of care [10]. However, clinical trials are typically focused on the treatment of one specific risk factor. A few clinical trials have implemented simultaneous management of multiple core risk factors (e.g., glycemia, hypertension and dyslipidemia), but even these studies do not evaluate nondiabetes-related comorbidities [11].

The prevalence of diabetes is projected to increase rapidly in individuals aged 75 years and older [12]. As the population ages, patients with diabetes are becoming increasingly complex to treat owing to both diabetes-related and diabetes-unrelated comorbidities [13]. For example, the prevalence of atrial fibrillation, chronic lung disease, depression and osteoarthritis are all increasing and each condition can interfere with diabetes management. In these complex patients, management decisions must be made that address not only the patient's diabetes but also their concurrent comorbid conditions [14]. In personalized care, decisions must also be made about how drugs interact with each

other, which risk factors need to be addressed most aggressively, how to balance symptoms with risk reduction and how to balance multiple guideline recommendations with patient preferences. For example, setting HbA1c goals of <7% may not be appropriate for a patient with limited life expectancy or mild disease [15], but clinicians currently lack the quantitative data necessary to guide the individualization of HbA1c goals.

■ Patient preferences

Separate from the generalizability of current research evidence to clinical care, different patients with similar demographic and comorbidity profiles may have very different personal goals and may value different outcomes [16]. These preferences can influence the decision of whether to pursue lifestyle interventions or to begin medical therapy, for example, or how soon to initiate insulin. For patients with inadequate insurance coverage in the USA, paying for multiple medicines can have a very real impact on nonhealth-related spending and these competing demands also need to be balanced. The term 'patient-centered care' has been coined to describe an approach to management that considers the patient as a whole rather than as the sum of different conditions in addition to patient preferences [17]. Part of this approach also recognizes that goals of management must align with patient preferences rather than solely on standard outcomes, such as risk factor control. Advances in this area will require the ability to measure patient-valued outcomes and to make management decisions based on these outcomes [18].

■ Heterogeneity of the diabetes phenotype

Even after considering the difficulty in applying population evidence to individuals with different risk profiles and modifying care based on individual preferences, a third important driver of personalization is the fact that Type 2 diabetes has a heterogeneous clinical course. Evidence from observational longitudinal studies reveals that patients presenting with Type 2 diabetes at earlier ages may have more rapid disease progression compared with patients presenting with a new diagnosis later in life [19–21], in addition to having more time to accumulate complications. These differences in the rate of disease progression and corresponding risk of long-term complications clearly require different approaches to aggressiveness of treatment and risk reduction. However, despite this recognized heterogeneity, most patients are generally treated similarly because we are unable to classify underlying differences that might affect therapeutic response. Moreover, recent trials aiming for very intensive glycemic control in patients with long-standing Type 2 diabetes have led to a critical reappraisal of the established metabolic goals of care [22,23] and concern that different treatment approaches may yield different outcomes with similar metabolic goals [24,25].

Diabetes clinical heterogeneity reflects the varied influences of both environmental factors (e.g., different diet and lifestyle behaviors) and genetic influences (with a heritable contribution estimated to represent 40%). In a few rare cases, such as neonatal diabetes due to Kir6.2 mutations, identifying the genetic causes of diabetes can dictate optimal treatment [26]. However, for the vast majority of patients, the underlying genetic architecture is complex and poorly understood, with multiple variants found that each contribute relatively little increased risk [2]. Given the complexity of physiologic pathways and the corresponding complexity of underlying genetic variation that determines different phenotypes (i.e., in insulin secretion, insulin resistance and lipid processing) there is a strong basis for considering Type 2 diabetes as an umbrella term for a myriad of subtly different pathophysiologic problems with similar final metabolic pathways. This framework is the primary rationale for genetic dissection and the hope for personalized therapy [27].

Approaches to individualizing care

Physicians already personalize care for their patients, either explicitly through shared decision-making, or implicitly through the unspoken triage decisions of what problems to focus on at a given visit [28]. Similarly, patients may choose on their own to modify management (i.e., patients may not adhere to medicines that they cannot afford or may choose not to adopt recommended lifestyle changes). While current guidelines recommend tailoring therapy through explicit discussions of risks and benefits, there is currently a paucity of evidence for how to effectively implement truly personalized care.

What is needed to enable more tailored therapy?

Here we describe a conceptual framework for how care might be personalized in the future

and suggest domains where further research is needed before we can fully achieve the goal of personalized medicine.

To personalize care, management decisions for each individual need to effectively address a series of questions:

- Does currently available evidence apply to this individual?
- If evidence appears to apply, is the recommended therapy concordant with other conditions?
- If evidence does not apply, how does treatment need to be modified?
- Do the predicted benefits of the treatment plan include an assessment of patient-valued outcomes (such as quality of life) and does the treatment benefit outweigh costs and risks?
- How do the patient's phenotype and genotype change treatment approaches? (i.e., Is there persuasive evidence for variation related to specific phenotypic or genotypic features that support different management approaches?)

The transition from guideline-based to personalized management will require advances in the following three areas.

■ Complex comorbidity modeling for more accurate individualization

Current diabetes risk engines can predict cardiovascular risk based on core diabetes-related factors, such as glycemia, blood pressure, dyslipidemia, smoking status, age, gender and family history. More complex tools may include renal function and other factors. Missing from the current approach is the potential impact of nondiabetes-specific factors. A wide range of conditions, such as depression, arthritis, hepatitis C infection, alcohol dependence – to name a few – could all interact with predicted diabetes progression and complication risk. With the increasing prevalence of sophisticated electronic medical record systems within large healthcare systems, the data necessary for complex modeling is increasingly available. Thus, further work on the epidemiology of complex comorbidities and specifically how disparate conditions interact with each other to change outcomes, is now possible. Results from future studies in this area may help clinicians to identify a wider range of complex patient profiles and develop treatment plans appropriate for each profile type.

Another diabetes-focused approach that would, nonetheless, provide more guidance than is currently available would be to develop a diabetes staging system using commonly available clinical variables. At present, HbA1c is often used both as a marker of disease severity (indicating individuals who are relatively insulin deficient, often with a longer duration of diabetes) and response to treatment. It would be helpful to develop and validate a staging system in a longitudinal cohort that could classify the baseline risk of individuals with diabetes so that evidence-based guidelines could be applied more cost effectively.

■ Shared decision-making for more collaborative care

Patient-centered care is a concept that has yet to find quantitative expression. While the premise that diabetes management that is concordant with patient preferences makes sense, there is a paucity of direct research to support this approach. Decision aids have generally proven to be helpful tools to promote informed decision-making, but are better suited for making single, discrete decisions [29]. The American Diabetes Association's conversation maps are another such tool that, while conceptually promising, may be less effective than individual education [30].

The ability to effectively elicit individual patient preferences and to clearly identify individual goals, abilities and concerns requires a high level of patient–provider communication. Few healthcare providers have undergone formal training in the skills and strategies required to engage patients in shared decision-making. Patients from different cultures and those with lower health literacy and numeracy present additional challenges to clear communication and the exchange of ideas between provider and patient required for shared decision-making [31]. Indeed, teaching physicians to practice using a collaborative approach may require as much work as understanding the genetics of diabetes.

Current approaches to diabetes self-management education have had proven success [32–34]. However, it is likely that the current education paradigm will need to be adapted to further incorporate patient-centered preferences. Even if such an approach results in greater treatment adherence and increased quality of life, the science of measuring preferences for a chronic progressive disease like diabetes remains in its early stages. Future advances are needed to develop tools to better capture patient preferences.

Similarly, tools are needed to help clinicians translate these preferences into management decisions that optimize health whilst also addressing patient-defined goals.

■ Potential role for genetic testing for genome-specific care

Personalized medicine seeks to harness the tools of genomics, proteomics and systems biology. Despite some early disappointments, rapid advances in diabetes genetic epidemiology hold promise for the identification of the spectrum of Type 2 diabetes subtypes. While not yet ready for clinical application, this approach may, in the future, help to identify patients who may respond better to specific drug classes, whose disease may progress more quickly or those who may be at increased risk for specific complications. Knowing that a patient has a genetic predisposition to retinopathy may suggest tighter glycemic control, whereas increased risk for renal disease could prompt early and aggressive angiotensin-converting enzyme-inhibitor therapy.

Conclusion & future perspective

We are currently in a state of transition in the clinical approach to diabetes management. The evidence-based revolution has been won and clinicians are now well versed in the clinical guidelines on how to effectively manage their patients with diabetes, although consistent application of these guidelines remains challenging in various populations and over time. We are now at the beginning of a second revolution in how we think about diabetes care, one that is explicitly patient centered and strives to personalize care. The factors driving this paradigm shift include the recognition that population-level study results do not generalize to all patients; demographic shifts in which an older patient population has increasing numbers of concurrent, nondiabetes-specific conditions that may interact with diabetes management plans; the increasing adoption of 'patient-centered' perspectives rather than disease-centered perspectives when defining high-quality care, advances in our understanding of the pathophysiology of disease and drug targets and the rapid and promising advances in our understanding of genomics and other fields, such as epigenetics and proteomics.

The ideal of personalized care is that each patient receives the management plan best suited to him or her. This means implementing a treatment strategy that is concordant with the patient's preferences, specific risks and unique underlying disease pathophysiology and drug metabolism profile. Although the benefit remains to be proven, such an approach holds the potential to substantially improve the care of patients with Type 2 diabetes.

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