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REVIEW

# Precision medicine in diabetes: an opportunity for clinical translation

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Metabolic disorders present a public health challenge of staggering proportions. In diabetes, there is an urgent need to better understand disease heterogeneity, clinical trajectories, and related comorbidities. A pressing and timely question is whether we are ready for precision medicine in diabetes. Some biological insights that have emerged during the last decade have already been used to direct clinical decision making, especially in monogenic forms of diabetes. However, much work is necessary to integrate high-dimensional explorations into complex disease architectures, less penetrant biological alterations, and broader phenotypes, such as type 2 diabetes. In addition, for precision medicine to take hold in diabetes, reproducibility, interpretability, and actionability remain key guiding objectives. In this review, we examine how mounting data sets generated during the last decade to understand biological variability are now inspiring new venues to clarify diabetes nosology and ultimately translate findings into more effective prevention and treatment strategies.

**Keywords:** precision medicine; diabetes; diabetes heterogeneity; omics

## Precision medicine

The concept of *precision medicine* has evolved from an initial focus on individualized preventive strategies and patient care (personalized medicine) to a wider and more realistic notion that intends to convey the principle that, although therapeutics are rarely developed for single individuals, subgroups of individuals with unique features may be increasingly defined and treated in more efficient ways. This is now possible owing to the comprehensive capture of multiple data points across orthogonal axes of information, the development of analytical methods that permit the interpretation of complex data and enable the construction of more refined categories, and concomitant advances in targeted therapeutics.

Precision medicine is not a new construct—but our ability to implement it in a sophisticated and rational manner has finally come of age. Indeed, the science of medicine has been historically focused around notions of subgroups and categorization. In

ancient Greek civilization, health (“a gift from the gods”) and illness (“divine punishment”) were presumed to be affected by a few categories, such as gender, geographic localization, social class, humors, diet, trauma, beliefs, and mindset.<sup>1</sup> From that initial understanding, the concept of health and disease has progressed, and the number of categories (now considered disease risk factors) has increased exponentially. This is due to the widespread adoption of the scientific method, by which clinical investigators observe, predict, test, and generalize.<sup>2,3</sup> Evidence-based medicine is the application of the scientific method in biomedicine and has become the gold standard to advance knowledge and make decisions about patient care. The continuous updating of the scientific method to maximize preventive strategies and patient care has launched thriving research initiatives to explore the ways in which several axes of biological information and environmental characteristics drive disease pathogenesis and influence responses to therapy.<sup>3</sup> However, as the scientific

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method is systematically deployed across all areas of medicine, it has become apparent that large disease heterogeneity and response variability exist. Thus, the generalizability of diagnostic groups and the extrapolation of average responses from clinical trials, predicated on the assumption that medical interventions should work ubiquitously in individuals sharing a limited set of similar characteristics, can often be misleading.<sup>4,5</sup>

The mounting troves of data generated during the last decade to understand biological variability are now inspiring new venues for complex disease prevention, treatment, and cure through a deeper understanding and characterization of underlying molecular processes.<sup>6,7</sup> One early step toward the historical change in the global reach of biological inquiry started just a few decades ago with the Human Genome Project, whose major contribution was to hand the world a complete resource of detailed information about the structure, organization, and function of the full set of human genes.<sup>8</sup> Since then, technological and analytical advances have enabled the design of genome-wide association studies (GWASs), which have generated the discovery of hundreds of associated loci across the human genome for many complex diseases of large public health impact.<sup>9–11</sup> Led by genomics, other high-throughput technologies have emerged recently, providing comprehensive information about the epigenome, transcriptome, proteome, metabolome, and microbiome. This information is allowing investigators to explore complementary biological axes in greater breadth and depth.<sup>12–17</sup> Although each layer of information provides relevant insights into disease nosology, the interplay between diverse biological layers, even within the same tissue or metabolic condition, hinders the translation of the newly generated knowledge, given that it cannot be assessed by a simplified reduction approach.<sup>18</sup> In addition, tissue-specific regulation and cross talk between tissues orchestrating the same molecular process in response to different environmental or physiological triggers presents an extra level of difficulty in unraveling the biological basis of complex diseases like diabetes.

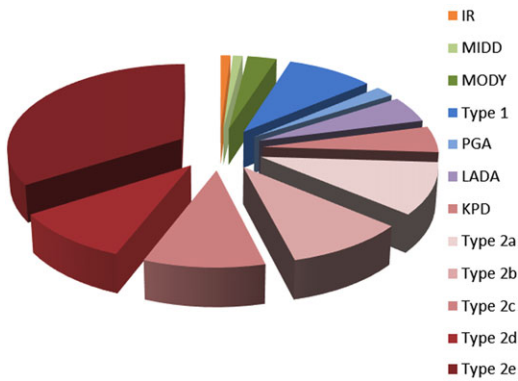
Some areas of biomedicine are more amenable to the integration of these features. In cancer, each tumor can be seen as a unique and localized set of genetic and epigenetic changes resulting in a definite molecular signature. Successful examples of

personalized medicine in cancer often rest on the direct detection of penetrant somatic mutations in the diseased tissue. For example, somatic mutations in dominant melanoma oncogenes, such as *BRAF*, have been shown to be relevant in some nonmelanoma cancers, making *BRAF* a generally targetable oncogene and practically redefining cancer types by their primary molecular pathogenic defects rather than their tissue of origin.<sup>19</sup> A potential source of heterogeneity in cancer cell response may be attributable to the specific tumor microenvironment, in part captured through chromatin regulation and catalyzing the emergence of chromatin regulation as a new druggable objective for resistant cancers.<sup>20</sup> Other approaches for resistant cancers include personalized vaccines that take advantage of differences in DNA sequence between tumor and healthy cells to re-engineer more efficient T cells.<sup>21</sup> For example, two recent phase I clinical trials showed that a personalized T cell–based vaccine to treat people with skin cancer successfully enhanced the immune response, and no signs of tumor recurrence were reported in the majority of participants after a follow-up period of up to 32 months after vaccination.<sup>22,23</sup>

Whether knowledge generated in cancer is ready to be implemented in other metabolic complex diseases, such as diabetes, is less clear. The genetic architectures of diabetes and cancer are quite different: both type 1 and type 2 diabetes (T1D and T2D, respectively) are caused by the combination of genetic predisposition and environmental triggers, with most germline variants (with the exception of the HLA region in T1D) conferring only modest effects on risk; whereas in cancer a specific high-penetrance somatic mutation in a given gene in a particular cell type is likely to start cancer initiation, in some cases also triggered by an external insult and modified by additional gene variants.<sup>11,24</sup>

### Diabetes is a heterogeneous disease

Diabetes, albeit with the common denominators of relative insulin deficiency and consequent elevated blood glucose, is a much more heterogeneous disease than the present classification into T1D and T2D suggests.<sup>25,26</sup> T1D, with a typical onset at an early age, develops as a result of autoimmune destruction of the insulin-producing  $\beta$  cells, whereas T2D is due to a combination of insulin resistance superimposed on an insulin-secretory



**Figure 1.** Heterogeneity of diabetes. The pie chart represents the multiple ways people can develop hyperglycemia and reach the diagnosis of diabetes. The size of each piece only represents an approximate proportion of prevalence in the population. IR, rare genetic forms of insulin resistance; MIDD, maternally inherited diabetes and deafness; MODY, maturity-onset diabetes of the young; type 1, type 1 diabetes; PGA, diabetes caused in the setting of polyglandular autoimmune syndrome; LADA, latent autoimmune diabetes of adults; KPD, ketosis-prone diabetes; type 2a–2e, hypothetical subgroups of type 2 diabetes.

defect. However, the spectrum of diabetes has broadened in the past few decades with the realization that several different overlapping mechanisms can lead to diabetes, suggesting that individuals might have features of different biological alterations (Fig. 1). For example, latent autoimmune diabetes of adults (LADA; also known as autoimmune diabetes in adults, type 1 and  $\frac{1}{2}$  diabetes, and slow-onset diabetes in adults) might constitute a category of diabetes on its own, since patients share features of both T1D (autoimmunity, eventual insulin dependence) and T2D (onset at later ages, insidious presentation).<sup>27,28</sup> Recent work suggests that the genetic architecture of LADA is closer to T1D than to T2D.<sup>29</sup> Ketosis-prone diabetes (KPD) in adults is another hybrid form of diabetes with features of both T1D and T2D, but without the autoimmune characteristics of LADA.<sup>30</sup> These individuals, often of Asian or Afro-Caribbean ancestry, are characterized by relative insulin deficiency and are prone to developing diabetic ketoacidosis.<sup>31</sup>

Despite these hybrid forms of diabetes, T2D is the major cause of diabetes worldwide and accounts for nearly 90–95% of diabetes cases. T2D by itself is also a heterogeneous disease, as patients can range from those with a predominantly insulin-resistance phenotype but with sufficient  $\beta$  cell

reserve to remain insulin independent to those who may require insulin treatment early in the course of their disease.<sup>26</sup> The need for escalation of therapy with additional agents differs across individuals, as does the likelihood of progression to specific macrovascular or microvascular complications. In addition, the influence of obesity on T2D risk varies greatly across populations, with individuals of East Asian descent developing T2D at much lower indices of adiposity.<sup>32,33</sup> As more diverse populations are examined, it is becoming apparent that differences in allele frequencies across populations may explain disparities in prevalence.<sup>34–36</sup>

### Subclassification of type 2 diabetes

Given the heterogeneity in diabetes phenotype, several attempts to define molecular subgroups of particular forms of diabetes through clinical features have been implemented (Fig. 1). For example, up to four different phenotypes have been described in KPD, depending on the presence or absence of islet cell autoantibodies ( $A^-$  or  $A^+$ ) and  $\beta$  cell functional reserve ( $\beta^-$  or  $\beta^+$ ).<sup>37</sup> This classification, based on both immunologic and  $\beta$  cell function criteria, has the highest accuracy and predictive value in classifying patients with KPD with regard to clinical outcomes and pathophysiologic subtypes.<sup>38</sup> In addition, a long-term longitudinal follow-up study including KPD  $A^- \beta^+$  patients has revealed that this phenotype comprises two distinct subtypes distinguished by whether T1D-associated HLA susceptibility is present or not.<sup>39</sup> In gestational diabetes (GDM), about half of women with GDM had predominant insulin-sensitivity defects with hyperinsulinemia, a phenotype that was linked with altered adipokine profiles, larger infants, and greater risk of GDM-related complications; these were not observed among women with GDM due to predominant insulin-secretion defects, suggesting uneven characteristics within GDM.<sup>40</sup> Finally, a recent data-driven cluster analysis of six simple clinical variables (age, body mass index (BMI), GAD antibody status, hemoglobin A1c, and homeostasis model assessments of  $\beta$  cell function and insulin resistance) measured at baseline in patients with newly diagnosed diabetes identified five replicable clusters of patients with different clinical presentations. The five diabetes subtypes (severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes,

and mild age-related diabetes) also showed varying degrees of risk of diabetic complications. For example, individuals with severe insulin-resistant diabetes had significantly higher risk of diabetic kidney disease, while those with severe insulin-deficient diabetes had the highest risk of retinopathy.<sup>41</sup>

The revolution of omics profiling technologies can help identify subgroups of individuals with diabetes sharing unique biological features. Among all available approaches for more detailed personalized profiling, assaying genetic variation has taken the lead and made rapid progress. This is the case for a number of reasons, including (1) the ability to query millions of variants across the human genome in a single experiment;<sup>42,43</sup> (2) the development of accurate analytical methods and stringent statistical standards to interpret results with appropriate statistical rigor;<sup>42</sup> (3) the unique feature that germline genetic variation is fixed in the individual and thus needs to be measured only once in the person's lifetime;<sup>44</sup> and (4) the potential to derive causal inference, since genetic variation is free from conventional confounding owing to the unidirectional arrow of time (the variant always precedes the phenotype and is unaffected by the disease process or its treatment) and the random independent assortment of alleles at meiosis.<sup>45</sup>

To date, well over 100 genetic loci have been identified in successive waves of GWAS meta-analyses as robustly associated with T2D and/or related traits.<sup>46–52</sup> Comprehensive sequencing studies that capture both common and rare variation suggest that most genetic variation influencing T2D appears to reside at common variant sites.<sup>11</sup> Although genetic risk variants at these loci have modest effects on disease predisposition (collectively accounting for 10–15% of overall disease risk),<sup>11,50</sup> the knowledge gained has paved the way to elucidate the molecular taxonomy of the disease and the potential identification of novel therapeutic approaches.<sup>42,53</sup> To highlight disease heterogeneity, ethnic-specific alleles are emerging, thanks to genotyping and sequencing experiments in diverse populations. For example, a nonsense polymorphism in the *TBC1D4* locus (with a minor allele frequency (MAF) of 17% in Inuit populations, but almost nonexistent in other groups), raises 2-h glucose and increases T2D risk 10-fold.<sup>54</sup> As *TBC1D4* is implicated in transducing the insulin signal in skeletal muscle, it is believed that these individuals suf-

fer from a type of T2D mostly defined by muscle insulin resistance and might benefit preferentially from treatment with an insulin sensitizer, a hypothesis that can be tested in a pharmacogenetic clinical trial.<sup>55</sup> Similarly, a risk haplotype in the *SLC16A11* locus is common (MAF < 40–50%) among people of Mexican or Latin American descent but rare among Europeans and absent in Africa; together with other such variants, it might explain some portion of the increased T2D prevalence in Mexico.<sup>34</sup> A recent functional study demonstrated that lower levels of monocarboxylate transporter 11 (the protein encoded by *SLC16A11*) in the plasma membrane of primary human hepatocytes are associated with T2D-relevant changes in fatty acid and lipid metabolism.<sup>56</sup> Though the mechanism of action is incompletely understood, therapies targeting this monocarboxylate transporter and enhancing its function in hepatocytes may be particularly effective in people whose risk of developing T2D is driven by this disrupted mechanism.<sup>57</sup> In another example, a missense polymorphism in *HNFI1A* (MAF of 2% in Mexicans with T2D) increases the risk of T2D fivefold.<sup>36</sup> Because carriers of loss-of-function mutations in this gene experience a more favorable response to sulfonylureas, it is possible that these patients might be better treated with those agents as well, at least early in their disease course. Finally, whole-exome sequencing data have uncovered a single coding variant in *PAX4* that was strongly associated with T2D, but only in people from East Asian countries, including Korea, China, and Singapore.<sup>11</sup>

Another approach to better define particular subtypes of T2D is to use T2D-associated genetic variants as biomarkers in unsupervised classification methods or aggregate them into biologically relevant polygenic risk scores (GRS). Using unsupervised clustering analysis of 37 established T2D susceptibility loci, it was shown that T2D risk loci may fall into different groups related to (1) insulin sensitivity, (2) insulin secretion, (3) insulin processing, and (4) insulin processing and secretion without a detectable change in fasting glucose levels.<sup>58</sup> Hierarchical clustering analysis using 19 common genetic variants associated with fasting insulin-based measures identified 11 variants associated with a metabolic profile consistent with a mild form of lipodystrophy.<sup>59</sup> A GRS composed of these 11 prioritized risk alleles was paradoxically associated with lower BMI but increased visceral-

to-subcutaneous adipose tissue ratio and caused metabolic alterations, such as higher triglycerides and elevated transaminases or hepatic steatosis and lower HDL or adiponectin. In a follow-up reciprocal analysis, a GRS of 11 favorable adiposity variants was associated with lower T2D relative risk and higher body fat percentage, with greater subcutaneous storage capacity.<sup>60</sup> Once variants are aggregated into physiologically meaningful clusters, the next step is to verify whether GRS based on such a classification can also group individuals in clinically meaningful categories, particularly at the extreme ends of the distribution.

As the number of T2D-associated variants continues to mount, the construction of GRS allows for a continuous and quantitative measure of T2D genetic susceptibility that can help to identify relevant subgroups. For example, with rising population obesity, distinguishing T1D and T2D in patients with new-onset diabetes has proven difficult, particularly in clinical scenarios, because more young people are developing T2D, and many individuals with T1D will be obese.<sup>61</sup> Accordingly, up to 15% of young adults with diabetes are estimated to be wrongly classified and consequently incorrectly treated, which may have consequences in poor glycemic control, inappropriate insulin regimens, and the risk of life-threatening ketoacidosis.<sup>62</sup> A study assessing a T1D GRS based on 30 T1D-associated risk variants provided evidence that the GRS is highly discriminative and indicative of T1D, especially in young adults, where the T1D GRS alone predicted progression to insulin deficiency.<sup>63</sup> In a separate study, a similar T1D GRS improved the discrimination of monogenic diabetes from T1D,<sup>64</sup> confirming the relevance of genetics to correctly classify individuals based on divergent pathophysiological processes.

Finally, more comprehensive methods based on high-dimensional data from electronic medical records combined with genetic information have been implemented to attempt to characterize the heterogenic complexity of T2D and its complications.<sup>65–67</sup> A recent study suggested that a topological analysis of many clinical features gives rise to three distinct subgroups of T2D:<sup>67</sup> subtype 1 was characterized by T2D microvascular complications, including diabetic nephropathy and diabetic retinopathy; subtype 2 was enriched for cancer malignancy and cardiovascular diseases;

and subtype 3 was associated most strongly with cardiovascular diseases, neurological diseases, allergies, and HIV infections. Distinct sets of genetic variants could be mapped to these subtypes. However, it is difficult to replicate these types of high-dimensional explorations, as their biological relevance is not obvious, and no clear clinical decision-making implications have emerged. For precision medicine to take hold in diabetes, reproducibility, interpretability, and actionability remain key guiding objectives.

Another angle to characterize diabetes into distinct categories and provide biological insights into early metabolic alterations is via particular metabolomic profiling.<sup>68,69</sup> During the last decade, metabolomics has emerged as an integrative tool for biological states through the global measurement of chemical endophenotypes that lie downstream of genomic, transcriptomic, and proteomic variability.<sup>70</sup> One key advantage of metabolomics is that the measured entity is closer to the organismal phenotype than genetic variation and integrates a number of biological processes; thus, the effect size on the trait of interest is typically larger. Disadvantages include the complex and incompletely characterized nature of the metabolome, the unknown nature of many measured metabolites, the diversity of technologies and data-analysis techniques used, and the correlational nature of most analyses where causal inference is challenging. As a result, generalizability and replication has been difficult, though standardized methods for metabolite identification and reporting are beginning to emerge.<sup>71</sup>

Despite intrinsic limitations, particular attention has focused on metabolomics of insulin resistance and T2D. Several large prospective analyses using either targeted or untargeted metabolomics approaches have validated the association between branched-chain amino acids (BCAAs) and aromatic amino acids with insulin resistance and T2D.<sup>72,73</sup> Beyond BCAA, downstream BCAA metabolic products, such as branched-chain ketoacids and acylcarnitines, were significantly elevated in both individuals with impaired fasting glucose and subjects with T2D compared with control subjects.<sup>74</sup> Other products of amino acids catabolism, such as 2-aminoadipic acid or  $\alpha$ -hydroxybutyrate, have been found to be strongly correlated with incident T2D.<sup>75,76</sup> These findings are consistent with a model in which excess of BCAAs contributes to

impaired efficiency of fatty acid oxidation, resulting in the accumulation of incompletely oxidized lipid species, perhaps of particular relevance in insulin resistance.<sup>70</sup> Whether these metabolite alterations are common to all patients with T2D or serve to identify specific subgroups requires further exploration.

Recently, GWASs have been integrated with high-throughput metabolomic profiling to provide biological insights into how genetic variation influences metabolism and how such metabolic differences in plasma can help to identify relevant genes within genomic regions associated with complex diseases.<sup>77</sup> In addition, the integration of genomics with metabolomics can help place specific metabolites on causal pathways. For instance, a study that pooled data from four European cohorts found that *CYP7A1*, which encodes the rate-limiting enzyme in bile acid synthesis, was associated with lower concentrations of deoxycholic acid and higher T2D risk.<sup>78</sup> In addition, this study also identified variants in or near the genes encoding sphingosine-1-phosphate phosphatase 1 (*SGPP1*), glucokinase regulator (*GCKR*), and fatty acid desaturase 1 and 2 (*FADS1/2*) that were associated with diabetes-associated phospholipids and T2D risk. Finally, using Mendelian randomization in combination with plasma metabolomics suggested a causal role for lower levels of palmitoleic acid and oleic acid on insulin resistance.<sup>79</sup> Two recent Mendelian randomization studies (see Ref. 45 for methodological details) have implicated BCAAs in the pathogenesis of T2D and suggested that genetically raised insulin resistance drives higher circulating fasting BCAA levels.<sup>80,81</sup> In a recent analysis of 1622 nondiabetic participants from the Framingham Heart Study, the combination of genetics, metabolomics, and clinical factors increased the prediction of future T2D.<sup>82</sup> In brief, a 62-variant GRS showed an area under the curve (AUC) of 64%; addition of metabolites increased the AUC to 82%, and the combination of genetics, metabolomics and clinical factors achieved an AUC of 88%. The results from this study suggest that metabolite and genetic traits also provide complementary information to each other for the prediction of future T2D. This emerging information may help classify individuals at high risk for different forms of T2D and potentially translate findings into more personalized prevention or treatment strategies.

The observation that the great majority of GWAS variants identified for T2D do not affect protein-coding sequence suggests that gene regulation has a central role in the development of the disease.<sup>83</sup> New analytical methods exploiting available data sets that describe gene expression patterns and epigenetic marks obtained from cells and tissues at different stages of development and disease states have become an extremely useful resource.<sup>84</sup> In diabetes, one of the most salient findings is the discovery that T1D GWAS signals localize to enhancer sequences active in the thymus, T and B cells, and CD34<sup>+</sup> stem cells, confirming the regulatory disruption of the immune component in the etiology of T1D.<sup>85</sup> A landmark study using integrative analysis was conducted for the fat-mass obesity (*FTO*) locus, the strongest genome-wide association signal for obesity.<sup>86,87</sup> In brief, using a variety of data sets, the authors predicted the cell type (preadipocyte) and regulatory element (enhancer) disrupted by the causal variant and linked the predicted enhancer (*ARID5B* motif) to two target genes (*IRX3* and *IRX5*) involved in early adipocyte differentiation. Finally, the investigators were able to restore the correct expression of the affected target genes in cells isolated from patients and a mouse model using CRISPR–Cas9 genome editing and to demonstrate major allele-dependent effects on thermogenesis in adipocytes.<sup>87</sup> Though additional mechanisms could be at play, these integration efforts illustrate how resource building can result in major biological insights into the functional consequences of genetic alterations, uncovering novel pathways that could be harnessed for therapeutic development. In addition, improved mechanistic understanding is a first step in determining whether such processes are uniformly operational across the entire phenotypic spectrum of diabetes or could serve to describe specific subtypes.

Convincing evidence suggests that the dysbiotic state conferred by gut microbiota composition is associated with metabolic diseases.<sup>88</sup> Previous profiles of the gut microbiome in T2D have found compositional changes between patients and healthy controls, showing increased capacity for oxidative stress resistance and a decreased capacity for flagellar assembly and riboflavin metabolism.<sup>89,90</sup> However, the human microbiome contains vast numbers of uncharacterized enzymes, limiting our functional understanding of this community and its effects

on host health and disease. A possible mechanism linking the gut microbiome and insulin resistance may be due to specific microbiota species (*Prevotella copri* and *Bacteroides vulgatus*), which have been reported to drive the association between biosynthesis of BCAAs and insulin resistance in ~200 individuals with insulin resistance.<sup>91</sup> However, given the large number of microbiota species and interconnected metabolic pathways between species, efforts to distinguish which bacterial species increases diabetes risk in a causal manner or to define diabetes subgroups according to metagenome characterization are still largely unrealized.

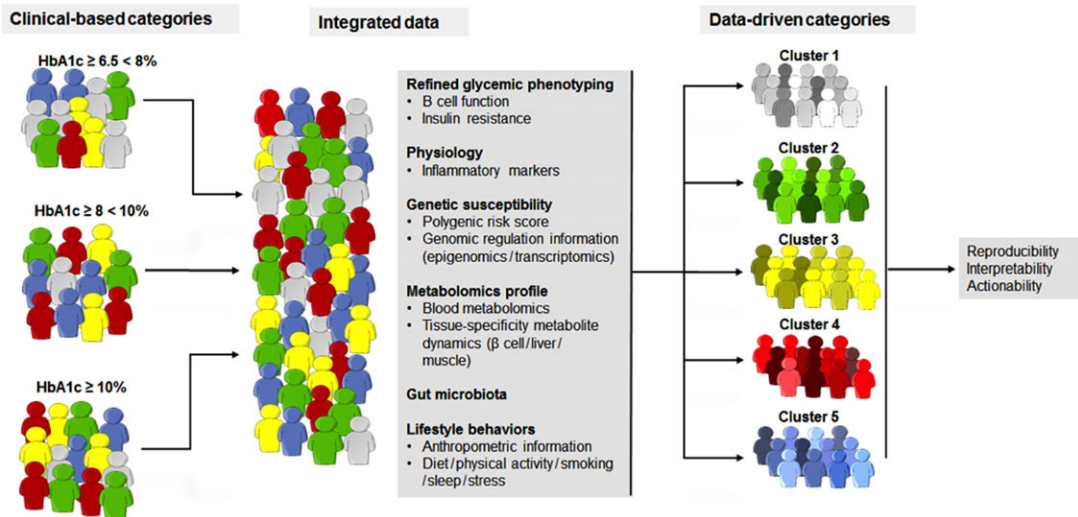
### Does omic information make a difference for treatment?

The clinical management of diabetes is currently based on reducing plasma glucose to levels that are associated with a low risk of developing long-term complications.<sup>92</sup> However, significant variability exists in response to these interventions, indicating that treatment heterogeneity may reflect underlying biological differences. For example, genetic factors can influence the glycemic response to metformin, explaining from 21% to 34% of its variance depending on how response is defined.<sup>93</sup> A better understanding of the underlying causes for differential pharmacological response of subgroups of diabetic individuals may catalyze the delivery of the most accurate intervention strategy to a given individual based on his or her unique characteristics.

For monogenic diabetes, the implementation of precision medicine can be considered an early success, given that there are discrete subgroups that are easily defined by molecular genetics. For example, neonatal diabetes is defined by an extreme phenotype (onset of hyperglycemia within the first 6 months of life), often caused by penetrant mutations in a well-understood locus (*ABCC8*, which encodes the sulfonylurea receptor SUR1 and the adjacent gene *KCNJ11* encoding its associated ATP-dependent potassium channel).<sup>94</sup> This biological understanding has led directly to genetically driven individualized therapy (high-dose sulfonylureas).<sup>95</sup> Other monogenic diabetes forms, such as maturity-onset diabetes of the young (MODY), also provide proof of concept that genetic information can guide therapy. The most common causes of MODY include mutations in the genes encoding the hepa-

toocyte nuclear factor 1 $\alpha$  (*HNF1A*) and the enzyme glucokinase (*GCK*) and *HNF4A*.<sup>96,97</sup> Individuals with loss-of-function *HNF1A* mutations, which cause MODY 3, are extremely sensitive to the hypoglycemic effects of sulfonylureas. This knowledge has key translational implications when the diagnosis of MODY 3 is genetically confirmed: in patients who were mistakenly diagnosed as having T1D (on the basis of the early onset of disease and lean body habitus), the clinician can discontinue insulin therapy and initiate treatment with sulfonylureas, whereas in those who were mistakenly diagnosed as having T2D (on the basis of absence of autoimmunity and a nonketotic presentation), the clinician can substitute metformin for low-dose sulfonylureas.<sup>98</sup> Individuals with a heterozygous, inactivating mutation in *GCK* (MODY 2) have a defect in glucose sensing; hence, glucose homeostasis is maintained at a higher set point, resulting in mild, asymptomatic fasting hyperglycemia (5.5–8.0 mmol/L) that shows little deterioration with age, does not require escalation of therapy, and is not associated with cardiovascular complications.<sup>99</sup> The general consensus is that treatment is not recommended outside of pregnancy.<sup>100</sup> Insulin treatment might be required during pregnancy to prevent excess fetal growth only if the fetus has not inherited the *GCK* mutation.<sup>101</sup> Similar to individuals with MODY 3, carriers of mutations in *HNF4A* (MODY 1) display progressive  $\beta$  cell dysfunction; hence, low-dose sulfonylureas is the preferred tailored intervention.<sup>102</sup> However, a subgroup of phenotypically different patients with MODY 1 due to a common mutation in *HNF4A* (p.R114W) was recently described.<sup>103</sup> These individuals showed reduced sensitivity to low-dose sulfonylurea treatment, reduced penetrance, and no effect on birth weight and therefore may need high-dose sulfonylurea treatment.

T2D is considerably different from monogenic diabetes. The genetic architecture of T2D is mostly composed of small-effect common variants that hinder the use of any of these variants as a handle to reverse the disease. However, the precise combination of risk and protective variants carried by any given individual is likely to be unique, offering potential translational opportunities.<sup>104</sup> Accordingly, research efforts are now moving to determine where the boundaries of risk lie and how to eventually predict whether a patient is likely to develop



**Figure 2.** Implementing precision medicine in diabetes. A hypothetical example illustrating how precision medicine might deconstruct traditional clinical-based categories through the study and integration of the many axes of biological information that can serve to parse current heterogeneous syndromes into homogeneous clusters. The example suggests that the way to prevent new cases of diabetes or treat individuals with diabetes should be tailored to the specific molecular event or pathway that raises glycemia.

T2D in his/her lifetime or respond differently to conventional treatments.<sup>105</sup> As a critical factor in T2D pathogenesis seems to be early  $\beta$  cell dysfunction, tailored interventions might be administered to individuals with specific  $\beta$  cell risk factors early in the disease course, when insulin secretion has not yet markedly deteriorated. Future T2D pharmacotherapy may focus on preserving normal glucose homeostasis by  $\beta$  cell–based interventions from different angles, including  $\beta$  cell genetic reprogramming, differentiation, or enhancement of activity.

Metformin is currently recommended as a first-line drug for the treatment of T2D: it is effective at reducing hyperglycemia primarily by inhibiting hepatic glucose production and secondarily by modestly increasing insulin sensitivity.<sup>106</sup> Whether metformin has different effects on  $\beta$  cell function preservation is a matter of debate. For example, the ADOPT study showed that the durability of metformin monotherapy was better than that of sulfonylureas, but it still resulted in a 21% failure rate at 5 years in participants with recently diagnosed T2D.<sup>107</sup>

Genetic studies for metformin response may help to prioritize which individuals are more likely to respond better to metformin and achieve greater  $\beta$  cell preservation. Initial candidate gene approaches focused on *SLC22A1* (encoding the organic cation

transporter 1) or *SLC47A1* (encoding the multidrug and toxin extrusion 1) have failed to produce a definite picture of the genetic determinants of metformin response.<sup>108</sup>

GWASs have identified two metformin response loci (*ATM* and *SLC2A2*). The *ATM* (ataxia telangiectasia mutated) locus, located in a large linkage disequilibrium block on chromosome 11 that includes a total of seven potential candidate genes, has been associated with glycemic response to metformin.<sup>109</sup> A functional study to comprehensively identify genes and regulatory elements associated with metformin treatment has showed that variants in linkage disequilibrium with the *ATM* GWAS lead SNP (rs11212617) had increased enhancer activity. Expression quantitative trait locus analysis and CRISPR–Cas9 activation suggest that this enhancer haplotype could be regulating *ATM* in the liver and activating transcription factor 3, leading to gluconeogenesis repression.<sup>110</sup> A noncoding variant in *SLC2A2* (encoding the facilitated glucose transporter GLUT2) represents another identified genome-wide signal for metformin response, and it was associated with reduction in hemoglobin A1c in 10,577 participants of European ancestry.<sup>111</sup> This regulatory variant influences GLUT2 expression in the human liver, identifying hepatic GLUT2 as an effector of metformin action. However, the



increased response to metformin in carriers of this variant did not prevent diabetes in participants from the Diabetes Prevention Program,<sup>112</sup> indicating that perhaps genetic influences on drug response are also dependent on the metabolic state of the individual, with differential interactions occurring at diverse stages of disease progression.

In terms of sulfonylurea response, a limited number of polymorphisms in sulfonylurea drug target genes and T2D risk genes has been studied, and most of the results have been limited to small, observational studies. Prior research has found that individuals carrying homozygous loss-of-function mutations in *CYP2C9* (encoding the cytochrome P450 2C9 enzyme responsible for liver sulfonylurea metabolism) improved glycemic control after sulfonylurea therapy.<sup>113</sup> It should be noted that, in all of these pharmacogenetic studies, while the effects seen thus far are interesting mechanistically, their magnitude is too small to underwrite individualization of therapy.

### Conclusions: a working model

Clinical decision making is, by necessity, dichotomous: on the basis of complex and often continuous information, the practitioner needs to decide whether to act or not to act, to intervene or to merely observe. One course must be taken among several possible options, and the key question is whether modern omics technologies will be able to capture enough biological variation to enable the construction of sensible discrete categories to facilitate rational decision analysis, or this will remain the province of “boutique” rare forms of diabetes.

The answer to that question will depend, to a great extent, on the underlying biology. In T2D, the emerging picture is one in which a large constellation of genetic factors (from many hundreds to a few thousands, according to some empirical estimates<sup>50</sup>) work in concert with environmental and demographic factors to increase T2D risk. The number of potential variations in these interactions can be linked to the colors on a painter’s palette,<sup>7</sup> where hues and tones are mixed, and individual primary colors might be difficult to discern. There may still be sections of the “McCarthy palette,” where a particular color (or genetic variant or environmental exposure) may predominate, in which case a targeted intervention may be feasible; and specific subtypes might be defined by the extremes along

empirical scores that combine genetic and other variables. Where that is possible, at least some individuals may be placed in strata in which specific surveillance, prevention, lifestyle, pharmacological, and/or surgical strategies might be deployed. Figure 2 hypothetically illustrates how precision medicine might deconstruct traditional symptom-based categories through the study and integration of several biological axes of information to parse current heterogeneous syndromes into homogeneous clusters.

As new treatments are introduced, it will be crucial to verify whether they are equally effective across all subtypes; if comparatively greater effectiveness is demonstrated for a specific segment of the population, this information may be used in a public health setting to prioritize the subgroups more likely to benefit. The body of knowledge that will guide these decisions must be developed, and the experiments designed to answer this question ought to be reproducible, interpretable, and actionable. Decision-making support tools must be implemented at the point of care, so clinicians can easily act on available information in a seamless fashion. The new technologies that generate data relevant to health outcomes will need to be scaled up and made accessible in community settings, so that they help us understand, rather than deepen, existing health disparities.

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### Competing interests

The authors declare no competing interests.

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