

The Need for Precision Medicine to be Applied to Diabetes

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Abstract

Precision medicine refers to the tailoring of medical treatment for an individual based on large amounts of biologic and extrinsic data. The fast advancing fields of molecular biology, gene sequencing, machine learning, and other technologies enable precision medicine to utilize this detailed information to enhance clinical management decision-making for an individual in the real time of the disease course. Traditional clinical decision making is based on reacting to a relatively limited number of phenotypes that are determined by history, physical examination, and conventional lab tests. Precision medicine depends on highly detailed profiling of the patient's genetic, morphologic, and metabolic makeup. The precision medicine approach can be applied to individuals with diabetes to select treatments most likely to offer benefit and least likely to cause side effects, offering prospects of improved clinical outcomes and economic costs savings over current empiric practices. As genetic, metabolomic, immunologic, and other sophisticated testing becomes less expensive and more widespread in the medical record, it is expected that precision medicine will become increasingly applied to diabetes care.

Keywords

diabetes, genes, omics, pharmacogenetics, phenotype, precision medicine

Introduction

Precision medicine is a modern concept used since 2011 to describe medical treatments tailored to the specific characteristics of each patient.^{1,2} In this model of care, standard history, physical exam, and laboratory tests are enhanced with “omics”³ to identify unique characteristics of the patient and their disease that guide clinical management decisions. The patient's response is then monitored with a range of conventional and omic data to confirm to modify initial management decisions. The combination of traditional gross and microscopic metrics combined with molecular profiling across multiple biological axes enables precision medicine.⁴ One promise of precision medicine is to identify patients who will benefit or not benefit from a particular treatment based on genetic and other factors.⁵

Recent cancer prevention, early detection, and treatment innovations are incorporating data about patient-specific clinical features along with genomic-based diagnostics and targeted therapeutics.⁶ This approach allows a more accurate characterization of at-risk individuals. These efforts at preventing diagnosing and treating cancer are emphasizing the incorporation of cancer phenotype and omic data, which can be combined with environmental factors to indicate a patient's risk of cancer.⁷ One distinctive feature in cancer

diagnostics is that genomic information is obtained from readily accessible tumor tissue.

Diabetes is a collection of disorders that share the common end result of hyperglycemia. Diabetes can be classified into the following general categories: (1) type 1 diabetes, due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency; (2) type 2 diabetes, due to a progressive loss of β -cell insulin secretion frequently on the background

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of insulin resistance; (3) gestational diabetes mellitus, diabetes first evident during pregnancy; (4) monogenic diabetes, caused by mutations in single genes, such as neonatal diabetes and maturity-onset diabetes of the young (MODY); and (5) secondary diabetes due to other causes, such as diseases of the exocrine pancreas or drugs like glucocorticoids.⁸ These distinguishing factors include (1) the age of onset, (2) the severity of loss of islet cell function, (3) the degree of insulin resistance, (4) the presence of diabetes-associated antibodies, and (5) the presence of severe mutations that alter protein function.⁹

Phenotype Identification of Diabetes

Traditionally phenotypic characteristics have been used to determine an individual's form of diabetes according to the above classification. Such characteristics are age of onset, body habitus, dependency on insulin, and history of ketoacidosis. The phenotype approach is not sufficient to distinguish all cases of type 1 diabetes from those with type 2 diabetes, because patients in both categories can have either extreme of these phenotype dyads. For example, people with autoimmune diabetes can also become obese, and people with type 2 diabetes can present in ketoacidosis.

The purpose of applying the precision medicine approach to diabetes is to further characterize an individual's condition beyond clinical phenotypes by the use of laboratory tests (including genetic, immune, and metabolic markers) and other information, not only to guide therapeutic decision-making but also to predict disease progression and clinical outcomes under various scenarios.

Examples of Applying Precision Medicine to Diabetes

The identification of single-gene mutations that cause diabetes with high penetrance (monogenic diabetes) provides a simple and accurate way to make precise diagnosis of diabetes subtypes and to use that information to guide therapy. For example, people who carry heterozygous mutations in the *HNF1A* or *HNF4A*, which encode β -cell nuclear transcription factors and represent two or more than a dozen genes known to cause MODY diabetes when mutated, are very sensitive to low-dose sulfonylurea therapy. In contrast, some people with activating mutations in *KIR6.2* or *ABCC8*, which encode components of the ATP-sensitive potassium channel in the β -cell and often present as neonatal diabetes, can still respond to very high-dose sulfonyl urea therapy and get off insulin with improved glucose management.¹⁰

Common forms of type 1 and type 2 diabetes also have a heritable component, but their genetic architecture is polygenic, ie, composed of many genetic polymorphisms which in combination with environmental factors give rise to the phenotype. Many polymorphisms related to T lymphocyte function have been identified as contributors to type 1 diabetes, and many

polymorphisms related to β -cell function have been associated with type 2 diabetes. The effect sizes of genes associated with type 2 diabetes are very small compared to the effects seen in monogenic diabetes. However, most people with monogenic diabetes are initially diagnosed with type 1 or 2 diabetes, and we continue to identify new genetic causes of monogenic diabetes, so it remains an important goal of precision medicine in diabetes to distinguish monogenic diabetes from type 1 and type 2 diabetes and determine best management practices based on the specific mutations that patients carry.

Hyperglycemia can cause epigenetic changes in vascular cells leading to protein-protein interactions followed by cardiovascular complications aberrant DNA methylation, imbalance of histone modifications, and a differential expression of some micro-RNAs, which have all been proposed as potentially useful prognostic biomarkers for the development of atherosclerosis in diabetes patients.¹¹

Cluster Analysis of Six Phenotypic Variables to Achieve Stratification

Stratification of patients with diabetes for prediction of response to treatments has been attempted with phenotypic classification alone and no genotyping. In 2018, Ahlqvist et al reported a cluster analysis of patients newly diagnosed with diabetes who were participants in five research cohorts in Scandinavia.¹² They analyzed the patients according to six phenotypic variables that could be measured at diagnosis. These variables at onset of diabetes included (1) body mass index, BMI; (2) age; (3) hemoglobin A1c concentration; (4) a homeostasis model assessment estimate of β -cell function, (5) a homeostasis model assessment estimate of insulin resistance, and (6) the presence or absence of glutamic acid decarboxylase antibodies. They identified five clusters of patients with very different characteristics and risks of diabetic complications. They labeled the clusters as severe autoimmune diabetes, severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes, and mild age-related diabetes (MARD) (see Table 1). A targeted genetic analysis of the cohorts demonstrated distinct genetic features for some of the clusters, indicating different pathophysiological processes.

Therefore, this six-phenotypic stratification into five subgroups with differing disease progressions was felt to offer promise in targeting treatments toward patients, according to their risks of developing complications.

A later study by Zaharia et al in 2019 divided a set of newly diagnosed type 1 or type 2 diabetes patients into the same five clusters that Ahlqvist identified. The five diabetes clusters showed different prevalence of nonalcoholic fatty liver disease (highest in the SIRD cluster) and diabetic neuropathy (highest in the SIDD cluster) at early stages of the disease and hepatic fibrosis (highest in the SIRD cluster) at later stages.¹³

Table 1. Five Clusters of Diabetes According to Ahlqvist et al.¹²

Number	Abbreviation	Name	Clinical features
Cluster 1	SAID	Severe autoimmune diabetes	Early onset, low BMI, poor metabolic control, and positive for the presence of GAD autoantibodies. Fastest time to sustained insulin use
Cluster 2	SIDD	Severe insulin-deficient diabetes	Early onset, low BMI, poor metabolic control, and negative for the presence of GAD autoantibodies. Highest risk of retinopathy. Likeliest to be treated with metformin
Cluster 3	SIRD	Severe insulin-resistant diabetes	Insulin resistance and high BMI. Highest risk of nonalcoholic fatty liver disease and high risk of chronic diabetic kidney disease
Cluster 4	MOD	Mild obesity related diabetes	Obesity but no insulin resistance
Cluster 5	MARD	Mild age-related diabetes	Old age and with obesity but no insulin resistance

Abbreviations: BMI, body mass index; GAD, glutamic decarboxylase.

This year Dennis et al developed a model to stratify participants in two large clinical trials of type 2 diabetes according to the five clusters of Ahlqvist et al to a set of four simple clinical features, so as to compare clinical outcomes.¹⁴ These features were (at the onset of diabetes) gender, age, BMI, and hemoglobin A1c. They found that stratifying patients into subgroups per the Ahlqvist method and then treating according to the likeliest beneficial drug for each subgroup was less effective at predicting favorable outcomes in progression of disease and its complications than simply stratifying patients according to a quantitative distribution of their specific simple clinical features. They concluded that various phenotypic stratification approaches to applying precision medicine offer an opportunity to improve outcomes in type 2 diabetes, but combining phenotypic measures is likely to be more effective than assignment to dichotomous subgroups. This result by Dennis underscores a major limitation of retrospective analyses. They suggest hypotheses for testing therapies on various subgroups defined by phenotypic and genetic features, but they do not explain whether different treatments of the subgroups result in true benefits.

Pharmacogenetics

Pharmacogenetics is the study of how genetic variation affects (1) the pharmacokinetic and pharmacodynamic response to a drug, (2) polymorphisms in drug targets that can affect therapeutic outcomes, and (3) the incidence of adverse events.^{15,16} For diabetes drugs, genetic variation can pertain to the glycemic response, side effects, risk reduction for cardiovascular effects, and reduction in progression of microvascular disease. Pharmacogenetics focuses on identifying which patients are most likely to benefit from a drug or which are most likely to avoid side effects. Genetic discovery predictive of drug response can focus on two approaches: The first approach is through understanding the natural history of the cause of the diabetes and how one set of patients is pathophysiologically different from another set of patients in their disease and in their cause of diabetes, so that a drug can be selected that will be most effective for that subgroup's

Table 2. Five Clusters of Diabetes According to Udler et al.¹⁷

Number	Name	Clinical features
Cluster 1	β -cell cluster	Increased PI levels, decreased Ins levels, and increased risk of CAD and ischemic stroke (including large and small vessel but not cardioembolic)
Cluster 2	Proinsulin cluster	β -cell dysfunction with decreased PI levels and decreased Ins levels, with no associated clinical features
Cluster 3	Obesity cluster	Obesity-mediated insulin resistance with no associated clinical features
Cluster 4	Lipodystrophy cluster	Lipodystrophy-mediated insulin resistance, increased risk of CAD, increased BP, and increased UACR
Cluster 5	Liver/lipid cluster	Abnormal liver metabolism-mediated insulin resistance, decreased creatinine clearance, and decreased UACR

Abbreviations: BP, blood pressure; CAD, coronary artery disease; Ins, insulin; PI, proinsulin; UACR, urine albumin-creatinine ratio.

pathophysiology. The second approach is to identify genotypes or other markers associated with altered drug transport or drug metabolism (both of which affect drug exposure and efficacy) so that patients with genotypes associated with altered drug outcomes can receive drugs most likely to be effective and/or safe.⁵

Using the first approach, in 2018, Udler et al reported a cluster analysis of 14,183 subjects with 94 T2D genetic variants and 47 diabetes-related metabolic traits from publicly available genome-wide association study (GWAS) datasets and biobanks.¹⁷ They identified five robust clusters of type 2 diabetes variants, which appear to represent biologically meaningful and distinct mechanistic pathways (see Table 2). Two clusters related to pancreatic β -cell function and three clusters related to pathways of insulin resistance. They found

that approximately 30% of the overall population had a genetic burden that placed them at the top 10% of one of these clusters. The investigators stated that the next step in this analysis would be to examine whether these individuals who fit squarely into one of the clusters would respond differentially to medications affecting the disrupted pathway, and whether they would demonstrate a differential rate of disease progression and development of complications. These clusters were largely consistent with those reported by Mahajan et al in an independent exercise.¹⁸

In regard to the second approach, to date, most of the genes associated with increased risk of diabetes have had little association with differential responses to various drugs. Most of the work in identifying variable responses to a diabetes drug have centered on metformin uptake and tolerance¹⁹; however, a small number of genes with cardioprotective properties in the presence of glucagon-peptide 1 receptor agonists²⁰ and sulfonylureas²¹ have been identified.

Current State of Pharmacogenetics

A literature review published last year for pharmacokinetic variants related to four drug classes for type 2 diabetes (metformin, sulfonylurea/glinides, thiazolidinediones, and glucagon-like peptide-1 receptor agonists/dipeptidylpeptidase 4 inhibitors) identified 64 genes and 200 variants.¹⁵ In a cohort of Swedish adults, the predictive accuracy for lifestyle risk factors was found to be similar to that yielded by genetic information for incident type 2 diabetes. In general, genetic studies have not been shown to predict disease progression or predict a significant difference in response to a pharmacologic treatment.^{15,22} It should be noted that while most pharmacogenetic studies for type 2 diabetes have focused on a single gene, joint contributions of multiple loci on the efficacy of various combinations of drugs for type 2 diabetes have recently also been identified.²³

Current State of Precision Medicine

Patients with diabetes may be able to benefit from classification according to the cause of diabetes, pathophysiology, and natural history, so that optimal treatments can then be selected. The most widely used factors for classification (the age of onset, the severity of loss of islet cell function, the degree of insulin resistance, the presence of diabetes-associated antibodies, or the presence of specific mutations)⁹ are intended to assign patients to one of the five types of diabetes described above. However, a patient can be mistakenly classified because the diagnostic criteria for the five broad types of diabetes encompass many subtypes that do not exactly fit the main defining criteria or else patients who do fit the defining criteria might still represent very different subtypes.

Information to classify types of diabetes is now widely available to supplement these five traditional classifying factors from various sources: (1) patient surveys of the natural

history of the disease (including family history, ethnicity, mental health, medications, and lifestyle)²⁴; (2) anthropomorphic measurements of body characteristics (sometimes based on paper tools based or more efficiently on digital tools); (3) measurements of circulating or urinary molecules or cells, which can include traditional lab tests or biomarkers, including information about continuous glucose concentrations²⁵; and (4) behavioral measurements of activities such as food intake²⁶ and exercise that are accessible from sensors.²⁷ Phenotypic and biomarker information are two traditional dimensions of classifying patients, but the premise of precision medicine is that more valuable characterization is possible by incorporating additional types of assessments that query relevant biological axes comprehensively. These domains, which can interact with the environment, include: inherited variation (genomics); the features that determine whether a gene is active or suppressed in a given tissue (epigenomics); levels of gene expression (transcriptomics); the proteins that arise from specific gene products (proteomics); small molecules generated by enzymatic reactions (metabolomics); or the set of microbial species that coexist with the human organism (the metagenome)^{28,29} (see Figure 1). Omics testing uses a variety of advanced lab analytical methods to determine the presence of genetic markers or circulating molecules whose presence and concentrations (1) are related to gene expression and environmental factors and (2) can predict clinical outcomes.³⁰

The reason why patients of similar phenotype respond differently to the same treatment is likely related to the interplay of multiple genotypes and other factors. To date, the common variants shown by GWAS to be associated with the development of type 2 diabetes have had only modest effect sizes. Their usefulness for predicting type 2 diabetes has been limited and is no better than classic risk factors such as age, BMI, and blood glucose.²⁴ However, the addition of detailed genetic testing to a precision medicine approach might improve the specificity to identify subgroups of patients with diabetes who can then be assessed for differential responses to medications in terms of safety and efficacy.³¹

Currently for diabetes, genetic markers are in most cases not sufficiently informative to assign precise therapy—excluding cases of MODY or neonatal diabetes, which are both characterized by genetic mutations. Attempts are now being made by various professional societies to create diabetes guidelines for helping therapy decisions to allow individualized diabetes therapy. These decisions are currently based mainly on the status of the patient and positive or negative side effects of different medications that are available.

The Need for Better Precision Medicine for Therapeutic Decisions (ADA Rx Guidelines)

A goal of diabetes precision medicine database generation programs is to develop a new classification of diabetes that will simplify treatment regimens in terms of a best combination of

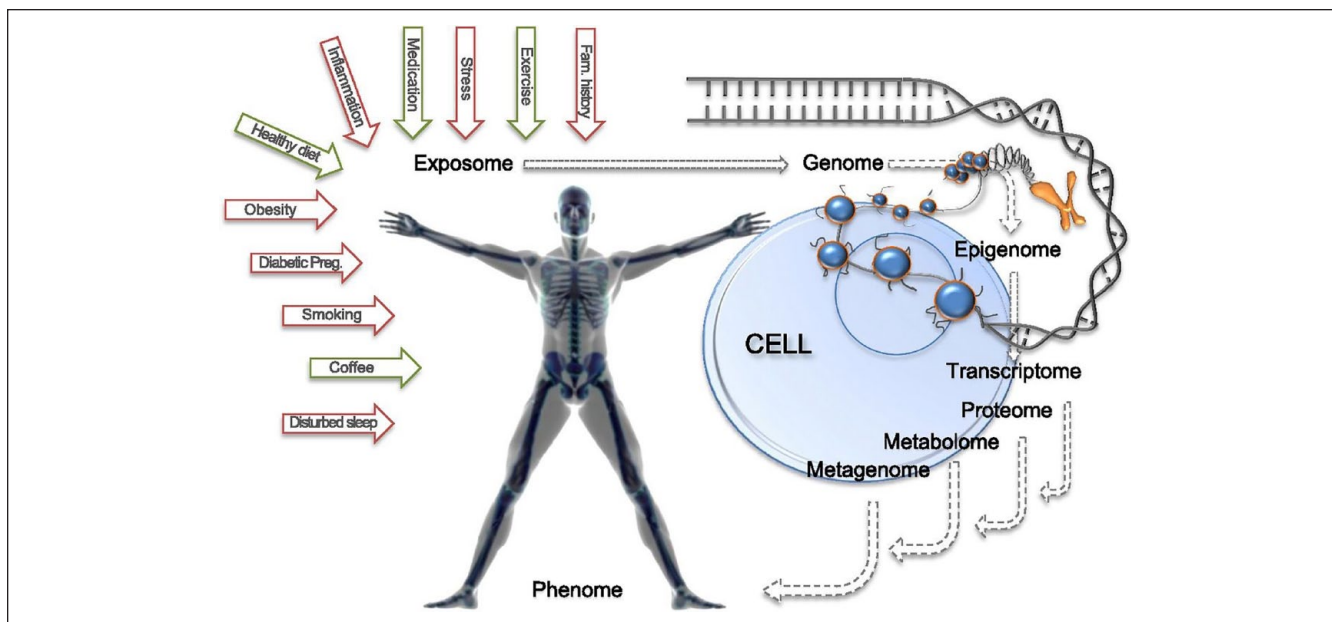


Figure 1. The sum of the interactions between nongenetic environmental and behavioral factors (the exposome) with genetic and quantifiable elements of human physiology (the physiome) comprising an individual's observable characteristics, which are known as the phenome. Reproduced with permission from Diabetes Care.²⁸

likely efficacy and unlikely side effects. Precision medicine will combine (1) individual data about genetic predispositions to diseases; (2) biomarker information about disease risks and responses; (3) environmental data; and (4) behavioral data derived from databases and sensors measuring glucose, lactate, cardiac electrophysiology, food ingestion, exercise, temperature, sweat rate, and global positioning.¹ These data will be used to create multifactorial risk scores and risk patterns as well as to accurately predict responses.³²

Currently, a clinician confronted with making a decision about prescribing a medication for type 2 diabetes is faced with many choices that all appear to be equally likely to provide benefit and there is little specific information available as to whether this specific patient is more or less likely than average to benefit from any of the drugs or whether the therapeutic effect will be sustained. Choosing on the basis of avoiding side effects often consists of considering whether a patient already shows signs of a problem to avoid the drug if it is known to frequently cause an exacerbation of this problem. Little specific information may be available to predict whether this patient is more or less likely than average to develop this adverse effect from this or any other drug. Current guidelines from professional organizations, such as the American Diabetes Association (ADA)³³ and the American Association of Clinical Endocrinologists³⁴, do not include genetic and genomic information for drug therapy. This type of information, which is generally unavailable at present, could facilitate a precision medicine approach to diabetes. Stratifying patients with type 2 diabetes into subgroups expected to have unique pharmacologic responses

would simplify the selection of the best drug treatments for type 2 diabetes. Future precision medicine flowcharts from professional organizations for everyday clinical diabetes care will likely link genetic, genomic, environmental, and behavioral information with treatment recommendations in three or more dimensions. It is expected that as genetic databases become established, then genotype and genomic information will become increasingly used to discover new drug targets and predict responses to drug treatments. Since type 2 diabetes appears to be a multifactorial disease where predisposition is also influenced by nongenetic or environmental factors, there is probably a limit to the precision that genetics alone can provide,²⁴ but it would be useful to better understand the interactions between various nongenetic environmental and behavioral factors with various genetic physiologic factors. Machine learning might eventually play a role in analyzing these interactions.³⁵

Major Precision Medicine Initiatives

A variety of precision diabetes initiatives have been launched since 2005 in the United States, Europe, Asia, and Australia.²⁴ They have been generally funded through public-private consortia. The largest of these is the Nordic Precision Medicine Initiative, which was formed in 2015 and is intended to assemble genetic and other biomedical data from over one million Nordic citizens in their biobanks.³⁶ The ADA has established a Precision Medicine in Diabetes Initiative that will, over the next five years, formulate a consensus statement on precision diabetes medicine and will

Table 3. The Six Objectives of the American Diabetes Association Precision Medicine in Diabetes Initiative.³⁷

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- (1) Improve diagnostics of known types of diabetes
 - (2) Establish what evidence we have and what evidence is needed to develop best practice guidelines and best practice study design
 - (3) Provide education to implement best practice guidelines
 - (4) Establish a research program to address open questions
 - (5) Accelerate the process for getting access to trials and for regulatory authorization
 - (6) Modify guidelines to incorporate new recommendations in precision medicine
-

launch complementary activities. The program's six objectives are listed in Table 3.

Conclusion

There is a need for precision medicine to be applied to diabetes in order to inform therapy decisions. Precision medicine can potentially utilize a vast amount of omic and other data to guide disease management and improve clinical outcomes. This paradigm, which is increasingly being successfully applied by oncologists, where the diseases have different genetic underpinnings than diabetes, has the potential to allow the selection of diabetes treatments that are tailor-made for each patient with diabetes. The hope is that precision medicine can use this information to improve the wellbeing of those with diabetes.

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