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EDITORIAL

Personalized Medicine for Diabetes

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Introduction

Personalized medicine is an emerging concept for treating diseases, which involves determining specific information about a particular patient and then prescribing a treatment that is specific for that patient.[1] Personalized medicine represents an approach for defining disease subtypes and defining biomarkers that can identify patients who are most likely to benefit from a specific treatment and other patients who are unlikely to respond or likely to experience side events.

Not every patient with diabetes with the same age, duration of disease, body mass index, and Hemoglobin A1c will respond the same way to a given treatment. Some patients respond to a treatment whereas others do not. The reason may be a genetic propensity to respond or not respond to a drug. The physician must assess every patient and then attempt to guess which treatment will work best. If the physician could be armed with specific personalized information about that patient, including information about their genetic makeup, then treatments could be tailored for each individual patient. This approach would then lead to better outcomes without wasting time on ineffective therapy. Outcome statistics, which indicate that a certain percentage of patients will respond to a specific treatment, are not always meaningful for a given individual. For some diseases and treatments if one treatment is used, then 100% will respond and if another treatment is used then 0% will respond and for other patients a different treatment might be 100% effective. The problem is that physicians do not know which treatment is likely to be effective in any given patient, so the treatment that works most often for the greatest number of patients is usually selected first, even though this treatment will not be effective for some patients.

Definition of Personalized Medicine for Diabetes

The definition of personalized medicine for diabetes (PMFD) is the use of information about the genetic makeup of a person with diabetes to tailor strategies for preventing, detecting, treating, or monitoring their diabetes. The practice of PMFD involves four processes. First is the identification of genes and biomarkers for diabetes as well as for obesity, which is the greatest risk factor for type 2 diabetes. Second, after these predictors of diabetes are identified, is allocation of resources to prevent or detect the diabetes and/or obesity phenotype in high-risk individuals, whose risk is based on their genotype. Third is selection of individualized therapies for affected individuals. The selection process involves deciding which drug to prescribe, what dose of drug to use, and which diet to prescribe. The selection process also accounts for which drug is least likely to cause side effects or toxicity. Fourth is measurement of circulating biomarkers of diabetes to monitor the response to prevention or therapy.

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Abbreviations: (KCNJ11) potassium inwardly rectifying channel, subfamily J, member 11, (OCT1) organic cation transporter 1, (PMFD) personalized medicine for diabetes

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Risk Identification

Few patients with type 2 diabetes have yet been found to have highly penetrant mutations of a single gene causing diabetes. The vast majority of type 2 patients have polygenetic forms of this disease in which each gene locus contributes only a small amount of risk.[2] Some of these loci identified to date include transcription factor 7-like 2, calpain 10, peroxisome proliferator-activated receptor γ, and potassium inwardly rectifying channel, subfamily J, member 11 (KCNJ11).[3] An example of how a gene can affect the response to a type 2 diabetes drug is the association of the common E23K variant in KCNJ11 with an increased risk for secondary failure to sulfonylurea in type 2 diabetes patients.[4] Another such example involves organic cation transporter 1 (OCT1), which is the major point of entry for metformin into hepatocytes and enterocytes. Individuals with OCT1 polymorphisms have a reduced response to metformin.[5] The pace of gene identification is now increasing because of new genotyping technologies. More accurate genotyping portends an increasingly important role for a personalized medicine approach to diabetes in the future.

The context of the genetic information used for applying personalized medicine must be considered. Multiple factors affect the response to a particular drug. The patient's genes are not the only determinant of success. Other factors that can confound the effects of a personalized approach specific to a genotype include other genes in addition to the one(s) being measured, environmental effects that can overwhelm the effects of a drug, diet, competing comorbidities, and interactions with other drugs. Type 2 diabetes is often caused by a combination of multigene susceptibility, environmental factors, and diet. In this disease, the effect of a therapy based on the activity of a single gene may be overwhelmed by many other confounding factors. If a single gene is a strong predictor of response to therapy for a disease, then the personalized medicine approach can still be effective.

Benefits of PMFD

The potential benefit of a personalized medicine approach to diabetes is the possibility of earlier interventions to prevent or treat the disease by using screening genetic tests. Patients who are at high risk for a chronic disease such as diabetes usually experience a prolonged asymptomatic period before the onset of the disease. Patients who are identified by genetic testing to be at high risk for diabetes can be directed to preventative measures, such as lifestyle modifications or medications, in order to delay or prevent the disease.[6] Genetic tests and biomarkers can be utilized for predicting the diagnosis and for monitoring the course of diabetes. Greater efficiency in drug development is possible if genetically[7] or nutritionally[8] determined drug targets are identified in subpopulations of patients with diabetes. Genetically determined polymorphisms of receptors, transporters, and metabolizing enzymes contribute to variable responses to drugs. Personalized medicine allows for personalized drug prescribing with less trial and error and less time wasted with an inadequate response or with side effects.[9] The result of such a personalized medicine approach would be a better outcome for the disease being treated, such as diabetes or obesity.

Research Initiatives

Five main types of research initiatives are currently being pursued in the area of personalized medicine. First, pharmacogenetics is the science that seeks to explain how people respond in different ways to the same drug treatment. This approach tests candidate genes for drug–patient interactions and promotes drugs that have a favorable effect on any gene that is responsible for some or all of the disease phenotype.[10] Second, pharmacogenomics is an approach that tests not genes but rather gene expression over time.[11] A person's DNA content (which comprises genes) does not change over time, but the RNA content (which reflects how much the gene is being utilized) does change over time. The measurement of gene products over time adds great complexity to the process for identifying genes that are integral to the disease state. Ultimately the relationships that are elucidated by pharmacogenomics (including the use of cell systems or even living organisms) are more robust than those from pharmacogenetics alone. Third, nutrigenomics is the approach that utilizes identifying genetically mediated responses to foods and then adjusting the diet to take advantage of these responses.[12,13] Fourth, biomarkers can be used to predict, diagnose, or monitor diseases. For example, autoantibodies can be measured to predict type 1 diabetes[14] and adipokines[15,16] can be measured to predict type 2 diabetes. Finally, systems biology[17,18] is an approach that measures interactions between the components of biological systems and how these interactions give rise to the function and behavior of that system. Systems biology analyzes complex data from multiple sources by utilizing such tools as transcriptomics (which assesses gene expression measurements), proteomics (which completely identifies

proteins and protein expression patterns of a cell or tissue), metabolomics (which identifies and measures all the small molecule metabolites within a cell or tissue), and glycomics (which identifies all carbohydrates in a cell or tissue).

Personalized medicine for diabetes will be applied to the prevention, diagnosis, treatment, and monitoring of diabetes. Genetic information will lead to advances in each of these clinical approaches to this disease. Examples of specific emerging inputs and responses related to PMFD are presented in **Table 1**. Blood glucose and Hemoglobin A1c levels are not included.

Barriers to PMFD

For personalized medicine to become established it will be necessary for people's genotypes to be analyzed completely, which is not currently possible on a large scale because of the great expense. The cost of performing such an analysis is coming down and it is expected that this type of test will soon be available for as little as $1000[76] within the next decade. The public's appetite for such genetic testing will be affected by the outcome of public policy debates on social and political barriers, including: (1) training sufficient medical genetics specialists to apply the results of genetic testing; (2) constructing an infrastructure to incorporate medical ethics into clinical trials using personalized genetic information; (3) creating guarantees of privacy for genetic records; (4) developing a regulatory oversight infrastructure to protect the public from abuses of genetic information; and (5) achieving the political will for insurance coverage and reimbursement to be available for personalized medicine because some treatments may increase in cost when the number of patients using them in a trial-and error approach is decreased greatly by switching to a personalized medicine approach.[77]

Stakeholders who will be affected by increased application of personalized medicine to diabetes include researchers, physicians, diabetes educators, geneticists, policy makers, patient advocates, clinical laboratories, pharmaceutical companies, diagnostics companies, information technology managers, payers, and government regulators.[78,79] Members of these groups will all have to work together to regulate personalized medicine for diabetes. These stakeholders will determine the degree of accuracy necessary for reporting the results of genome testing and the process for selecting which patients will be eligible for treatments based on such information. Both of these factors in the logistics of running personalized medicine programs are currently regulated only lightly.

Genome Databases

The realization of new drugs for personalized diabetes therapy could be accelerated by the establishment of a Genome Commons.[80] Such a publicly accessible electronic database of human genetic variation and its effects, incorporating both human and nonhuman experimental data, would be culled from locus-specific databases, diagnostic laboratories, and the scientific literature. This database would be a repository of common human inheritance and a tool for interpreting human genomes. This online repository with analytical software could be used as a tool for classifying genetic variations as to their clinical significance and as a reference tool for generating reports by clinical laboratories performing large-scale genome sequencing studies. This resource would be funded publicly to prevent private monopoly pricing for diagnostic information or private patenting of genes. A comprehensive knowledge base that incorporates information about pharmacogenomics for diabetes and other diseases is the Pharmacogenetics Research Network and Knowledge Base (**Figure 1**) maintained by Stanford University[81] at http://www.pharmgkb.org/do/serve?objId=PA153627758&objCls=Pathway.

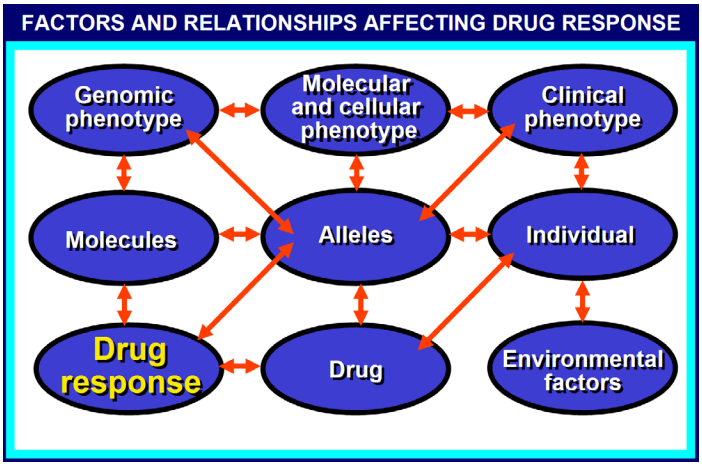

Figure 1. Data elements modeled in the Pharmacogenetics Research Network and Knowledge Base, adapted from Klein and colleagues.[81]

Conclusions

Personalized medicine for diabetes will provide great benefits. Widespread adoption of this approach will occur only when the identification of risk factors through genotype or through biomarkers is accompanied by effective therapy. Personalized medicine will be utilized to treat cases of diabetes with specific approaches that will be effective for a given patient but not necessarily effective for another patient with similar height, weight,

Table 1.
Applications of Personalized Medicine for Diabetes

Input	Response
PREVENTION	
Genetic studies identifying people at high risk for type 1 diabetes[19] Genetic studies identifying people at high risk for type 2 diabetes[20] Genetic studies identifying people at high risk for diabetic nephropathy[21] Genetic studies identifying people at high risk of obesity[22]	Immune therapy for preventing onset of type 1 diabetes[23] Vaccine to prevent type 1[24] Drug therapy to prevent nephropathy[25] Lifestyle modification to prevent type 2 diabetes[26] Drug therapy to prevent type 2 diabetes—multicenter trials sponsored by industry[27]
DIAGNOSIS	
Neuropathy and NH2-terminal fragment of the brain natriuretic peptide[28]	Early diagnosis of diabetic neuropathy—tight control of DM[29]
TREATMENT	
Genetic studies demonstrating subgroups within type 1[30] Abnormal insulin molecule[31] Abnormal release (LADA)[32] Clinical classification of new-onset, ketosis-prone patients into subgroups[33] Classification of autoimmune diabetes into late-onset type and type 1 diabetes[34] Genetic studies demonstrating subgroups within type 2[35] Mechanisms of the cause of type 2 must be understood and presented[36] Genetic variations in response to common diabetes drugs, e.g., metformin[28] and sulfonylureas[38] Distinction of MODY from type 2 DM[390] Genetic studies of neonatal diabetes[40] Nutrigenomic studies of food impact[41]	Type 1: Early initiation of early treatment to avoid complications, such as intensive insulin therapy,[42] immune therapy,[43] or gene therapy[44] Type 2: Early initiation of thiazolidinediones[45] or insulin[46] to preserve islet function[37] LADA: Early initiation of insulin to maintain euglycemia in patients with this diagnosis[47] Ketosis-prone diabetes therapy depends on classification[48] MODY—sulfonylurea therapy and focus on specific vascular risks[49] Neonatal diabetes: switch from insulin to sulfonylureas[50] Dietary therapy of type 2 diabetes[51] Exercise therapy of type 2 diabetes[52]
MONITORING	
Type 1: Biomarkers of autoimmunity—autoantibodies[53] and antigens,[54] cytokine levels,[55] and inflammatory serum markers[56] Type 2: Lipids,[57] C-reactive protein:[58] cytokines,[59] retinol-binding protein,[60] and other inflammatory markers,[61] New markers of glycemia in addition to glucose and hemoglobin A1c Glycemic variability[62] Advanced glycated end products[63] 1,5-Anhydroglucitol[64] Glycated Albumin[65] Exhaled methyl nitrate[66] Physiologic hypoglycemia detection[67] Smart Shirt[68] and Smart Glove for detecting diabetic autonomic neuropathy[69]	Type 1: Immune intervention[70] Technology: continuous glucose monitoring,[71] insulin pump therapy,[72] and artificial pancreas[73] Type 2: Anti-inflammatory therapy with thiazoldinediones or statins[74] Treatments of elevated levels of C-reactive protein[75]

Abbreviations: DM, diabetes mellitus; LADA, latent autoimmune diabetes; MODY, maturity onset diabetes of the young.

and glucose levels. Personalized medicine will also be used to prevent diabetes before the disease appears. Personalized medicine care for diabetes will become an increasingly important part of the fight against diabetes.

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