The Impact of Precision Medicine in Diabetes: A Multidimensional Perspective

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In his State of the Union address on 20 January 2015, President Barack Obama announced the Precision Medicine Initiative. Although the concept of "precision medicine" has been present for nearly a decade, many interpretations of precision medicine exist. At its core, precision medicine is a model that proposes the custom delivery of health care, with medical practices, testing, decisions, and treatments tailored to the individual patient level (1). Diagnostic tests and therapies are selected on the basis of not only the specific 'omics signature (e.g., genomics, transcriptomics, methylomics, proteomics, methylomics) but also the specific risk factor profile and health history obtained from the electronic health record.

In March 2015, National Institutes of Health (NIH) Director Collins established a working group to develop a plan for creating and managing a collection of 1 million volunteers to comprise a precision medicine research cohort. On 17 September 2015, Dr. Collins accepted the framework that would establish the Precision Medicine Initiative, which includes providing the support to build the infrastructure for recruitment of the cohort, collection of the health data, banking of specimens, and launching research. This initial effort for precision medicine represents a major commitment of funds from the NIH. In this regard, President Obama allocated $215 million in fiscal year 2016 to support the initiative, and $130 million alone was targeted for the research participant cohort.

Clearly, the Precision Medicine Initiative ushers in a paradigm change in the way we approach patient care. Specifically, it launches a new era of research, technology, and policy in this area, one in which the participant, the health care practitioner, and research merge into an individual-level relationship focused on the maintenance of health and the prevention and treatment of common human diseases. But, given that the editorial team at *Diabetes Care* desires to provide the most up-to-date information on topics of interest relevant to our disease focus, we ask the question, "what does precision medicine mean for diabetes?" We feel this is a relevant and very timely question that allows opportunities for an even deeper consideration of precision medicine and diabetes. Thus, during our *Diabetes Care* Symposium 2016, held at the Scientific Sessions of the American Diabetes Association, we had two presentations that started our discussion on precision medicine in diabetes. Dr. Judith Fradkin spoke of the response that the National Institute of Diabetes and Digestive and Kidney Diseases (the "diabetes" institute at NIH) is taking as a participant in the Precision Medicine Initiative, including targeting support of investigator-initiated grants (2). Dr. Jose Florez reflected on the promise of genomics for developing better predictors of risk of diabetes and its complications, as well as the likelihood of using pharmacogenomics to better tailor treatment of disease (3). The articles by Fradkin et al. (2) and Florez (3) were published in the July 2016 issue of *Diabetes Care*.

With the aim of disseminating information on a more comprehensive examination of precision medicine and its role in diabetes, our editorial team is featuring a collection of articles in this issue of *Diabetes Care* that may help to put the question in context. These articles are grouped into two components. The first series of articles represents the impact of precision medicine on diabetes from the pharmacogenomic, public health, and regulatory perspectives. The second series of articles provides research that reflects the role of genetic factors and biomarkers on diabetes diagnosis, the impact of environment, predictors of complications, and response to treatment (4–12).

The emerging availability in genomic and electronic health data in large populations is a powerful tool for bringing precision medicine to diabetes. On this topic, Floyd and Psaty (4) discuss the potential application of genomics to the prediction, prevention, and treatment of diabetes. They use examples

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from other disease states to illustrate some of the challenges in the implementation of research findings in practice. They point out that a major barrier to the application of genomics in diabetes care, particularly for type 2 diabetes, is the lack of actionable genomic findings. For use in clinical practice, genomic data (or any 'omics data) requires a framework for evaluating the validity and clinical utility of this approach. This framework includes an improved integration of genomic data into electronic health records as well as establishing a translatable clinical decision support system. A critical component of implementing these novel technologies will be providing educational resources for clinicians that will permit optimal use of these new forms of "big data." The increasing availability of genomic data in large populations linked with electronic health data may become a powerful resource for genomic discovery. Examples from other areas of medicine offer lessons about the limitations of these data that can help guide the direction of future research. Efforts to identify optimal approaches in all of these domains will be required to bring diabetes into the era of genomic medicine.

Over the past decade, there have been rapid advances in the molecular technologies available for interrogating the genome, generating huge amounts of data on each individual with exome or whole-genome sequencing. As with any advance in technology, the understanding and utilization of the data lags behind the generation of the data. Eventually, the clinical marketplace sees the proliferation of genomic testing protocols; however, there are many uncertainties regarding the use and value of such tests. As noted by Arnett and Claas (5) when discussing precision medicine in the context of public health, a critical component in the use of these data that comprise "precision medicine" is the ability to translate these results into useful health knowledge that may make a difference. The authors note that the challenges faced by public health practitioners include the shifting landscape upon which the discipline is built, with precision medicine now offering individual-level multi-omics, environmental, and lifestyle profiles within population strata. They summarize and contrast the differences in what is thought of traditionally as "public health" (focused on populations) from "precision public health" (focused on the individual). There are many novel relationships to be established, including those between public health practitioners and clinical scientists. Past practices have been to provide better population-level health, designing interventions to increase the number of people in the population benefiting from the intervention and decrease the number who could be, but are not, benefiting. However, this is not targeting individuals where there is a wide range and variable biologic response when interventions are applied to the entire population. In contrast, the futuristic approach of precision public health intervention retains the goal of classical public health, yet there has to be a precise targeting of population strata that most benefit from the intervention.

The U.S. Food and Drug Administration (FDA) plays an important role in drug development and which technologies are appropriate to consider. There has been no question that this agency has a very tough job and has faced criticism in the past, often relating to perceived barriers to drug or device adoption for treatment of specific medical outcomes. However, as noted by Meyer (6) in a review of this topic in this issue of *Diabetes Care*, the FDA has also sought to promote personalized medicine, which the immediate past commissioner of the FDA characterized as "the tailoring of medical treatment to the individual characteristics, needs and preferences of each patient." The FDA's definition also suggests considerations such as individual patient preferences and social situation to optimally meet a specific patient's therapeutic needs. Thus, Meyer's perspective focuses on both type 1 diabetes and type 2 diabetes as primary disease states and notes that while significant advances have been made in the understanding of the pathogenesis and mechanisms of both diseases, these advances have yet to be translated into preventive or treatment paradigms that incorporate precisely targeted interventions. In addition, there is discussion of the regulatory consideration regarding precision medicine as it relates to the prevention and/or treatment of diabetes. Meyer notes that the differences in understanding the etiology and risk factors inform how precision medicine may be relevant in the development and regulatory approval of targeted interventions. Drug regulation by the FDA and other agencies requires both maturity of evidence and presence of demonstrable results to inform that regulation. Thus, while there is much promise in incorporating precision medicine into the prevention and therapy of the common forms of diabetes, it is clear there is a paucity of data in this area and more evidenced-based research will be required to inform regulators in order to advance precision medicine.

In contrast to the common forms of diabetes (type 1 and type 2) that are etiologically complex, monogenic diabetes, although rare and due to a single gene defect, is an important diagnosis in pediatric clinics and is often difficult to diagnose. Fortunately, certain biomarkers (islet autoantibodies and C-peptide) permit systematic testing. As reported by Shepherd et al. (7) in this issue, the prevalence of monogenic diabetes in the U.K. pediatric clinics was estimated using a systematic approach of biomarker screening and targeted genetic testing, an obvious approach in precision medicine. In six pediatric clinics in South West England and Tayside, Scotland, a total of 808 patients (79.5% of the eligible population) under 20 years of age with diabetes were studied. Those with a positive urinary C-peptide–to–creatine ratio ($\geq$0.2 nmol/mmol) were evaluated for the presence of islet autoantibodies (GAD and IA2). Those patients without autoantibodies (pediatric diabetes with endogenous insulin production but islet autoantibody negative) had genetic testing for the 29 identified causes of monogenic diabetes. A total of 2.5% (20/808) of patients had monogenic diabetes (cases due to known genes: 8 *GCK*, 5 *HNF1A*, 4 *HNF4A*, 1 *HNF1B*, 1 *ABCC8*, 1 *INSR*). Critically, the majority of monogenic diabetes cases (17/20, 85%) were managed without insulin treatment. Remarkably, a similar proportion (27/808, 3.3%) was diagnosed with type 2 diabetes. This report does advance our clinical approach as it demonstrates that a pathway involving biomarkers and genetic screening is practical and that this approach can be used to distinguish pediatric patients with monogenic forms of diabetes from those with type 1 and type 2 diabetes, each with different treatment requirements.

In contrast to the approach to diagnose monogenic forms of diabetes, in

which there are clear single-gene causes, the contribution to the genetic basis of type 1 and type 2 diabetes is much more complicated in the general population. Recently, however, a study of the Greenlandic Inuit population identified a common nonsense mutation in the *TBC1D4* gene that substantially increased the risk of type 2 diabetes. The function of the *TBC1D4* variant was shown to exclusively increase postprandial glucose. In the report by Manousaki et al. (8), the frequency and effect of the *TBC1D4* mutation on glucose metabolism and type 2 diabetes was determined in two related populations—the Canadian and Alaskan Inuit. Using a key component of the precision medicine toolkit (sequencing the coding regions of the human genome, the "exome"), exome sequencing was conducted on samples from 114 Inuit from Canada (to detect the *TBC1D4* variant) and targeted sequencing was performed in 1,027 Alaskan Inuit samples obtained as part of the Genetics of Coronary Artery Disease in Alaskan Natives (GOCADAN) Study. The authors report that the *TBC1D4* mutation was present in 27% of Canadian and Alaskan Inuit; further, having two copies of the mutation was associated with biochemical changes, as shown by higher glucose and insulin levels 2 h after an oral glucose load. The mutation in the *TBC1D4* gene is common among North American Inuit and results in elevated postprandial glucose and an underdiagnosis of type 2 diabetes unless an oral glucose tolerance test is performed. These authors show that accounting for genetic factors in Inuit diabetes care provides an opportunity to implement precision medicine in this population.

Precision medicine in diabetes diagnosis is only one component of clinical practice. A major issue in the care of the patient with diabetes is tailoring the best treatment and dosage. In the article by Dujic et al. (9), the impact of genetic factors on gastrointestinal intolerance to metformin treatment was considered. In the Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) study, it has been shown previously that reduced-function alleles of the *OCT1* gene are associated with increased intolerance to metformin. Recently, it has been suggested that the serotonin reuptake transporter (*SERT*) might also be involved in metformin intestinal absorption. Thus, the authors show the association between a *SERT* polymorphism and metformin gastrointestinal intolerance as evaluated in 1,356 fully tolerant and 164 extreme metformin-intolerant patients. The number of low-expressing *SERT* S* alleles significantly increased the odds of metformin intolerance. Furthermore, there was a multiplicative interaction between the *OCT1* and *SERT* genotypes, suggesting a complex genetic control of metformin intolerance. These results suggest that metformin gastrointestinal side effects could be related to the reduced intestinal serotonin uptake, a critical component of precision medicine related to a primary line of treatment of the most common form of diabetes.

Another pharmacogenetic approach to treatment response in type 2 diabetes was demonstrated with the use of thiazolidinediones (TZDs), compounds that are transported into the liver by OATP1B1 (encoded by the *SLCO1B1* gene) and metabolized by the CYP450 2C8 enzyme (encoded by the *CYP2C8* gene). Although variants in the *CYP2C8* gene (the *CYP2C8**3 allele) have been shown to alter TZD pharmacokinetics, the *CYP2C8**3 allele has not been shown to alter efficacy. In the article by Dawed et al. (10), 833 patients with type 2 diabetes treated with pioglitazone or rosiglitazone were genotyped for the *CYP2C8* and *SLCO1B1* functional variants. The *CYP2C8**3 variant was significantly associated with reduced glycemic response to rosiglitazone and less weight gain, whereas the *SLCO1B1* 521T>C variant was associated with enhanced glycemic response to rosiglitazone. Those patients with both genotypes (super responders) had a significantly greater HbA_{1c} reduction. Interestingly, neither of the variants had a significant impact on pioglitazone response. These results show that variants in *CYP2C8* and *SLCO1B1* have a large clinical impact on the therapeutic response to rosiglitazone and highlight the importance of studying transporter and metabolizing genes as a predictor of treatment response. However, it should be noted that these two genetic variants increase glycemic efficacy to rosiglitazone but also increase weight gain. The data presented in this study advance the practice of precision medicine in diabetes by identifying those individuals who can benefit from the therapeutic advantages of TZDs and also provide comment on other effects of these agents such as weight gain.

Weight loss is a primary recommendation for risk reduction of type 2 diabetes; however, there are many individuals for whom weight loss (and maintenance of loss) cannot be achieved. Fibroblast growth factor 21 (FGF21) is involved in regulation of energy balance and adipose metabolism, and genetic variants in the *FGF21* gene have been associated with macronutrient intake preference.

The study by Heianza et al. (11) determined whether an *FGF21* genotype was an effect modifier of weight-loss diets that varied in macronutrient intake. The authors measured changes in adiposity in a 2-year randomized diet intervention trial that included 715 overweight or obese individuals. Body composition was assessed with dual energy X-ray absorptiometry. The authors reported an interaction between the *FGF21* genotype and carbohydrate/fat intake on 2-year changes in waist circumference, percent total fat mass, and percent trunk fat. Further, their data were consistent with an *FGF21* genotype interaction with dietary carbohydrate/fat intake on changes in central adiposity and body fat composition among overweight or obese individuals. The authors suggest that the *FGF21* genotype could be a critical component in the use of potential precision dietary interventions. In particular, their results suggest that a particular dietary pattern (i.e., high-carbohydrate/low-fat diet) may be beneficial for overweight or obese individuals only in that subgroup of patients who carry the carbohydrate intake–decreasing allele of the *FGF21* gene.

A major clinical outcome of diabetes is increased risk of cardiovascular disease and associated mortality. Shah et al. (12) conducted an ancillary study of 2,667 subjects with type 2 diabetes in the intensive treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to identify genetic determinants of increased cardiovascular mortality. Genetic variants were significantly associated with cardiovascular mortality in two genomic regions (10q26 and 5q13), and these were examined in both ACCORD and in a Joslin Clinic cohort. The investigators determined that a genetic risk score defined by the two most significantly associated variants modified the risk of cardiovascular mortality in response to intensive versus standard treatment. These findings have potential implications for the

development of precision medicine approaches for the treatment of patients with type 2 diabetes while reducing risk of cardiovascular disease.

This issue's focus on precision medicine is meant to provide a glimpse of what the future may hold for diabetes care as well as the issues involved in the implementation and success of this transformative model of care. The goal of the Precision Medicine Initiative is to construct a research cohort that will "broadly reflect the diversity of the U.S. population by including participants from diverse social, racial/ethnic, and ancestral populations living in a variety of geographies, social environments, and economic circumstances, and from all age groups and health statuses. Information from the cohort will be a broad, powerful resource for researchers working on a variety of important health questions" (13). These articles focus specifically on a translational theme related to implementing the principles of precision medicine, which are often nested in basic science, into the realm of clinical practice. In addition, they provide insight into the many challenges in refining the diagnostic and therapeutic pathways for optimal management of the individual with diabetes, given the individual diversity in genomic profile and environmental exposures. Even with 1 million volunteers, the number with a specific disease may be large, yet when partitioned into specific subgroups, it becomes small. Thus, the promise of precision medicine in general, and the Precision Medicine Initiative specifically, will reside in implementing a comprehensive translational approach enlisting the efforts of those in basic science, clinical science, and population science working in partnership.

The *Diabetes Care* editorial team is delighted to provide our readers a view of precision medicine from experts in the field as well as targeted research reports. We believe that these articles, along with other recent reports in *Diabetes Care* and other journals, are helping provide a framework of interpretation as well as managing expectations. As always, our goal at *Diabetes Care* is to stimulate thinking that will assist both clinical care and research efforts. It's what we do!

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