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Genetic Risk Scores in Diabetes: Potential for Disease Prediction, Classification, and Precision Medicine

Mark O. Goodarzi, MD, PhD[1]

1 *Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Health Sciences University, Los Angeles, CA, USA.*

Abstract: Genome-wide association studies have discovered a large number of susceptibility variants for type 1 (T1DM) and type 2 diabetes mellitus (T2DM). This has facilitated numerous studies exploring the potential of genetic risk scores (GRS) to improve disease prediction and diabetes classification. Given the unique genetic architecture of T1DM, in which genetic variants explain ~90% of the heritability, GRS for T1DM are highly predictive for disease development, alone and in combination with clinical factors. T1DM GRS also effectively distinguish T1DM from other types of diabetes. Though composed of a greater number of variants, T2DM GRS have more modest ability to predict and classify diabetes. On the other hand, T2DM variants have been classified into subclusters that reflect diverse pathophysiologic processes underlying T2DM. GRS based on these clusters have been used to dissect the underpinnings not only of T2DM but also of related disorders such as polycystic ovary syndrome and pancreatogenic diabetes. They may also one day prove useful in precision medicine, allowing selection of drug therapy targeted to each patient's underlying physiologic deficits. However, much work validating use of GRS in the clinic will need to be accomplished before the full potential of GRS can be realized.

Key words: Type 1 diabetes, type 2 diabetes, type 3c diabetes, insulin secretion, insulin resistance, single nucleotide polymorphism, genetic risk score.

Outline:

1. Introduction

Diabetes mellitus is one of the most common medical conditions, affecting 12% of the general population and nearly 30% of people aged 65 and older in the US. Type 1 diabetes mellitus (T1DM) is characterized by insulin deficiency, in most cases caused by autoimmune destruction of insulin-producing beta-cells. Type 2 diabetes (T2DM) is characterized by insulin resistance and insulin deficiency. In most cases, insulin resistance is thought to arise first. People who are able to mount a sufficient hyperinsulinemic response (by increasing insulin secretion and/or reducing insulin clearance) are able to maintain normoglycemia despite insulin resistance. In this framework, failure of beta-cells to compensate for insulin resistance is the gateway to T2DM.

Abbreviations used in this paper: T1DM, type 1 diabetes mellitus, T2DM, type 2 diabetes mellitus; GWAS, genome-wide association studies; CP-DM, chronic pancreatitis associated diabetes mellitus; GRS, genetic risk score; MODY, maturity onset diabetes of the young; PCOS, polycystic ovary syndrome; SNP, single nucleotide polymorphism; LADA, latent autoimmune diabetes of adults; AUC, area under the curve; CP, chronic pancreatitis.

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Both T1DM and T2DM have a genetic component. Since the advent of genome-wide association studies (GWAS) nearly 20 years ago, a large number of genetic variants (single nucleotide polymorphisms, SNPs) have been discovered for both conditions, with larger and larger studies continuing to increase the number of SNPs. Of note, little overlap has been seen between T1DM and T2DM SNPs. T1DM SNPs have confirmed the importance of immune mechanisms in disease pathophysiology. An early lesson from T2DM genetic studies is that the beta-cell failure necessary for disease development has a strong genetic component.[1]

The availability of robust SNPs for T1DM and T2DM have made it possible to study whether genetic information can be applied clinically. Given that the effect on odds of disease for individual SNPs is modest, the most promising tool for application of genetics is the genetic risk score (GRS). GRS are calculated by taking the sum of disease-promoting SNP alleles (0, 1 or 2 for biallelic SNPs) at each susceptibility variant, with each weighted by its effect size (e.g., log of the odds ratio for association with diabetes). Not only are GRS more statistically powerful than individual SNPs, they are also a biologically relevant construct, given that GRS represent genetic burden broadly rather than by individual SNPs. After all, an individual's genetic risk is determined by the totality of risk-increasing alleles inherited from their parents. This review will describe the research examining use of GRS to both predict diabetes as well as to distinguish between different types of diabetes. It will also discuss possible future use of GRS to assist clinicians in selecting treatment for their patients with diabetes.

2. Genetic Risk Scores in the Prediction of Type 1 Diabetes

Approximately 50% of risk for T1DM is heritable. GWAS in T1DM have been conducted mainly in European origin cohorts and have focused on autoimmune T1DM. T1DM has a unique genetic profile as a polygenic disorder. Unlike other complex disorders such as T2DM, where all of the susceptibility variants have modest effects (odds ratios less than 1.4), genetic risk of T1DM is dominated by alleles and haplotypes of the Major Histocompatibility Complex (MHC), including HLA class I and HLA class II genes that confer >50% of the heritability of T1DM. The remaining landscape of T1DM genetics consists of over 100 non-HLA SNPs, most of which have odds ratios <1.3.[2,3] In aggregate, the HLA and non-HLA variants explain ~90% of the heritability of T1DM, also in contrast to T2DM. Given this unique genetic architecture, combining HLA tagging variants with even a handful of non-HLA SNPs in a GRS yields high predictive value for development of T1D, with area under the curve of the receiver operating characteristic (AUC) of 0.82-0.87.[4] HLA-tagging variants alone are highly predictive of T1DM (AUC 0.78-0.82), with addition of 9 non-HLA SNPs yielding similar AUC as addition of 40 SNPs (AUC 0.82-0.87), with the increment in predictive ability being statistically significant.[5] Several papers have focused on a GRS composed of 30 T1DM variants, including 5 SNPs that tag HLA class I and class II risk and protective alleles. A model combining clinical features (age at diabetes diagnosis and BMI), islet autoantibodies (GAD and IA-2), and the 30-SNP T1DM GRS achieved a very high AUC of 0.97 for prediction of T1DM defined clinically[6] and histologically.[7] Thus, T1DM GRS encompassing HLA and non-HLA variants have high promise for future clinical application, especially when used in concert with other risk factors.

While an impressive body of work (described above and below) has arisen from the 30-SNP T1DM GRS, its developers recently constructed an improved version (called the T1D-GRS2), based on 67 SNPs.[8] This GRS captures essentially all variation in the HLA region (accounts for 18 HLA DR-DQ haplotype combinations and their interactions, whereas the 30-SNP GRS tagged only 3 HLA haplotypes) as well as non-HLA genetic variation. The T1D-GRS2 was superior (AUC 0.921-0.927) in its ability to predict T1DM versus the original 30-SNP GRS (AUC 0.886-0.893).[8] It also outperformed the original GRS in its ability to distinguish T1DM from T2DM. Given the minimal genetic overlap between T1DM and T2DM, the GRS similarly discriminated T1DM from healthy controls as it did T1DM from T2DM. Given its more extensive coverage of the HLA region, the T1D-GRS2 performs well for T1D prediction and diabetes classification (AUC 0.90 discriminating T1DM from T2DM in a multi-ethnic cohort) in non-European racial and ethnic groups.[9,10] Furthermore, T1D-GRS2 recently showed promise in characterizing novel forms of diabetes, including immune checkpoint inhibitor-induced diabetes[11] and ketosis prone diabetes.[12] T1D-GRS2 was also able to detect decreased beta-cell function 9 months before T1DM diagnosis[13] as well as predict worsening beta-cell function after diagnosis.[14,15] T1D-GRS2 was associated with each transition in stages of T1DM, including autoantibody positive to stage 1, stage 1 to stage 2, and from stage 2 to stage 3 (clinical) T1DM.[16]

3. Genetic Risk Scores in the Prediction of Type 2 Diabetes

GWAS of common complex disorders such as T2DM have identified many SNPs, each with a marginal effect on risk.[17] Statistically, this has been represented by GRS. Early in the GWAS era, investigators assessed whether GRS could predict future T2DM. The early efforts that constructed the GRS based on low numbers of T2DM SNPs (16 to 19) found that addition of the GRS to clinical risk factors added minimally to the predictive value.[18-20] In contrast, more recent GRS based on higher numbers (>60) of SNPs

have demonstrated meaningful ability to predict T2DM, both alone as well as when combined with clinical risk factors. GRS composed of 65 SNPs have been found to significantly predict T2DM in European and Asian cohorts, with AUC of ~0.6.[21,22] Addition of GRS (based on 48 to 84 SNPs) to clinical predictors significantly increased the predictive value (yielding AUC of 0.71 to 0.84) as well improved model reclassification and discrimination properties.[22-26]

The above GRS were constructed based on SNPs associated with T2DM at genome-wide significance levels ($p<5x10-8$). It has been recently recognized that including additional SNPs that did not achieve genome-wide significance may improve the predictive ability of the GRS.[27] Algorithms and software have been developed to determine the optimal number of SNPs that should be included.[28,29] Addition of large scale GRS to clinical risk scores has been found to improve the ability to predict T2DM.[30-32] In a study of the UK Biobank (n=202,529, 3.7% incident T2DM), the AUC of a clinical score (based on age, sex, ethnicity, family history of diabetes, hypertension, BMI, and waist circumference) was 0.80, which improved to 0.83 with addition of large scale GRS.[33] In terms of clinical use of GRS, a drawback to such scores (typically based on hundreds of thousands of SNPs) is the complexity of their calculation and variability depending on the SNP genotyping platform used. It is most likely that initial GRS application in clinical scenarios will consist of GRS calculated using SNPs meeting genome-wide significance levels. Such defined lists of relatively common SNPs will be able to be derived from most genotyping platforms.

4. Genetic Risk Scores to Distinguish Different Types of Diabetes

Given that there is essentially no overlap between T1DM and T2DM genetic variants, GRS can be applied to distinguish between the two. Among 3,887 individuals, the 30-SNP GRS for T1DM and a 69-SNP GRS for T2DM were able to discriminate between the two types of diabetes, with better performance of the T1DM GRS (AUC 0.88) versus the T2DM GRS (AUC 0.64).[34] The 30-SNP T1DM GRS was investigated in 223 young adults with diabetes aged 20-40 (a group where there is often diagnostic uncertainty); the T1DM GRS was able to identify those who progressed to severe insulin deficiency <3 years from diagnosis and had low C-peptide (i.e., T1DM) with an AUC of 0.87.[34] Furthermore, T1DM GRS, autoantibody status, and clinical features (age of diagnosis, BMI) were independent and additive predictors of severe insulin deficiency (combined AUC 0.96), highlighting the potential clinical utility of GRS.[34] A similar T1DM GRS was used to estimate the prevalence of T1DM in a sample of 13,250 individuals who had developed diabetes in the first six decades of life; those identified by the T1DM GRS had lower BMI, earlier insulin requirement, and higher rates of diabetic ketoacidosis than those with T2DM.[35] The 30-SNP T1DM GRS also demonstrated utility in identifying unrecognized T1DM among patients with T2DM who require insulin treatment.[36] In a cohort of infants with neonatal diabetes, the 30-SNP T1DM GRS was able to distinguish maturity-onset diabetes of the young (MODY) from T1DM.[37] In concert with autoantibody testing, the 30-SNP T1DM GRS was able to exclude people with T1DM from inappropriate genetic testing for monogenic diabetes.[38] Another study determined GRS for T1DM (based on 47 SNPs and 23 variants in the HLA region) and T2DM (based on 72 SNPs) in young adults with clinically-defined T1DM, latent autoimmune diabetes of adults (LADA), or T2DM.[39] Similar to the findings above, the T1DM GRS (AUC 0.80) was better able to discriminate T1DM vs T2DM than the T2DM GRS (AUC 0.64). Higher T1DM GRS was associated with younger age of diabetes onset, undetectable C-peptide, and insulin as initial treatment while higher T2DM GRS was associated with diet or oral therapy vs insulin therapy. Genetically, those with T1DM and LADA were indistinguishable, suggesting that LADA is a particular presentation of T1DM, rather than a distinct condition or an intermediate trait between T1DM and T2DM. Thus, not only can GRS separate different types of diabetes, it may also reveal whether certain types arise from similar etiologies. This was supported by subsequent GWAS for LADA, which found that the leading genetic signals for LADA are shared with T1DM; reduced effect size of HLA alleles and other subtle genetic differences (including possible contribution from T2DM genes) may explain the later age of presentation and slower progression rate versus childhood T1DM.[40,41]

The T1D-GRS2 outperformed the 30-SNP T1DM GRS in its ability to distinguish T1DM from T2DM. Given the minimal genetic overlap between T1DM and T2DM, the GRS similarly discriminated T1DM from healthy controls as it did T1DM from T2DM. Given its more extensive coverage of the HLA region, the T1D-GRS2 performs well for T1D prediction and diabetes classification (AUC 0.90 discriminating T1DM from T2DM in a multi-ethnic cohort) in non-European racial and ethnic groups.[9,10] Furthermore, T1D-GRS2 recently showed promise in characterizing novel forms of diabetes, including immune checkpoint inhibitor-induced diabetes11 and ketosis prone diabetes.[12]

T3cDM is a term used to describe diabetes that occurs with diseases of the exocrine pancreas, including acute and chronic pancreatitis (CP) and pancreatic cancer. T3cDM accounts for approximately 2% of cases of diabetes, with 66% of cases occurring after acute pancreatitis, 18% of cases arising in association with pancreatic cancer, 14% of cases arising with chronic pancreatitis, and 2% of cases related to cystic fibrosis.[42] Despite the fact that pancreatitis is responsible for 80% of cases of T3cDM, the pathophysiology of post-pancreatitis diabetes is unknown; it is thought that the pancreatitis-induced inflammation may lead to beta-cell dysfunction and/or insulin resistance.[43] To date, there has been no published large scale GWAS for any type of T3cDM. Until that becomes available, investigators have used robust T2D GRS to investigate T3cDM. The first such study hypothesized that if diabetes mellitus associated with CP (CP-DM) is truly a distinct disease entity, patients with CP-DM should be genetically distinct (in terms

of genetic risk variants for diabetes) from patients with typical T2DM.[44] The study included 1,631 subjects from the North American Pancreatitis Study 2 (NAPS2) and 2,685 subjects from the Multi-Ethnic Study of Atherosclerosis (MESA), all of European origin. Sixty SNPs robustly associated with T2DM in genome-wide association studies were used to construct a GRS (weighted sum of T2DM risk-increasing alleles). The mean GRS was identical between 321 subjects with RAP/CP-DM and 423 subjects with T2DM, and the GRS of each diabetic group was significantly higher than that of 3,554 non-diabetic controls.[44] Exploratory analyses attempting to enrich the T3cDM group for pancreatogenic diabetes, such as eliminating diabetes diagnosed before CP, requiring pancreas-specific comorbidities, or removing those with a family history of diabetes, did not improve the ability of the GRS to distinguish between CP-DM and T2DM. These data suggest that CP-DM may be a subtype of T2DM, whereby individuals at genetic risk for T2DM progress to diabetes due to beta-cell function being compromised by CP. Regardless of whether CP-DM is distinct from T2DM, the occurrence of diabetes in patients with CP greatly increases their morbidity, necessitating ways to predict which patients with CP will develop diabetes. Given that the above study established that aggregate genetic predisposition for T2DM is a risk factor for CP-DM, studies are underway to determine whether addition of a T2DM GRS to a clinical prediction model[45] will improve its performance.

5. Genetic Insight in the Heterogeneity of T2DM Pathophysiology

A recent large-scale GWAS meta-analysis for T2DM included over 2.5 million participants (428K with T2D) and discovered 1289 independent SNPs in 611 loci.[17] This study went on to cluster the 1289 SNPs based on their association with 37 cardiometabolic traits (e.g., BMI, SBP, HDL cholesterol), yielding eight mechanistic clusters (beta-cell with high proinsulin, beta-cell with low proinsulin, obesity, lipodystrophy, liver/lipid, metabolic syndrome, residual glycemic, body fat) representing diverse pathways to T2DM.[17] The names assigned to each cluster reflected their patterns of associations with the cardiometabolic traits. For example, the lipodystrophy SNPs were associated with increased triglycerides, low HDL cholesterol, high liver fat percentage, low gluteofemoral adipose tissue volume, and low body fat percentage. To validate the cluster assignments, the investigators evaluated the association of each cluster in cohorts with deep phenotyping of insulin secretion (by homeostatic model assessment of beta-cell function or oral glucose tolerance test) and with insulin sensitivity (by homeostatic model assessment of insulin resistance or euglycemic clamp). As expected, the beta-cell with high proinsulin and the beta-cell with low proinsulin clusters were associated with decreased insulin secretion. The body fat, metabolic syndrome, obesity, and lipodystrophy clusters were associated with decreased insulin sensitivity. The residual glycemic and liver/lipid clusters were associated with both decreased insulin secretion and decreased insulin sensitivity.

The clusters also exhibited differential association with regions of open chromatin (i.e., regions with active gene expression)[17]; for example, SNPs in both beta-cell clusters were highly associated with open chromatin in islet tissues including fetal islet, alpha, beta, and gamma cells. Metabolic syndrome SNPs were found in open chromatin in fetal mesangial cells, fetal endothelial cells, and pericytes. Lipodystrophy SNPs were predominantly found in open chromatin for adipocytes. These results not only reinforce the distinct processes underlying each cluster but also provide insight into their mechanisms.

The clusters may also have value in determining whether specific components of diabetes pathophysiology differentially explain complications of diabetes. In terms of microvascular complications, an obesity cluster GRS was associated with the highest risk of end stage diabetic nephropathy whereas the beta-cell with high proinsulin GRS was associated with a lower rate of this complication.[17] On the other hand, several clusters, including beta-cell with high proinsulin, body fat, and obesity, were associated with proliferative diabetic retinopathy. Regarding the macrovascular outcomes of coronary artery disease, ischemic stroke, and peripheral artery disease, only the obesity cluster GRS was associated with all three.

The T2D SNP clusters can also provide insights into the pathophysiology of conditions related to diabetes. For example, SNPs in the beta-cell with high proinsulin cluster were strongly associated with gestational diabetes and SNPs in the obesity cluster were associated with polycystic ovary syndrome (PCOS), highlighting the importance of deficiencies in insulin secretion in gestational diabetes and insulin resistance in PCOS.[17] The obesity cluster association with PCOS aligns well the widely accepted notion that insulin resistance is common in PCOS as well as with Mendelian randomization studies demonstrating that obesity is a causal factor for PCOS.[46]

A recent study evaluated association of GRS for the eight subclusters of T2D SNPs with CP-DM.[47] The insulin resistance clusters (body fat, lipodystrophy, obesity, and metabolic syndrome) exhibited the strongest association with CP-DM. This suggests that genetically-driven insulin resistance is a key factor in CP-DM. The beta-cell failure that is necessary for diabetes to develop is most likely related to islet damage from pancreatitis, rather than genetically-driven beta-cell failure.

6. Potential for GRS in Precision Medicine

While GRS for diabetes overall may enhance prediction when added to clinical models (especially for T1DM), the availability of subsets of T2D GRS that correspond to specific pathophysiologic processes raises the possibility of their use in precision medicine. In contrast to T1DM, wherein insulin is the main treatment, there are over a dozen different types of medications that are available for use in T2D, including sulfonylureas, biguanides

(metformin), rapid acting insulin secretagogues, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, amylin analogs (pramlintide), colesevelam, quick-release bromocriptine, sodium glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide-1 receptor (GLP-1) receptor agonists, dual GLP-1/glucose-dependent insulinotropic polypeptide (GIP) receptor agonists (tirzepatide), and insulin. This highlights the need for ways to choose the right medication for the right patient.

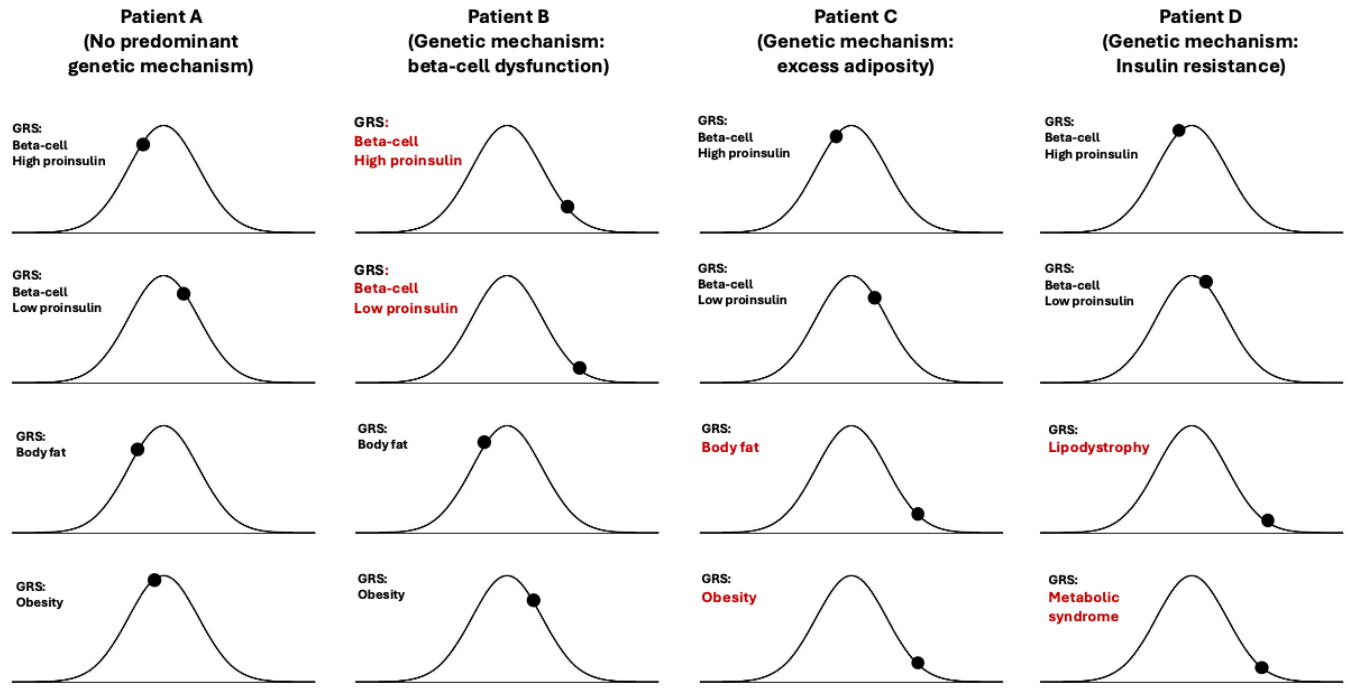
Until recently, metformin was widely recommended as the first line agent for treatment of T2DM, with little attention to specific patient details. Currently, more attention is being paid to whether the patient has risk factors for or a history of coronary artery disease, heart failure, or chronic kidney disease, for which cases GLP-1 receptor agonists or SGLT-2 inhibitors may be considered as initial therapy instead of metformin. This represents progress, but is focused on complications of diabetes. It would be preferable to tailor medication choices based on underlying pathophysiologic processes that lead to diabetes in the first place. It is feasible that in the future, genome-wide SNP genotyping or even whole genome sequencing will become routinely available in health care. At that point, GRS for any condition can be calculated in patients, as long as large-scale GWAS for the condition have identified the SNPs to use in GRS construction. Let us imagine four patients who were recently diagnosed with T2DM. In all four patients, their physician has obtained their GRS for subclusters of T2DM SNPs (Figure 1).

GRS in populations have a normal distribution. Thus, ~68% of individual patient GRS scores will fall within one standard deviation and 95% of individual patient GRS scores will fall within two standard deviations of the population mean. GRS scores falling near the mean may not be clinically relevant. Patient A represents such a patient, in which case genetic information will not be useful in determining how to treat their diabetes. In such cases, clinical features and patient preference can be used to choose initial treatment. On the other hand, Patient B, while having close to average scores for body fat and obesity GRS, has extreme values for the two beta-cell GRS. This suggests that genetically deficient insulin production is a key factor in the genesis of their diabetes. This patient may benefit from early treatment with insulin. Whether such patients could be treated with sulfonylureas or rapid-acting insulin secretagogues would need future research. There is precedent in MODY (monogenic conditions characterized by beta-cell deficiency), in which sulfonylurea treatment is very effective for specific types of MODY.

Patients C and D both have near average values for the two beta-cell GRS. Patient C has extreme values for body fat and obesity GRS. As genetically-driven excess adiposity may be a key factor in their diabetes, they may benefit from diabetes medications that potently induce weight loss, such as GLP-1 receptor agonists or dual GLP-1/GIP receptor agonists. Patient D has extreme values for lipodystrophy and metabolic syndrome GRS. This patient may benefit most from insulin sensitizing medications such as metformin or thiazolidinediones.

While using genetic information to choose initial diabetes treatment is an attractive notion, much work needs to be done before this can become a reality. Once genome-wide data become widely available clinically, clinical trials will have to be conducted to determine whether GRS-

Figure 1. Example Patient GRS



guided treatment leads to improved outcomes compared to clinically-guided treatment. Reference ranges will need to be established and will vary by race. The fact that most GWAS have studied predominantly European-origin individuals will pose a major challenge to the use of GRS in other race/ethnic groups. Trials will be needed to determine whether specific GRS profiles respond to specific agents. Cost-effectiveness analyses will also need to be conducted, especially because it remains to be determined how many patients will resemble Patient A (GRS not useful) versus the more informative patients with extreme GRS values. Ultimately, GRS data may serve as one more datapoint that health care providers use to make decisions, with GRS data being taken into consideration jointly with clinical features (e.g., chronic kidney disease suggesting use of an SGLT-2 inhibitor), cost issues (e.g., which medications are covered by insurance), and patient preferences (e.g., patient refuses to use injectable medications).

7. Conclusion

While genome-wide genotyping is not yet widely available in clinical settings, it is not hard to envision a future when this becomes commonplace. That will be an opportunity to determine whether years of research in GRS can be used to create tools to improve the ability to predict diabetes, classify or distinguish between different types of diabetes (especially in patients with uncertain diagnoses), and to select treatments that target the main underlying physiologic deficits in each patient with diabetes.

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Corresponding Author:

Mark O. Goodarzi, MD, PhD
Division of Endocrinology, Diabetes, and Metabolism
Cedars-Sinai Health Science University
Los Angeles, CA, USA
mark.goodarzi@cshs.org

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