COMMENTARY

Found in Translation: A Type 1 Diabetes Genetic Risk Score Applied to Clinical Diagnosis

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We are entering a new era in which the explosion of genomic and biological information across multiple developmental and metabolic states is poised to transform the practice of medicine (1). It is now possible to center scientific investigation in the key model organism, the human, and to deploy modern technologies to acquire an unprecedented trove of biological data at multiple time points in the life of an individual (2).

The genomic revolution illustrates how big data sets can begin to yield biological and clinical insight. Concurrent advances in genotyping and sequencing technologies, in our understanding of human genetic variation, and in the statistical methodologies needed to interpret genetic findings have all led to a meteoric expansion in genetic knowledge (3). Meta-analyses of genome-wide association studies (GWAS) and ongoing comprehensive sequencing experiments are yielding a plethora of genetic associations from an agnostic vantage point, which can open unsuspected windows into the pathophysiology of metabolic phenotypes, including type 1 (4) and type 2 (5,6) diabetes.

However, whether this emerging body of knowledge will deepen our understanding of health and disease and lead to improved outcomes in public health remains to be seen. A frequent criticism of large-scale genomic studies is that so far they have failed to deliver on the hyped hopes that the human genome would usher in personalized medicine. Given the empirical observation that most genetic effects for complex phenotypes are modest, skeptics rightly argue that their utility for individualized prediction has not been proven, and they jump to conclude that the substantial public investment in resources, effort, and human capital in this line of investigation has been a wash.

Geneticists may counter that skeptics seem to ignore how genetic studies have illuminated pathophysiological mechanisms that remained obscure, such as the seminal involvement of neuronal circuits in the genesis of obesity (7), the primary role of genetically driven β-cell failure in type 2 diabetes (8), or the significant overlap of gene sets in autoimmunity (9). Genetic studies have identified drug targets that were either known (e.g., *PPARG* for thiazolidinediones [10], *ABCC8/KCNJ11* for sulfonylureas [11], and *HMGCR* for statins [12]) or completely novel (*PCSK9* [13]), illustrating that actionable biology can be detected through these approaches. Human geneticists also argue that not enough time for clinical translation has elapsed since many of these findings came to light, in comparison with the time scales required for the translation of other fundamental discoveries such as the cause of AIDS or the contribution of dyslipidemia to coronary artery disease.

Nevertheless, it is fair to admit that the penetration of nascent genetic findings into the clinic, particularly for prediction and diagnosis, has been timid at best. Our track record for the past decade does raise the question of whether precision medicine will ever become a reality, or it will remain science fiction.

The article by Oram et al. (14) in this issue of *Diabetes Care* is an elegant first step in the right direction. Cognizant of the modest effect of single variants on disease risk but aware of the growing list of single nucleotide polymorphisms (SNPs) associated with type 1 (15) and type 2 (16) diabetes, the authors aggregated the risk alleles at all diabetes-associated SNPs to construct genetic risk scores (GRSs) that together explain a larger proportion of the variance in each of the two types, and thereby increase statistical power. This is particularly pertinent for type 1 diabetes, which is somewhat unique among complex diseases in that its genetic architecture combines a very strong effect at the *HLA* region with a multitude of weaker effects at other loci. Thus, a GRS for type 1 diabetes, which includes two SNPs that tag the high-risk *HLA* haplotypes DR3 and DR4-DQ8 (and thus

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goes beyond classic *HLA* typing), achieves an area under the receiver operating characteristic curve (c-statistic) as high as 0.88 (with 1.0 indicating 100% sensitivity and specificity). In contrast, the GRS for type 2 diabetes, which does not include genetic markers as strong as *HLA* for type 1 diabetes, only achieves a c-statistic of 0.64, consistent with prior publications (17,18). Although the mean type 1 diabetes GRS was significantly higher in type 1 diabetes cases than in type 2 diabetes cases (0.279 vs. 0.229), there was substantial overlap between the two distributions.

Having established the technical and clinical validity of the GRS for type 1 diabetes, Oram et al. (14) point the way to its clinical utility by estimating sensitivity and specificity rates at various thresholds in an attempt to improve separation. A GRS of >0.280 to diagnose type 1 diabetes would exclude 95% of those without type 1 diabetes (specificity) but would only capture 50% of all type 1 diabetes cases (sensitivity); similarly, when dialed to >0.234 the same GRS would detect 95% of all type 1 diabetes cases but only exclude 53% of those without.

These scores were initially tested in the data set from the Wellcome Trust Case Control Consortium. To the extent that this consortium contributed to the GWAS meta-analyses that identified some of the same SNPs included in the GRS, the discovery and validation data sets are not completely independent, allowing for the potential of overfitting. To allay this concern and provide additional clinical insight, Oram et al. (14) tested their type 1 diabetes GRS in the independent South West England cohort of 223 participants with diabetes diagnosed between the ages of 20 and 40 years. Their clinical outcome was severe insulin deficiency, defined as the need for continuous insulin treatment earlier than 3 years from diagnosis in the setting of a documented low C-peptide. In this context, the type 1 diabetes GRS performed similarly as before, with a c-statistic of 0.87 and sensitivity and specificity rates comparable to those attained in the Wellcome Trust Case Control Consortium. Interestingly, the GRS provided information that was orthogonal to that furnished by clinical predictors such as autoantibody status, BMI, and age at diagnosis.

It thus appears that these forward-looking investigators have generated an innovative genetic tool that may be helpful in specific clinical situations (Fig. 1). The unmet medical need arises from the critical differences in the therapeutic approaches to newly diagnosed type 1 versus type 2 diabetes, and the risks involved in making the wrong prescription decision. A person with type 1 diabetes who is misdiagnosed may not receive insulin at first and thus be exposed to life-threatening diabetic ketoacidosis; conversely, a person with type 2 diabetes who is mistakenly thought to have type 1 diabetes will receive insulin injections unnecessarily (but not unsafely, as his or her diabetes could still be well treated). Such diagnostic challenges include the obese, antibody-negative patient with type 1 diabetes and the lean, antibody-positive young patient with type 2 or monogenic diabetes. Such cases do exist, in that obesity has become much more prevalent (and can therefore affect patients with autoimmune diabetes) and autoantibody testing in clinical practice, where only one autoantibody might be checked at a single point in time, is not 100% discriminatory. In this sense, the age bracket examined by the authors (20–40 years) is particularly pertinent, and the finding that genetic testing complements other clinical features is appealing. Further advantages of genetic testing include that it only needs to be done once in the individual's lifetime, it is not dependent on the disease time course, and it can be done cheaply and accurately. Capitalizing on its technical validity and having proven its clinical validity, studies that demonstrate further clinical utility (e.g., in other ethnic groups or in specific clinical scenarios) would help advance the field.

In the end, the clinician's ability to absorb, assimilate, and translate genomic information will likely determine the extent of its impact on public health. Currently, clinicians trained in the most advanced settings are still woefully unprepared to make meaningful use of the data accumulating at a dizzying scale. Which pieces of information are clinically actionable and should be incorporated

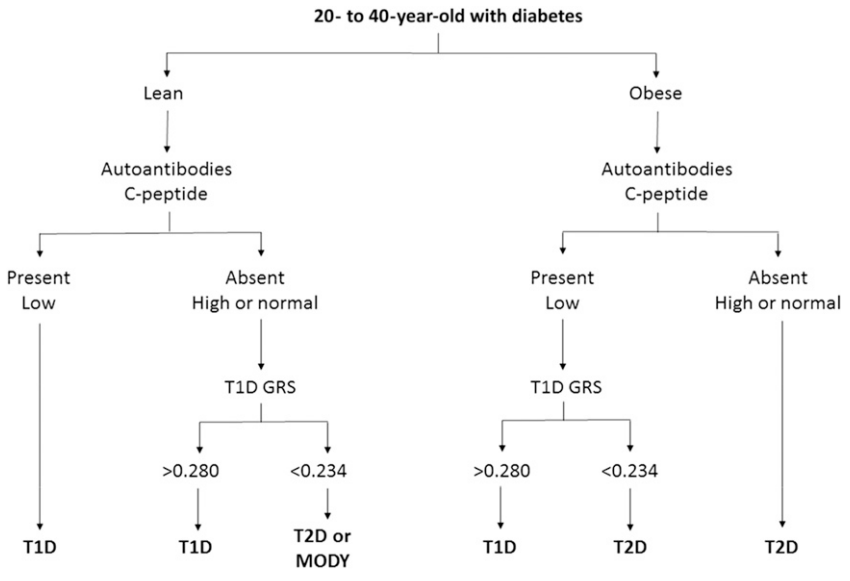

Figure 1—Potential use of the type 1 diabetes GRS described here in challenging clinical scenarios. The typical situation involves newly diagnosed diabetes in a young patient (20–40 years of age). A lean body habitus, particularly in people of European descent, would usually point toward type 1 diabetes (or more rarely monogenic diabetes), whereas an obese patient, particularly of African, Hispanic, Middle Eastern, or South Asian ancestry, is more likely to have type 2 diabetes. The presence of autoantibodies and low or undetectable C-peptide would confirm type 1 diabetes in the lean patient, and the absence of autoantibodies and normal or high levels of C-peptide would confirm type 2 diabetes in the obese patient. Where autoantibodies and C-peptide results seem counterintuitive, the T1D GRS may help guide the diagnosis toward or away from type 1 diabetes, particularly if very high (>0.280) or very low (<0.234) (see text for details). T1D, type 1 diabetes; T2D, type 2 diabetes; MODY, maturity-onset diabetes of the young.

into medical practice need to be tested in a rigorous fashion, weighed rationally, acted upon, and disseminated in a didactic manner. The article by Oram et al. (14) exemplifies how this can be done.

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