Leveraging Genetics to Improve Cardiovascular Health in Diabetes: The 2018 Edwin Bierman Award Lecture

Alessandro Doria

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The past decade has witnessed an exponential increase in our ability to search the genome for genetic factors predisposing to cardiovascular disease (CVD) and in particular coronary heart disease (CHD). Identifying these genes could lead to the development of innovative strategies to prevent the cardiovascular complications of diabetes by allowing us to *1*) create predictive algorithms for the identification of patients at especially high risk of CVD so that these individuals can undergo preventive interventions early in the natural history of the disease; *2*) discover as yet unknown disease pathways linking diabetes to atherosclerosis, which can be used as targets for the development of new CVD-preventing drugs specifically directed at subjects with diabetes; and *3*) devise personalized programs increasing the cost-effectiveness of preventive interventions by tailoring them to the genetic background of each patient. Substantial progress has been made in each of these three areas as exemplified by the recent development of a CHD genetic risk score improving CHD prediction among subjects with type 2 diabetes, the discovery of a diabetes-specific CHD locus on 1q25 pointing to glutamine synthase (*GLUL*) and the γ-glutamyl cycle as key regulators of CHD risk in diabetes, and the identification of two genetic loci allowing the selection of patients with type 2 diabetes who may especially benefit from intensive glycemic control. Translating these discoveries into clinical practice will not be without challenges, but the potential rewards, from the perspective of public health as well as that of persons with diabetes, make this goal worth pursuing.

Despite better glucose-lowering therapies and better control of other cardiovascular risk factors, people with diabetes continue to experience a two- to fourfold higher cardiovascular risk than subjects without diabetes (1), making cardiovascular disease (CVD) (including coronary heart disease [CHD], peripheral artery disease, and cerebrovascular disease) one of the most frequent chronic complications of diabetes. Cardiovascular risk is especially high among patients with type 2 diabetes (T2D) due to the proatherogenic comorbidities such as insulin resistance, hypertension, and dyslipidemia that accompany this form of the disease (2). While efforts are being made to curb the ongoing diabetes epidemic, new strategies must be developed to avoid the adverse cardiovascular effects of diabetes when this cannot be prevented. In particular, there is the need for new preventive programs that, by targeting the mechanisms linking the metabolic alterations of diabetes to atherosclerotic disease, are specifically directed to subjects with diabetes.

IMPROVING PREVENTION OF CVD IN DIABETES THROUGH GENETICS

The approach taken toward this goal by my group and others has been to leverage genetics. Genetic factors have been known for many years to modulate the development and progression of CVD. This evidence has been mainly gathered in the general population (3), but a few studies have shown that the genetic factors are involved in CVD etiology among subjects with diabetes as well. For example, in a study by Wagenknecht et al. (4), 40% of the variance of coronary calcium content (an index of atherosclerotic burden) was accounted for by familial, presumably genetic factors. The estimate was minimally affected by adjustment for HDL cholesterol, BMI, or hypertension, indicating that this effect was not due to familial clustering of traditional risk factors. Similar heritability estimates (41% after adjustment for other risk factors) have been obtained using carotid-intima thickness as an index of subclinical

Research Division, Joslin Diabetes Center, Boston, MA
Department of Medicine, Harvard Medical School, Boston, MA
Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA

Corresponding author: Alessandro Doria, alessandro.doria@joslin.harvard.edu

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atherosclerosis (5). As schematically illustrated in Fig. 1, identifying the genetic factors shaping the individual susceptibility to CVD can serve three purposes.

1. Development of predictive algorithms allowing the early identification of patients at especially high risk of CVD so that these individuals can undergo preventive interventions early in the natural history of diabetes, before the onset of significant CVD.
2. Discovery of as yet unknown cellular pathways that link the metabolic alterations of diabetes to atherosclerosis and that can serve as targets for the development of new CVD drugs specifically directed at subjects with diabetes.
3. Personalization of CVD prevention programs that are based on a genetically determined sensitivity of individual patients to pharmacological or lifestyle interventions.

Below, I first provide a brief summary of the findings of genetic studies of CVD obtained to date in the general population, focusing on CHD since this has been the most studied cardiovascular outcome. I then discuss the relevance of these findings to the population with diabetes, with special emphasis on the latest developments in each of the three areas discussed above.

THE SEARCH FOR GENES PREDISPOSING TO CHD IN THE GENERAL POPULATION

The past decade has witnessed a major paradigm shift in our ability to search for genetic factors contributing to complex disorders. Until 2006, limitations of genotyping technology restricted studies to a small number of candidate genes selected on the basis of the incomplete knowledge of disease pathophysiology available at the time of the investigation. With the advent of new platforms allowing the interrogation of hundreds of thousands, if not millions, of genetic loci in a single assay, and with the genome-wide characterization of the correlation among genetic variants (so called linkage disequilibrium), it has become possible in the past 12 years to conduct genome-wide association studies (GWAS) allowing the screening of the entire genome for common genetic variants contributing to human disorders without the need for a priori hypotheses (6). This approach has been extensively applied to CHD, leading as of December 2017 to the identification of 204 single nucleotide polymorphisms (SNPs) at 160 genomic locations that are associated with CHD in the general population at genome-wide significant levels ($P < 5 \times 10^{-8}$, to account for an average of about 1 million independent SNPs investigated in each study) (7–17). A summary of these findings is provided in Fig. 2, in which the strength of the association between each SNP and CHD, as estimated by odds ratios (ORs), is plotted against the SNP position along the genome. As in the case of other multifactorial disorders, the magnitude of these genetic effects is rather modest, with ORs that are in most cases smaller than 1.2 (as compared with OR >2.0 for traditional CHD risk factors such as male sex or smoking). The weakness of these effects can be explained by the location of the vast majority of these SNPs in noncoding, regulatory regions of the genome, where they exert subtle effects on gene expression rather than affecting protein function. It also relates to the fact that due to the need to maximize power and to the finite number of SNPs that can be included in genotyping arrays, GWAS have been limited to common variants, which are such because of their relatively benign nature.

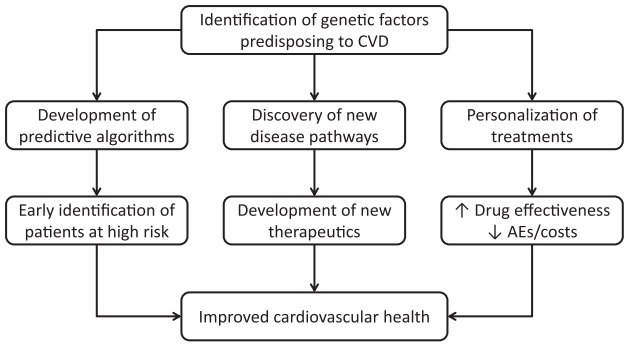

Figure 1—Schematic representation of the potential applications of genetic research on CVD in diabetes. AE, adverse events.

LEVERAGING GENETICS TO DEVELOP PREDICTIVE ALGORITHMS

Using genetic data to improve disease prediction is perhaps the most obvious application of genetic research on CHD. It is also the most ambitious as it requires strong genetic effects, which, as noted above, are not the norm for CHD or, for that matter, for any other complex disorder. Indeed, the predictive ability of individual SNPs pales in comparison with that of traditional cardiovascular risk factors such as serum cholesterol or blood pressure. However, the large number of genetic markers found to be associated with CHD raises the possibility of increasing the predictive usefulness of these markers by considering them in aggregate, for instance by building genetic risk scores (GRS) obtained by summing the number of risk alleles carried by a person at each CHD locus. Efforts based on this approach were initially disappointing due to the small number of genetic markers that were available when these studies were carried out and the rudimental way in which predictive performance was measured (18). However, more recent studies, taking full advantage of the abundant crop of CHD loci identified to date, indicate that this strategy can be effective (19–21).

This is exemplified by a study that we recently conducted in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial—a large cohort of patients with T2D at high cardiovascular risk who took part in a large clinical trial testing the effectiveness of intensive glycemic, blood pressure, and serum lipid controls in preventing CVD events (22). Among white subjects in this cohort

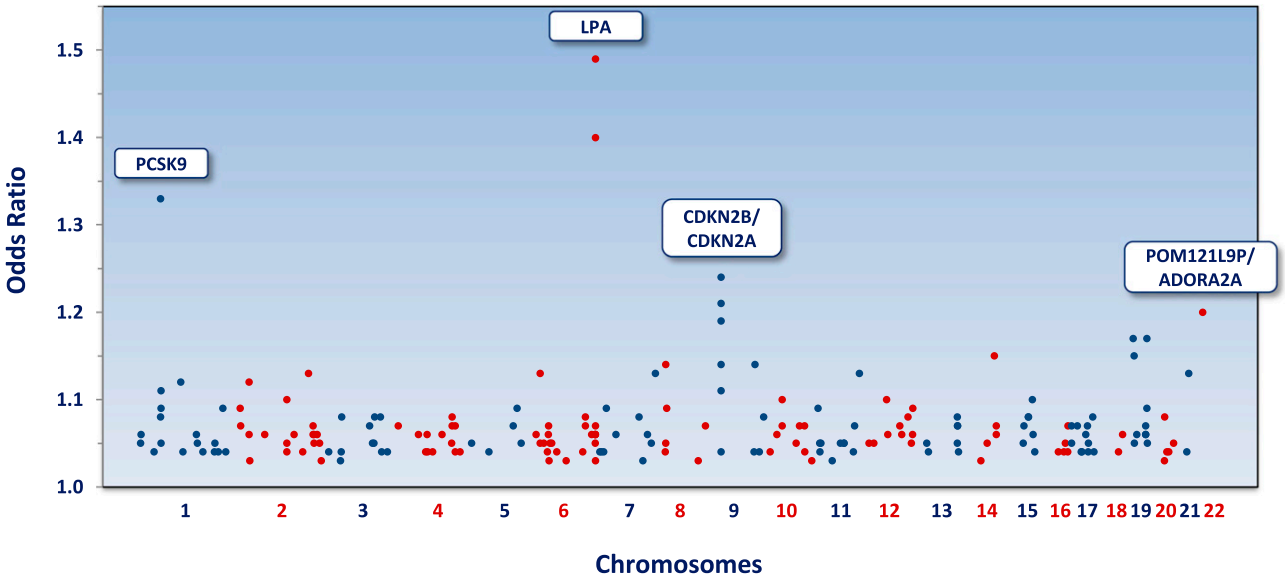

Figure 2—Loci identified as being associated with CHD as of December 2017. Each dot represents a SNP independently associated with CHD. Data are from references 7–17. Symbols of genes adjacent to associations with OR ≥1.2 are reported above the corresponding dots. *ADORA2A*, adenosine A2a receptor; *CDKN2A/CDKN2B*, cyclin dependent kinase inhibitor 2a/2b; *LPA*, lipoprotein(A); *PCSK9*, proprotein convertase subtilisin/kexin type 9; *POM121L9P*, POM121 transmembrane nucleoporin like 9, pseudogene.

(n = 5,360), a GRS based on all 204 SNPs reported in Fig. 2 (GRS_{204}) was strongly associated with a positive CVD history at study entry (OR per GRS_{204} SD 1.40, 95% CI 1.32–1.49, $P = 3 \times 10^{-27}$) as well as with an increased risk of major CHD events during follow-up (average follow-up length 4.9 years; hazard ratio [HR] per GRS_{204} SD 1.27, 95% CI 1.18–1.37, $P = 4 \times 10^{-10}$) (19). As shown in Fig. 3*A*, this translated into an increase in the risk of major CHD events of 50% for individuals in the second GRS_{204} tertile and 76% for those in the third GRS_{204} tertile as compared with those in the first—an effect that was not influenced by the interventions investigated in the trial. The association between GRS_{204} and CHD was confirmed in another cohort of patients with T2D (the Outcome Reduction With Initial Glargine Intervention [ORIGIN] trial), indicating that, in aggregate, the CHD loci identified in the general population are associated with CHD also among people with diabetes.

In terms of performance as predictor of CHD events, if evaluated by traditional methods such as the area under

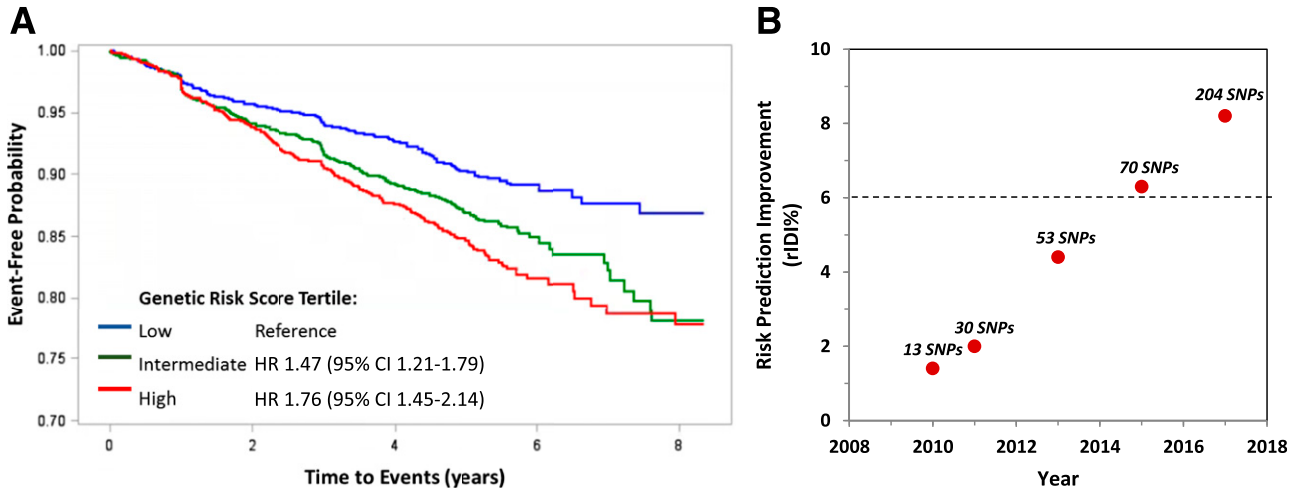

Figure 3—Association of GRS with CHD. *A*: Kaplan-Meyer curves for major CHD events (MCE) stratified by tertiles of a GRS derived from 204 SNPs in the ACCORD clinical trial. *B*: Improvement in the MCE discrimination (rIDI%) provided by GRS according to the number of SNPs associated with CHD that were available from 2010 to 2017. The number of SNPs used for each GRS is provided above each estimate. Adapted from Morieri et al. (19).

the receiver operating characteristic curve, the GRS_{204} did not add much information to a predictive model based on clinical risk factors such as age, sex, history of CHD, total and HDL cholesterol, smoking, and hypertension (area under the curve difference +0.007, $P = 0.04$). However, if performance was evaluated using more advanced methods based on the ability to reclassify patients' risk, such as the relative integrated discrimination index (rIDI) and net reclassification improvement (23), the GRS_{204} showed a substantial improvement in prediction when added to clinical risk factors. In particular, addition of the GRS_{204} led to an rIDI improvement of 8%—a value above the threshold of 6% that was used by the American Heart Association (AHA) and American College of Cardiology (ACC) to decide whether a new biomarker was worth the addition to the AHA-ACC equation to predict the risk of atherosclerotic cardiovascular disease (ASCVD) (24). It should also be noted that the GRS's performance may increase in the future with the discovery of additional genetic loci associated with CHD, as has happened during the past decade (Fig. 3*B*). While the improvement in predictive performance associated with each additional variant is progressively decreasing due to the smaller genetic effects that are being identified, this could be offset by the increased pace of discovery of new variants associated with CHD made possible by the increasingly large genetic studies and new sequencing technologies. But even if the GRS performance does not increase in the future, this is already at a level warranting its introduction into clinical practice. The ability to identify patients with diabetes at especially high cardiovascular risk very early in the natural history of the disease (theoretically, as early as at birth) would improve allocation of resources and increase the power of clinical trials of new interventions by allowing selection of participants at high risk of cardiovascular events. In clinical practice, sharing this information with patients may enhance motivation and improve adherence to preventive treatments.

LEVERAGING GENETICS TO DISCOVER NEW DISEASE PATHWAYS

There has been much research on how diabetes may foster atherogenesis, and some possible mechanisms have emerged, such as the induction of oxidative stress by hyperglycemia, the formation of advanced glycation end products, and activation of protein kinase C (25). Alterations of lipid metabolism, either induced by diabetes or part of the insulin resistance syndrome that precedes and accompanies T2D, have also been implicated (25). However, while these pathways may play a role, their identification has not yet led to the development of novel interventions to prevent CVD that are specifically aimed at severing the link between the diabetic milieu and CVD. Given the complexity of atherosclerosis, there may be other mechanisms linking diabetes to atherogenesis that could be more easily targeted with interventions. The idea then is to try to identify these as yet unknown pathways by leveraging the information about the function of the genetic variants associated with CVD. It should be emphasized that pursuing this goal does not require the same large genetic effects that are necessary for prediction purposes. Since the magnitude of a genetic effect depends more on the severity of the genetic variant (in terms of disruption of genomic function caused by the nucleotide substitution) than the biological relevance of the pathway affected by it, even a modest genetic signal resulting from a "mild" genetic variant can point, if statistically robust, to an important biological node between diabetes and CVD.

If we assume that the variants in Fig. 2 affect CHD risk by affecting nearby genes, some of these CHD loci appear to involve pathways that are known to play a role in lipid metabolism and atherogenesis such as those including the products of *PCSK9* (1p32), *LPA* (6q25), *LPL* (8p21), *LDLR* (19p13), *APOA*1 (11q23), *APOB* (2p24), and *APOE* (19q13). However, in the vast majority of cases, no obvious candidate genes can be found in the vicinity of the CHD-associated SNPs. Thus, the 160 CHD loci (204 SNPs) identified to date offer unprecedented potential for the "out of the box" identification of new mechanisms of disease, which would be difficult if not impossible through the incremental increase in knowledge offered by pathophysiology studies. An example of this is the signal on chromosome 9p21—the first locus found to be associated with CHD through a GWAS and one of the strongest and most replicated ones to date (26–28). While the exact mechanisms of this genetic effect have not been elucidated yet, they appear to involve differences in the expression of *CDKN2A* and *CDKN2B*—two nearby genes coding for inhibitors of cyclin-dependent kinases (p16 and p 15) that control cell proliferation and aging and are highly expressed in endothelial and inflammatory cells (29). Alterations of cell cycle determining a proliferative phenotype of vascular cells such as smooth muscle cells had already been implicated in atherogenesis (30), but these findings have given new strength to this hypothesis. Of note, as we have shown in the Joslin Heart Study, the effect of the 9p21 locus appears to be especially strong among people with T2D due to an interaction between the risk allele and poor glycemic control (31). This raises the hypothesis that a proliferative cell phenotype may act as a permissive factor for the atherogenic effects of hyperglycemia. If this is proven, the pathways controlled by p16 and p15 would become a prime target for interventions aimed at severing the link between high glucose and atherosclerosis, although the potential adverse effects of targeting the mechanisms controlling cell cycle and proliferation will have to be carefully investigated.

These findings also suggest the possibility that other genetic effects interacting with hyperglycemia or other metabolic alterations of diabetes may exist and that for some of these loci, the interaction may be so strong that the genetic effect can only be observed in the presence of diabetes. If this hypothesis is true, identifying these

genetic effects may be especially illuminating for our understanding of the etiology of atherosclerosis in diabetes. Based on this premise, we conducted a GWAS for CHD specifically among patients with T2D (32). This was a collaboration among the Nurses' Health Study (NHS), Health Professionals Follow-Up Study (HPFS), Joslin Heart Study (JHS), Gargano Heart Study (GHS), and Catanzaro Study (CZ). The best evidence of association was found on chromosome 1q25, where a SNP (rs10911021) reached *P* values of 1×10^{-5} in the screening set (NHS + HPFS), 4×10^{-4} in the replication sets (JHS + GHS + CZ), and 2×10^{-8} in the screening and discovery sets meta-analyzed together (Fig. 4). The risk allele was associated with a 36% increase in the odds of CHD per copy—an effect larger than most of the CHD loci identified in the general population. Importantly, no association (OR 0.99) was found between this locus and CHD in subjects without diabetes from the NHS and HPFS, resulting in a significant SNP × diabetes interaction (2.6×10^{-4}). By contrast, significant associations between this locus and cardiovascular outcomes were found in other populations of subjects with T2D, including the Look Ahead Study, the Joslin Kidney Study, and the Gargano Mortality Study, consistent with this being a CHD locus specific for diabetes (33,34).

In terms of function, the lead SNP at this locus (rs10911021) is placed in a noncoding region and can be therefore postulated to influence CHD risk by affecting gene expression. Consistent with this hypothesis, experiments with human umbilical vein cells (HUVEC) harvested from multiple individuals with different 1q21 genotypes have shown that homozygotes for the risk allele have 30% lower expression of the *GLUL* gene, which immediately flanks the SNP on the telomeric side (Fig. 5*A* and *B*) (32). *GLUL* codes for glutamine synthase, the enzyme catalyzing the synthesis of the amino acid glutamine from glutamate and ammonia (Fig. 5*C*) (35). Both glutamine and glutamate are involved in critical cellular functions, and alterations of their levels within endothelial cells or other cells relevant to vascular biology may affect cellular pathways involved in atherogenesis. In metabolomic experiments, we could not find associations between the 1q25 locus and glutamate or glutamine serum levels. We observed, however, an association between risk allele and lower pyroglutamic/glutamic ratio (32). The meaning of this finding is unclear, but since pyroglutamic acid is the immediate precursor of glutamic acid in the γ-glutamyl cycle, one can hypothesize that this is a sign of malfunction of this pathway, which is responsible for the production of the natural oxidant glutathione (Fig. 5*C*). The 1q25 risk allele might then

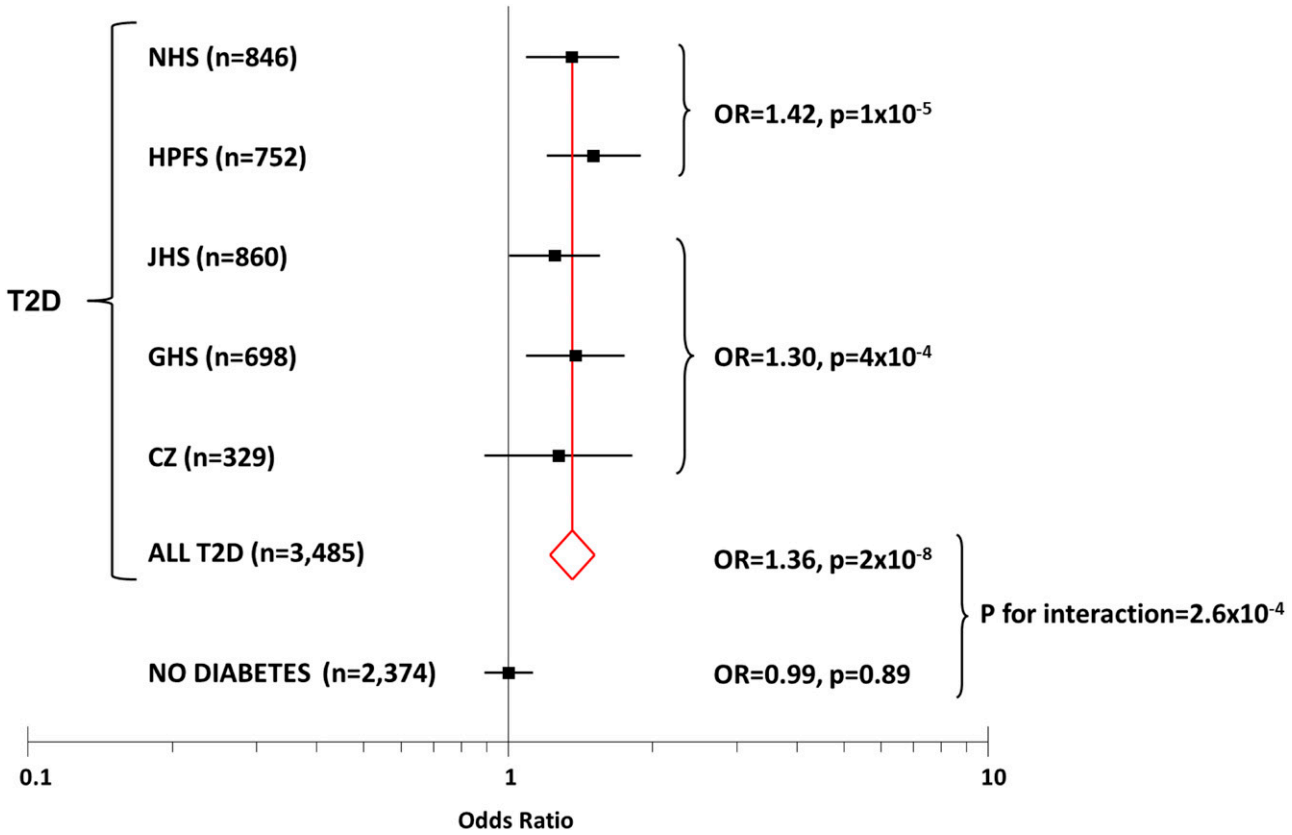

Figure 4—Results of a GWAS for CHD specifically conducted among subjects with T2D. A full GWAS was conducted in the NHS and HPFS and the top SNPs investigated in the JHS, GHS, and CZ (32).

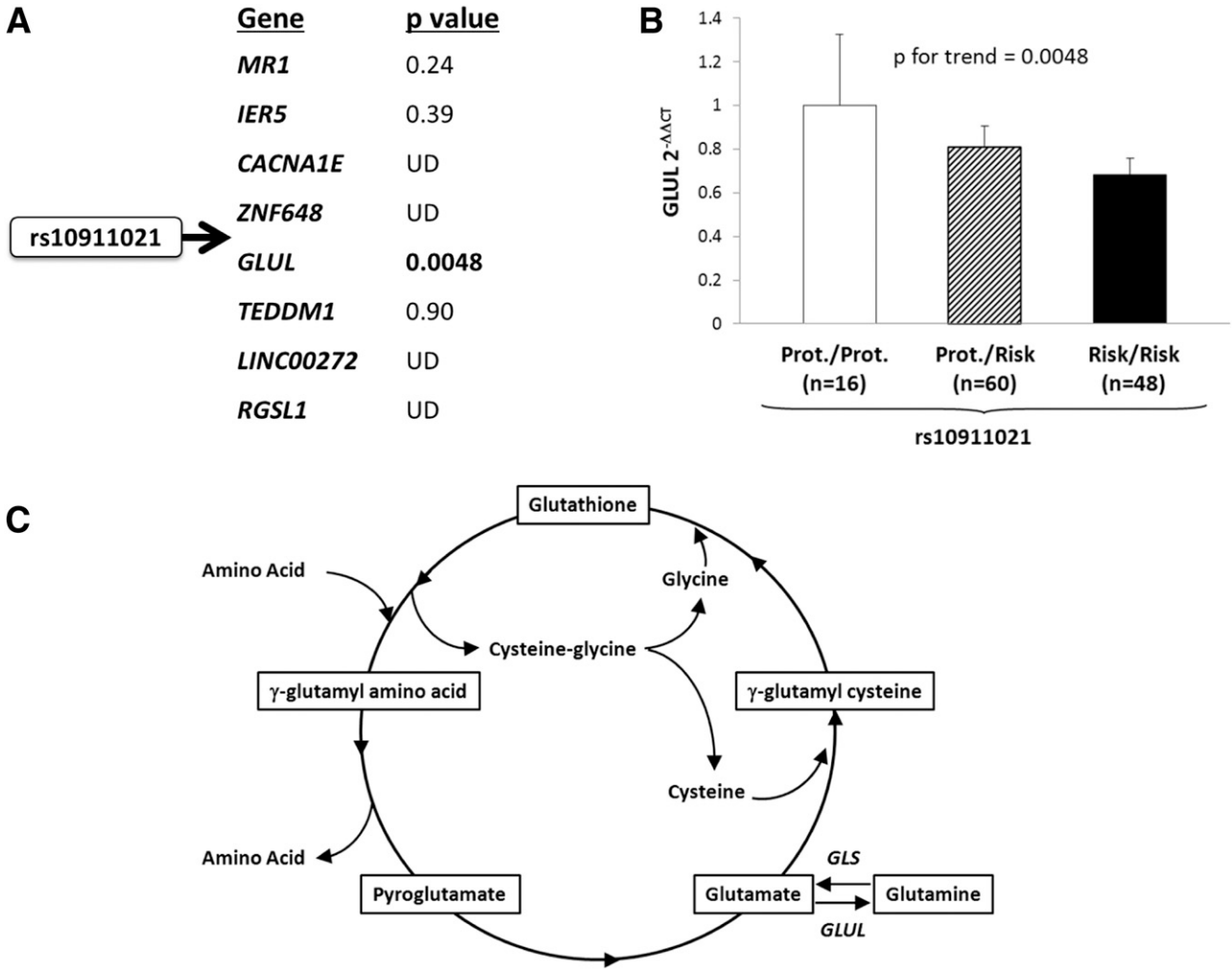

Figure 5—Association between 1q25 CHD locus and *GLUL* expression. *A*: Association between lead 1q25 SNP (rs10911021) and expression of nearby genes in HUVEC. *B*: GLUL expression by rs10911021 genotype in HUVEC. *C*: Relationship between GLUL and the γ-glutamyl cycle. GLS, glutaminase; GLUL, glutamine synthase; Prot., protective allele; Risk, risk allele. Data are from Qi et al. (32).

cause increased CHD risk by decreasing the intracellular levels of glutathione and increasing susceptibility to oxidative stress, to which individuals with diabetes are already prone (36). We are investigating this hypothesis through targeted and untargeted metabolomic studies of HUVEC. If this hypothesis can be proven, this would point to stimulation of GLUL activity as a possible way to prevent CHD in diabetes by boosting the natural defenses against oxidative stress rather than treating patients with antioxidant agents, which has been repeatedly shown to be ineffective.

LEVERAGING GENETICS TO PERSONALIZE PREVENTION PROGRAMS

The third application is to use genetic markers to tailor preventive treatments to personal needs in order to maximize the cost-effectiveness of these interventions. This use of genetics has received much attention by the lay press, but outside of cancer, there are only few examples of successful implementation of this approach. One of these concerns the preferential use of sulfonylureas rather than insulin to treat patients with Mendelian forms of neonatal diabetes due to rare mutations in the potassium channel coded by the *KCNJ11* gene (37). However, as of now, genetic testing is not used in clinical practice to guide the treatment of common, polygenic forms of diabetes.

Rather than looking for genetic markers that could be used to decide which glucose-lowering drug to use, my group has tried to apply this approach to the clinical decision of how low blood glucose should be pushed in order to prevent cardiovascular complications in T2D. Meta-analyses of large randomized clinical trials have shown that intensive glycemic control can lower the risk of myocardial infarction and other major cardiovascular events in T2D (38,39). This tenet is also supported by observational studies showing that genetic factors predisposing to hyperglycemia are associated with a higher risk of CHD independently from T2D and other cardiovascular

risk factors (40). However, intensive glycemic control has significant psychological and financial costs and may also have detrimental effects, including a paradoxical increase in cardiovascular mortality. In the ACCORD trial, intensive glycemic control (i.e., targeting HbA_{1c} to <6%) led to an 18% reduction in nonfatal myocardial infarction, but such beneficial effect was offset by a 29% increase in cardiovascular deaths, which led to premature termination of the trial (41). The question that we asked was whether it was possible to identify genetic markers allowing us to select patients who can take advantage of the beneficial effects of intensive glycemic control without experiencing the detrimental effect of an increased risk of a cardiovascular death. Through a GWAS of the intensive glycemic arm of ACCORD, we found two loci that were significant ($P < 5 \times 10^{-8}$) predictors of cardiovascular mortality and could therefore be used for this purpose: one placed on chromosome 5q13 and the other on chromosome 10q26 (Fig. 6) (42). These two loci were not associated with cardiovascular mortality in the standard treatment arm, resulting in significant gene × treatment interactions ($P = 0.0004$ and $P = 0.004$, respectively). When these two markers were considered together in a GRS, built as discussed above in the section on the development of predictive algorithms, subjects with GRS = 0 (i.e., with no risk allele) experienced a marked reduction of both fatal and nonfatal events in response to intensive glycemic control (−76% and −44%, respectively), those with GRS = 1 (i.e., one risk allele at either locus) experienced a 30% reduction in nonfatal events and a neutral effect on fatal events, and those with GRS ≥2 experienced a threefold increase in fatal events without deriving any benefit on the risk of nonfatal events (Fig. 7). These findings must be replicated in other studies before they can applied to clinical practice, but their transformative potential to optimize blood glucose goals among patients with T2D is quite clear. Patients with a low risk score could enjoy maximal beneficial effect of more intensive HbA_{1c} intervention. Conversely, this risk score could identify patients at higher risk of CVD fatal events, thereby suggesting either a modified HbA_{1c} target or more intensive clinical monitoring of CVD symptoms.

While the goal of this study was to personalize diabetes treatment, these two markers can also be used to gain new mechanistic insights into the pathways linking glycemic control to CVD, as discussed in the previous section. Using existing serum biomarker data, our group has identified a decrease in the circulating levels of active glucagon-like peptide 1 (GLP-1) as a possible mechanism through which the 5q13 risk allele may increase cardiovascular mortality during intensive glycemic control (43) (Fig. 8). GLP-1—a peptide

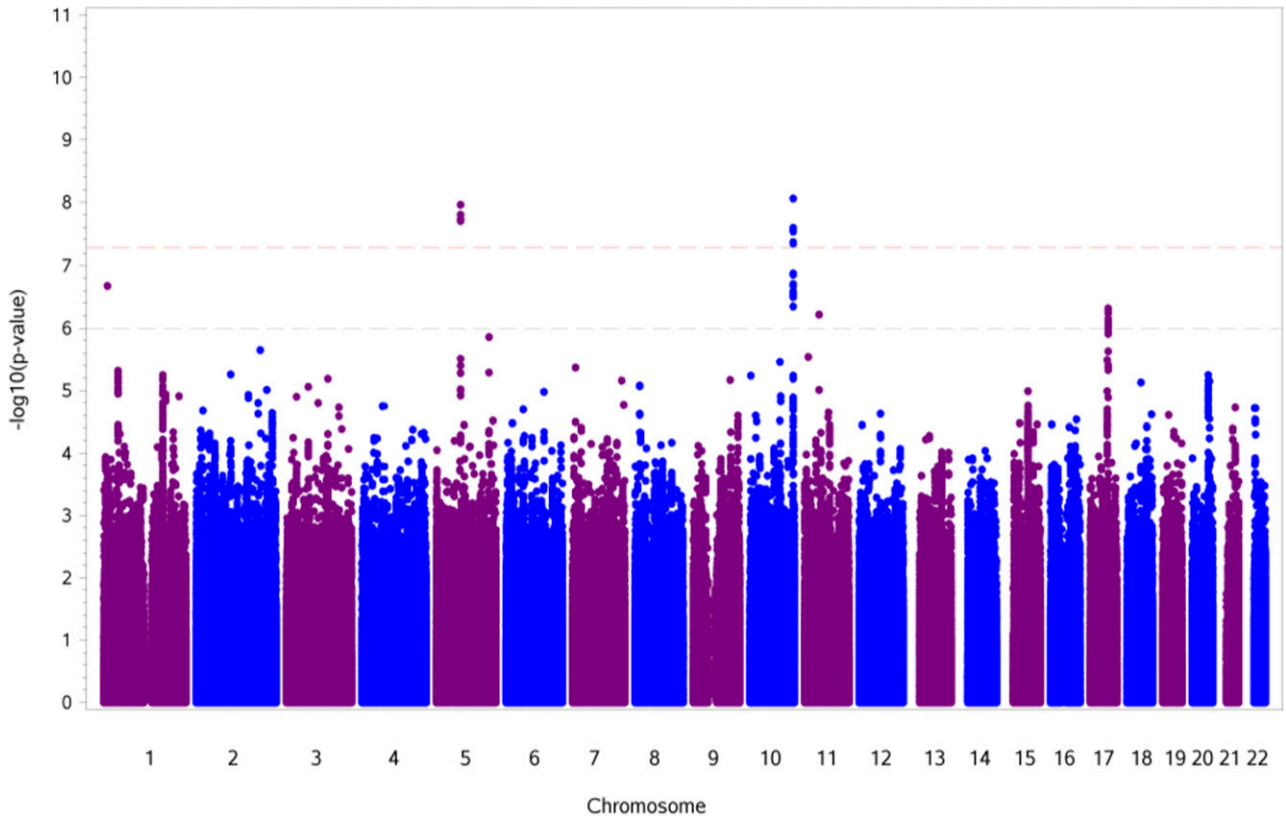

Figure 6—Identification of genetic loci predicting cardiovascular mortality in the ACCORD intensive glycemic control treatment arm. The chart shows the genomic distribution of $-\log_{10} P$ values (Manhattan plot) for association with time to cardiovascular mortality in a GWAS of 2,667 self-reported white ACCORD participants randomized to intensive glycemic control. The red dashed line corresponds to genome-wide significance ($P = 5 \times 10^{-8}$); the gray dashed line corresponds to notable significance ($P = 1 \times 10^{-6}$). From Shah et al. (42).

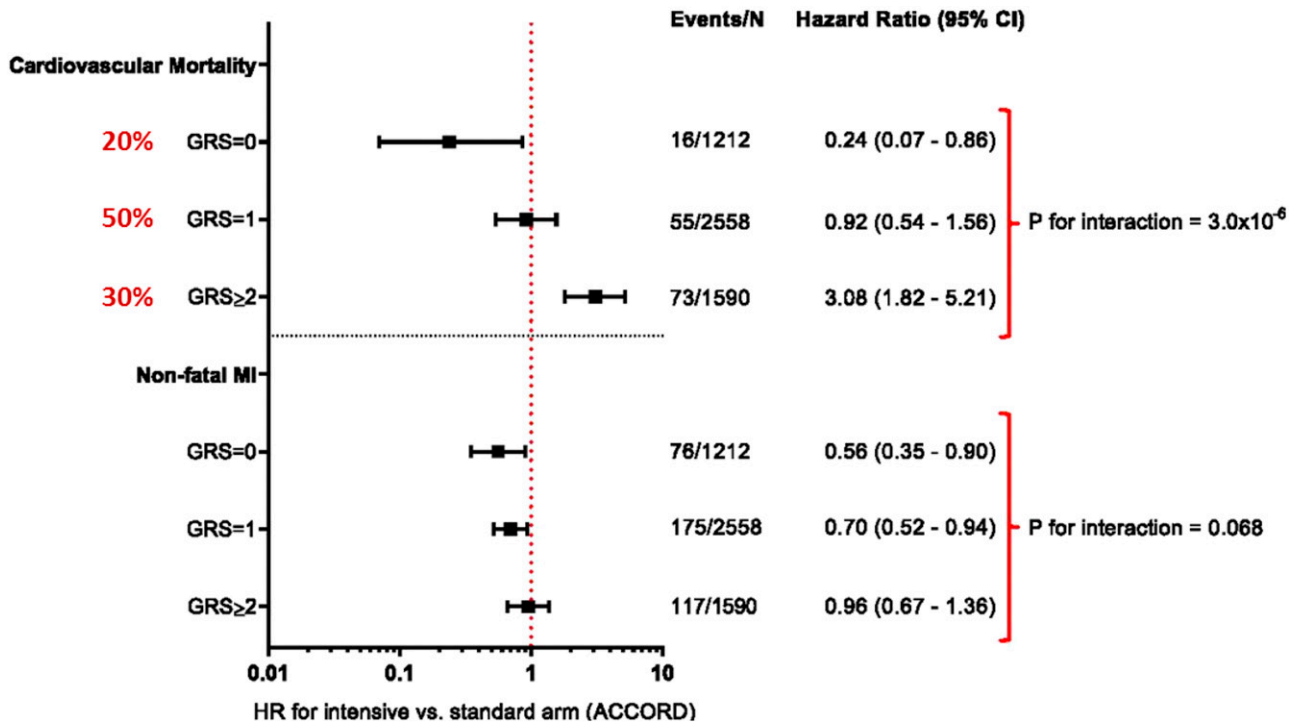

Figure 7—Genetic modulation of the effect of intensive versus standard glycemic treatment on cardiovascular mortality and nonfatal myocardial infarction. GRS obtained by summing number of risk alleles at the 5q13 and 10q26 loci. HRs <1 and >1 indicate beneficial and detrimental effects of intensive glycemic control, respectively. The numbers on the left of the GRS categories indicate the percentage of ACCORD participants in each GRS class. Adapted from Shah et al. (42).

derived from posttranslational processing of proglucagon and secreted in the blood stream by intestinal L cells—is mostly known for its incretin effects on the pancreatic β-cells contributing to the anabolic response to an oral intake of nutrients (44). However, GLP-1 has also been shown to have beneficial effects on left ventricular function as well as a wide array of antiatherogenic actions including decrease of inflammation, smooth muscle proliferation, and platelet aggregation; improvement of endothelial function; and increased plaque stability (45). In agreement with this, synthetic GLP-1 receptor agonists are effective in preventing cardiovascular mortality among subjects with diabetes (46). In the case of the 10q26 locus, we could not identify a serum biomarker associated with the risk allele as we did for the 5q13 locus. However, an analysis of data from the Genotype Tissue Expression (GTEx) database suggests an association between 10q26 risk variant and increased expression of the *O*-6-methylguanine-DNA methyltransferase (*MGMT*) gene in which it is located. In addition to being involved in DNA repair, MGMT functions as a negative regulator of estrogen receptors (47), which have been linked, although not unequivocally, to atherosclerosis and thrombosis (48,49). Efforts are under way by my group to gather more evidence in support of these findings. Confirming the link between 5q13 and the GLP-1 axis would solidify the role of endogenous GLP-1 as a cardioprotective factor, open a novel mechanistic pathway for cardiovascular mortality in patients with diabetes, and suggest personalized treatment modalities. For example, patients with the 5q13 risk genotype may especially benefit at the cardiovascular level from glucose-lowering strategies based on the use of GLP-1 receptor agonists or GLP-1 degradation inhibitors (dipeptidyl peptidase 4 inhibitors), which would be a major personalized therapeutic advance. Connecting 10q26 to the *MGMT* gene would point to an as yet unidentified pathway involved in atherogenesis.

Such an approach can be extended to other interventions. One example is the lipid-lowering drug fenofibrate, which was tested in the ACCORD-Lipid subtrial and yielded a very modest benefit on cardiovascular outcomes (50). In an initial study, we have observed a negative interaction ($P = 0.01$) between use of fenofibrate and a common gain-of-function variant of lipoprotein lipase (LPL p.S447*) (51). Specifically, fenofibrate was beneficial in p.S447 homozygotes but not in carriers of the gain-of-function p.S447* allele, suggesting that activation of LPL is a major mechanism of the beneficial effect of fenofibrate and that treatment of patients in whom this pathway is already activated is superfluous. As with the genetic modulators of the effects of intensive glycemic control, it is too early to translate this finding into clinical practice, but the potential therapeutic implications of these data are obvious.

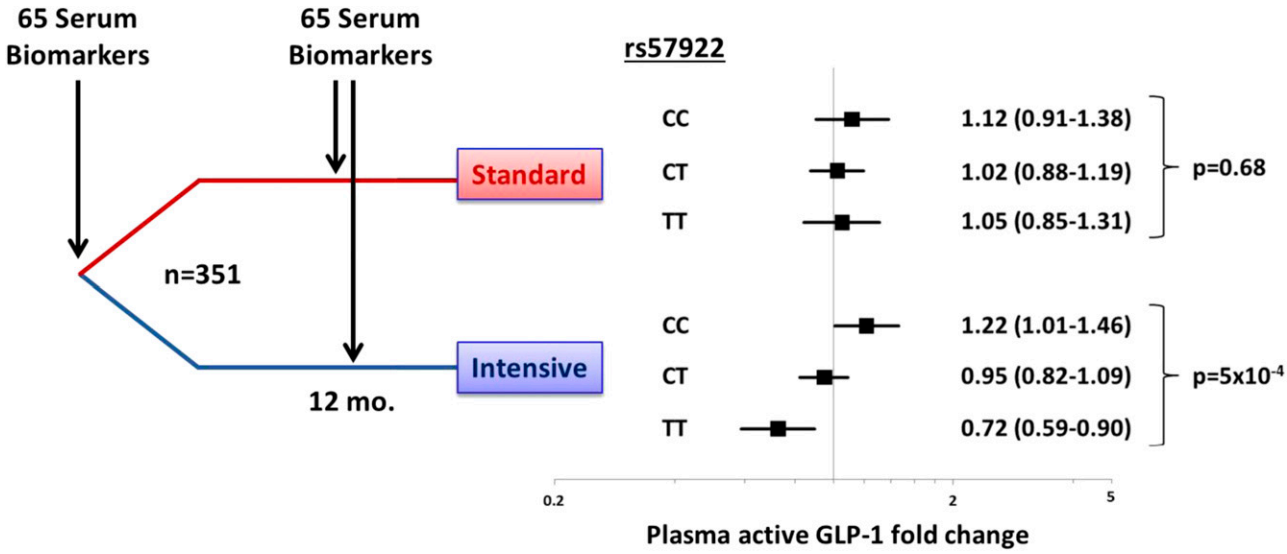

Figure 8—Interaction between intensive glycemic control and 5q13 locus (rs57922) on plasma active GLP-1 levels. Numbers to the left of the *P* values are 12 month-to-baseline GLP-1 ratios (95% CI). Data are from Shah et al. (43).

HOW DO WE TRANSLATE THESE FINDINGS INTO NEW PREVENTIVE STRATEGIES?

During the past two decades, we have made significant advances in our knowledge of genetic factors predisposing to CVD and in particular CHD. However, we still have a long way to go in translating these findings into new diagnostics and therapeutic approaches that can improve cardiovascular health in patients with diabetes. As with other multifactorial disorders, three important questions must be addressed in order to achieve this goal. The first one relates to how we can facilitate the introduction of genetic testing for increased CVD risk into clinical practice. Several companies showed considerable interest in developing and marketing genetic tests to predict risk for complex disorders when the first GWAS were published. However, interest quickly waned when the limitations of the small number of genetic markers available at that time became obvious. Now that the number of available markers has made genetic testing a viable approach, that interest must be revived. At the same time, we should educate clinicians about the availability and usefulness of these genetic tests. The second question is how to speed up translation of genetic signals into disease pathways that can be targeted with new interventions. As discussed earlier, this is a challenging process due to the fact that most of the variants associated with CVD are in noncoding regions. Thus far, we have been proceeding in a piecemeal fashion, focusing on the closest genes as the best candidates for a genetic effect and incrementally moving to more distant genes when the closest ones yielded negative results. We need instead a more systematic approach in which the troves of transcriptomic, proteomic, and metabolomic data increasingly available in the public domain are integrated with GWAS results from the very start. We will also need to engage vascular biologists early in the process, even if this may not be easy at a time when nothing more than a genetic association is available. Finally, on the side of personalized medicine, the question relates to when we should decide that a personalized treatment algorithm can be introduced in clinical practice. In other words, how strong should the evidence be to deem an algorithm ready for clinical use? The mantra in genetic research has been "replication, replication, replication," but more often than not, clinical trials are unique, making opportunities for replication very scant, if any. Thus, we will need to conduct new clinical trials specifically designed to validate personalized treatment algorithms. If this is not a viable proposition, we will need to learn how to leverage observational data from electronic medical records and biobanks. Addressing these questions will be challenging and will require substantial investments, but the potential rewards, both from the perspective of public health and that of persons with diabetes, certainly justify these efforts.

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