

# Genetic Architecture of Type 2 Diabetes: Recent Progress and Clinical Implications

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With the exception of rare monogenic disorders, most type 2 diabetes results from the interaction of genetic variation at multiple different chromosomal sites with environmental exposures experienced throughout the lifespan (1). This complex genetic architecture has important consequences for understanding the pathophysiology of type 2 diabetes, both for researchers seeking mechanistic insight into disease progression and for clinicians hoping to translate this new genetic information into more effective patient management.

With nearly two dozen genes associated with type 2 diabetes, including some genetic variants that appear to modify responses to commonly prescribed diabetes medications and lifestyle interventions, we may be on the verge of a new era in which a patient's individual genetic profile can add useful information to clinical care. Indeed, commercial companies are already offering genome-wide genetic profiling that includes information related to diabetes risk (2). Further advances in type 2 diabetes genetic discovery hold the promise, as yet unrealized, of enabling clinicians to individualize care for their patients by basing their clinical decisions on patient risk for disease progression, propensity to develop specific complications, and likely response to different medication classes. At present it is unknown whether individual genetic information may also serve to effectively motivate patient behavior change, a cornerstone of diabetes and pre-diabetes management. In this review of polygenic type 2 diabetes, we focus on recent dis-

coveries made via linkage analyses, candidate gene association studies, and genome-wide association (GWA) scans and highlight potential clinical applications of new genetic knowledge to risk prediction, pharmacologic management, and patient behavior. Monogenic diabetes has recently been reviewed elsewhere (3).

## Progress in gene discovery

### Linkage studies and candidate genes.

In contrast to monogenic disorders, where results from single mutations lead to predictable phenotypes, the complex genetic architecture of susceptible and protective alleles in polygenic type 2 diabetes is more difficult to discern. Indeed, accumulating data suggest that type 2 diabetes is likely a collection of many closely related diseases with varying but often overlapping primary mechanisms that involve both impaired insulin secretion and insulin resistance. Adding to the challenge, type 2 diabetes is generally diagnosed later in life as a consequence of significant interactions of life-long environmental influences with multiple genetic factors. Because of the limited individual impact of single genetic loci, a full understanding of the complex gene-gene and gene-environment interactions in this disease has proven quite challenging.

In the first phase of diabetes gene discovery, investigators used techniques based on linkage analysis to identify potential diabetes-associated genes. This approach, best suited for discovering genes with strong effects within relatively small family-based studies, involves genotyping affected family members for a set of mark-

ers to identify regions that are co-inherited more commonly in affected family members and therefore potentially point to a genomic region containing a susceptibility locus.

One of the first successes in type 2 diabetes genetic research was a study conducted in Icelanders that identified a linkage peak on chromosome arm 5q (4). Focusing on the various linkage peaks identified in that initial study ultimately led to the association of transcription factor 7-like 2 (*TCF7L2*) with an increased risk of type 2 diabetes. Interestingly, the *TCF7L2* association does not explain the originally observed linkage. In a subsequent case-control study of 3,774 Caucasian subjects from Iceland, Denmark, and the U.S., these investigators reported an estimated allelic risk of 1.56 ( $P = 4.7 \times 10^{-18}$ ) (5). The effect of the risk allele appears to be additive; one allele confers ~40% relative risk of diabetes, whereas two copies confer 80% relative risk (6). This remains the largest effect size of all known type 2 diabetes genes identified to date. The precise mechanisms by which *TCF7L2* variants increase risk are not well understood, although various lines of evidence suggest that they involve the enteroinsular axis and impaired insulin secretion and possibly reduced  $\beta$ -cell proliferation (7,8).

Candidate genes are previously discovered genes that, based on their inferred physiologic role, are hypothesized to contribute to the disease of interest if abnormal. In the case of type 2 diabetes, genes related to glucose transport,  $\beta$ -cell function, and insulin secretion would all be considered reasonable candidates for contributing to the genetic basis of disease. Association studies simply compare the relative frequencies of each variant allele in case and control subjects and determine whether one is overrepresented in disease. To date, four genes identified using candidate gene association studies have been convincingly associated with type 2 diabetes:

*PPARG*. A proline-to-alanine change in codon 12 (P12A) of the peroxisome proliferator-activated receptor  $\gamma$  (*PPARG*) gene was the first genetic variant to be definitively implicated in the

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common form of type 2 diabetes (9,10). Since this initial work, the preponderance of evidence has conclusively supported the association of *PPARG* with type 2 diabetes with an odds ratio (OR) of  $\sim 1.2$  (11).

**KCNJ11.** The potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) gene, first described in the context of neonatal diabetes, encodes the  $\beta$ -cell  $K^+$  channel and is functionally closely related to the sulfonylurea receptor *SUR1*, encoded by *ABCC8*. These genes are adjacent to each other on chromosome 11. Work on this locus has confirmed that a less drastic change in a gene implicated in a rare monogenic subtype of diabetes (12) can indeed contribute to its more common form: single nucleotide polymorphism (SNP) E23K of *KCNJ11* has now been convincingly associated with type 2 diabetes. Subsequent large-scale studies and meta-analyses have consistently associated the lysine variant with type 2 diabetes with an OR of  $\sim 1.15$  (13,14).

**WFS1.** Another monogenic form of diabetes is Wolfram syndrome, caused by mutations in the Wolfram syndrome 1 (*WFS1*) gene. A recent evaluation of common variants in 84 candidate genes yielded two SNPs in *WFS1* that were robustly ( $P \sim 10^{-7}$ ) but modestly (OR  $\sim 1.11$ ) associated with type 2 diabetes in a case-control study comprising  $\sim 24,000$  samples (15). This association has reached genome-wide significance through replication in independent cohorts (16), and the risk variants appear to affect  $\beta$ -cell function (17).

**HNF1B.** Further research on this *MODY* (maturity onset diabetes of the young) gene has produced a conclusive association of an intronic SNP (rs757210) in hepatocyte nuclear factor 1b (*HNF1B*) (previously known as *TCF2*) with type 2 diabetes. A combined analysis of  $>15,000$  samples yielded an overall OR of 1.12 and a  $P$  value of  $<10^{-6}$  (18), with results replicated in two other large-scale studies (19,20).

**GWA studies.** Recent dramatic increases in the rate of diabetes gene discovery have occurred with the advent of GWA studies. This new approach has resulted from the confluence of several key scientific achievements: 1) successful sequencing of the entire human genome, leading to 2) identification of the several

million SNPs (common variations in a single base pair that explain the vast majority of human heterozygosity), which in turn led to 3) genotyping of 3.8 million SNPs in 270 DNA samples by the International HapMap Project (HapMap) to create a subset of haplotype-tagging SNPs (so-called “tag SNPs” that can serve as efficient proxies for localizing variation within narrow stretches of the genome). These advances in our understanding of the human genome proceeded in concert with two additional key steps: 4) the development of affordable, high-throughput genotyping technologies and 5) several large multicenter collections with well-characterized phenotypes assembled and shared through international collaborations.

The first GWA scan for type 2 diabetes (and all others that followed) was validated by the clear replication of the *TCF7L2* association (21). This study also discovered a missense SNP in *SLC30A8* (OR 1.26,  $P < 10^{-6}$ ) and common variants in *HHEX* (OR 1.21,  $P < 10^{-5}$ ) as novel type 2 diabetes associations. The recognition that *SLC30A8* encodes a  $\beta$ -cell zinc transporter expressed in insulin-containing granules (22) and the *HHEX* gene encodes a transcription factor involved in early pancreatic development (23) provided initial reassurance that the GWA approach was useful for identifying functionally relevant loci.

Shortly after this first GWA study, three other groups conducted high-density GWA analyses and shared results ahead of publication. Published jointly, these studies confirmed the known *TCF7L2*, *KCNJ11*, and *PPARG* loci as well as the *HHEX* and *SCL30A8* findings; they also identified *CDKAL1* (OR 1.12,  $P < 10^{-10}$ ), *IGF2BP2* (OR 1.14,  $P < 10^{-15}$ ), and *CDKN2A/B* (OR 1.20,  $P < 10^{-14}$ ) as new type 2 diabetes loci (24–26). *CDKAL1* (*CDK5* regulatory subunit associated protein 1-like 1) is hypothesized to lead to  $\beta$ -cell degeneration by modulating *CDK5/CDK5R1* activity.

Other GWA scans have corroborated the *HHEX* and *SCL30A8* associations, independently detected the *CDKAL1* signal (27), and identified variants in the *FTO* gene that were associated with an obesity phenotype linked specifically to glycemic dysregulation (28,29). In the combined meta-analyses “Diabetes Genetics Replication And Meta-analysis” (<http://www.well.ox.ac.uk/DIAGRAM/>), the separate type 2 diabetes GWA scans from four leading groups (24–27) were analyzed to

yield six new loci (*JAZF1*, *CDC123-CAMK1D*, *TSPAN8-LGR5*, *THADA*, *ADAMTS9*, and *NOTCH2-ADAM30*) associated with type 2 diabetes at genome-wide statistical significance (30). The putative functional mechanisms by which currently identified genes may affect type 2 diabetes risk are listed in Table 1. To date, most genetic variants identified in type 2 diabetes relate to  $\beta$ -cell function rather than insulin resistance (31).

As of yet, most GWAs have been conducted in European ancestry populations. Because minor genetic variation accumulates over time, ancestral groups that became geographically separated many generations ago may yield different GWA scan results. Thus, a major next step for type 2 diabetes genetic research is to extend association studies to samples from populations with differing mutational and demographical histories (32). Studies in other populations may reveal novel susceptibility loci such as *KCNQ1*, first discovered in Asian populations and uncommonly found in European populations (33). Moreover, as we move toward the clinical application of genetic information for individualized diabetes care, race/ethnic-specific results may be needed to optimally interpret an individual's genetic risk.

### Clinical application of diabetes genetic information

By discerning structure in the patterns of gene variation, subtle phenotype differences may be recognized in ways that cannot be achieved with current phenotyping methods. The rapid increase in GWA-related publications has fueled expectations that genetic factors can be used to construct susceptibility profiles that will help in the prediction, prevention, and treatment of type 2 diabetes, thereby ushering in a new era of “personalized medicine.” In the following sections we outline the current knowledge base and potential clinical implications of diabetes genetic testing in four clinical care domains.

#### 1) Predicting risk of developing diabetes.

A major clinical role for genetic testing in medicine has been to predict an individual's risk for developing disease. This works particularly well in monogenic disorders with Mendelian inheritance and reliable penetrance. Examples include testing for the *BRCA* genes in breast and ovarian cancer and preconception testing for carrier status in parents at risk for cystic fibrosis. Such genetic testing holds two

Table 1—Type 2 diabetes-associated genes

Gene region	Function	Marker	Description	Risk allele	OR	P
<i>TCF7L2</i>	Transcription factor; transactivates proglucagon and insulin genes	rs7903146	Intronic	T	1.37	$1.0 \times 10^{-48}$
<i>PPARG</i>	Transcription factor involved in adipocyte development	rs1801282	Missense: P12A	C	1.19	$1.5 \times 10^{-7}$
<i>KCNJ11</i>	Kir6.2 K <sup>+</sup> channel; risk allele impairs insulin secretion	rs5219	Missense: E23K	T	1.14	$6.7 \times 10^{-11}$
<i>WFS1</i>	Endoplasmic reticulum transmembrane protein	rs10010131	Intron-exon junction	G	1.15	$4.5 \times 10^{-5}$
<i>HNF1B</i>	Transcription factor involved in pancreatic development	rs757210	Intronic	A	1.12	$5 \times 10^{-6}$
<i>SLC30A8</i>	β-Cell zinc transporter ZnT8; insulin storage and secretion	rs13266634	Missense: R325W	C	1.12	$5.3 \times 10^{-8}$
<i>HHEX</i>	Transcription factor involved in pancreatic development	rs1111875	7.7 kb downstream	C	1.13	$5.7 \times 10^{-10}$
<i>CDKAL1</i>	Homologous to <i>CDK5RAP1</i> , CDK5 inhibitor; islet glucotoxicity sensor	rs7754840	Intronic	C	1.12	$4.1 \times 10^{-11}$
<i>IGF2BP2</i>	Growth factor binding protein; pancreatic development	rs4402960	Intronic	T	1.14	$8.9 \times 10^{-16}$
<i>CDKN2A/B</i>	Cyclin-dependent kinase inhibitor and p15 tumor suppressor; islet development	rs10811661	125 kb upstream	T	1.20	$7.8 \times 10^{-15}$
<i>FTO</i>	Alters BMI in general population	rs8050136	Intronic	A	1.17	$1 \times 10^{-12}$
<i>JAZF1</i>	Transcriptional repressor; associated with prostate cancer	rs864745	Intronic	T	1.10	$5.0 \times 10^{-14}$
<i>CDC123-CAMK1D</i>	Cell cycle/protein kinase	rs12779790	Intergenic region	G	1.11	$1.2 \times 10^{-10}$
<i>TSPAN8-LGR5</i>	Cell surface glycoprotein implicated in gastrointestinal cancers	rs7961581	Intronic	C	1.09	$1.1 \times 10^{-9}$
<i>THADA</i>	Thyroid adenoma; associates with <i>PPARG</i>	rs7578597	Missense: T1187A	T	1.15	$1.1 \times 10^{-9}$
<i>ADAMTS9</i>	Secreted metalloprotease expressed in muscle and pancreas	rs4607103	38 kb upstream	C	1.09	$1.2 \times 10^{-8}$
<i>NOTCH2</i>	Transmembrane receptor implicated in pancreatic organogenesis	rs10923931	Intronic	T	1.13	$4.1 \times 10^{-8}$
<i>KCNQ1</i>	Pore-forming subunit of voltage-gated K <sup>+</sup> channel ( <i>KvLQT1</i> ); risk allele impairs insulin secretion	rs2237892	Intronic	C	1.49	$1.7 \times 10^{-42}$

core principles: that the genetic testing improves risk prediction beyond readily available data such as family history, physical exam findings, and basic laboratory tests, and that the test results provide “clinically actionable” information.

Given the strength of the evidence from landmark studies of diabetes prevention (34–36), identifying patients in the pre-diabetic stage for intensive lifestyle management or metformin therapy has the potential to significantly reduce the incidence and subsequent morbidity and mortality of type 2 diabetes. With this potential benefit in mind, researchers have investigated whether genetic testing can improve the identification of high-risk patients. Of the genes confirmed to date, *TCF7L2* has the highest OR for predicting diabetes. Among pre-diabetic subjects enrolled in the Diabetes Prevention Program (DPP), for example, patients

with the risk-conferring TT genotype (at rs7903146) of *TCF7L2* had an 81% increased risk of progressing to diabetes over 3 years (hazard ratio 1.81 [95% CI 1.21–2.70],  $P = 0.004$ ) compared with patients with the CC allele (6). This corresponds to an incidence of 18.5 new diabetes cases per 100 patient-years versus 10.8 per 100 patient-years for patients without the TT allele. However, only ~10% of patients with pre-diabetes have the TT genotype, limiting the applicability of this test.

The generally weak effects of other risk-associated gene loci discovered thus far has led researchers to combine all confirmed gene loci into aggregate measures of diabetes risk. In the past year, four studies have been published that have aggregated diabetes risk-associated genetic loci to predict diabetes risk in different populations. For example, Lyssenko et al.

(37) genotyped 16 SNPs and examined clinical factors in 16,061 Swedish and 2,770 Finnish subjects. Type 2 diabetes developed in 2,201 (11.7%) of these subjects during a median follow-up period of 23.5 years. The addition of specific genetic information to clinical factors only slightly improved the prediction of future diabetes, with an increase in the area under the curve (AUC) from 0.74 to 0.75 ( $P = 10^{-4}$ ).

Using data from the Framingham Offspring Study, Meigs et al. (38) tested a “genotype score” approach that summed the number of risk-conferring alleles from a panel of the 18 loci known to be associated with type 2 diabetes (Table 1). Using this approach, patients that developed diabetes (255 of the 2,377 participants studied over 28 years of follow-up) had higher genotype scores ( $17.7 \pm 2.7$  vs.  $17.1 \pm 2.6$  among those that did not de-

velop diabetes,  $P < 0.001$ ), which corresponded to a sex-adjusted OR for diabetes that increased by 12% per each incremental increase in risk allele number. However, in a model including age, sex, family history, BMI, fasting glucose, systolic blood pressure, HDL cholesterol, and triglycerides, the area under the receiver-operating characteristic curve (AUC) testing the ability to discriminate risk of diabetes was 0.900 without the genotype score and 0.901 with the score ( $P = 0.49$ ), indicating that the genotype score provided only a slightly better prediction of risk than knowledge of common risk factors alone. Other studies using the same 18 genetic loci approach have yielded similar results: Among participants in the Rotterdam study, adding the 18 polymorphisms to a predictive model based on age, sex, and BMI only increased the AUC from 0.66 (0.63–0.68) to 0.68 (0.66–0.71) (39); and in a case-control study from the Genetics of Diabetes Audit and Research Tayside Study, the AUC increased from 0.78 to 0.80 (40).

Taken together, the results of these genetic predication studies indicate that genetic information may have the greatest yield before other risk factors have appeared (e.g., at birth or in youth, provided this leads to actionable interventions) and also that genetic prediction tools may only prove useful once many more markers are discovered. While future genetic predication tools may serve a valuable role in identifying particularly high-risk-patient subgroups, for current diabetes prevention efforts, individualized genetic information to guide therapy or motivate behavior change may have the most clinical impact among patients who have already been identified as at-risk for diabetes by other methods.

**2) Predicting diabetes-related complications.** The rate of progression to cardiovascular disease, renal dysfunction, retinopathy, and other diabetes-related complications is known to differ among patients with similar diabetes duration and glycemic control, raising the possibility that individuals may have a genetic predisposition to specific complications. For example, the heritability of creatinine clearance is estimated to be  $\sim 0.63$  (41) and that of glomerular filtration rate may be as high as 0.75 even when controlled for A1C (42). While there have been some promising initial studies in the areas of cardiovascular disease (43) and microvascular complications (44), this area has yet to yield clinically applicable results.

**3) Response to treatment and pharmacogenomics.** In addition to predicting risk for diabetes or related complications, a more detailed understanding of an individual's genetic background may help guide treatment. Although many genes have now been reproducibly associated with type 2 diabetes, much less is known about gene-drug interactions. Similarly, the putative genetic predisposition of selected individuals to the development of side effects is presently unexplored. The promise of this clinical application of genetic testing is that we can choose the "right" treatment for the "right" patient, based on both expected response and propensity for adverse side effects.

**PPARG.** An early focus of type 2 diabetes pharmacogenetic studies has been the common functional *PPARG* P12A variant, since this nuclear receptor is the known drug target of the thiazolidinediones (TZDs). Four published studies have examined the effect of *PPARG* P12A on the response to TZDs. Blüher et al. (45) found that among 131 diabetic subjects treated for 26 weeks with pioglitazone, the percentage of responders (defined as a  $>20\%$  decrease in fasting glucose or a  $>15\%$  decrease in A1C) did not differ between proline homozygotes and alanine carriers. Similarly, in the TRIPOD (Troglitazone in Prevention of Diabetes) study, the P12A variant did not predict failure to increase insulin sensitivity in response to troglitazone (46). In the DPP cohort, no effect of *PPARG* P12A or five other *PPARG* polymorphisms was seen in response to troglitazone therapy (47). In contrast, when Kang et al. (48) examined the response of 198 type 2 diabetic patients to rosiglitazone, they found that 15 carriers of the P12A polymorphism had a better response to TZD therapy than Pro12Pro homozygotes. Patients with the alanine allele had a larger reduction in fasting glucose and A1C than those without the allele, although the sample size was small. Thus, knowledge of allelic variation at this locus does not yet offer a rationale for therapeutic choices.

**KCNJ11.** A monogenic form of permanent neonatal diabetes offers an illustrative paradigm for pharmacogenetic testing. Carriers of specific mutations at *KCNJ11* can be safely transitioned from insulin to sulfonylurea therapy (49). In contrast, the impact of the *KCNJ11* genetic variation on the effectiveness of

sulfonylurea therapy in common type 2 diabetes is unclear. Sesti et al. (50) genotyped *KCNJ11* in 525 Caucasian type 2 diabetic patients and investigated whether failure to respond to sulfonylurea therapy (defined as fasting plasma glucose  $>300$  mg/dl despite combined sulfonylurea-metformin therapy and appropriate diet) was due, in part, to the risk allele. The authors found carriers to have a relative risk of failure of 1.45 compared with E23E homozygotes. Also, the risk allele was associated with an earlier onset of diabetes and worse metabolic control in nonresponders. These results stand in contrast to those of the UKPDS (UK Prospective Diabetes Study), in which the authors found no significant association of the E23K variant with response to sulfonylurea therapy in 364 newly diagnosed type 2 diabetes patients (13).

**ABCC8.** A recent trial by Feng et al. (51) offers a glimpse of what future pharmacogenetic testing may entail. In this study, 1,464 recently diagnosed Chinese type 2 diabetic patients were treated for 8 weeks with the sulfonylurea gliclazide. In this cohort, Ser/Ser homozygotes at *ABCC8* A1369S (a locus known to be closely correlated with *KCNJ11* E23K that encodes sulfonylurea receptor SUR1) had a 26.1% decrease in fasting plasma glucose compared with a 31.6% decrease in Ala/Ala homozygotes (which translates into a significant difference of  $\sim 0.7$  mmol/l or 12.6 mg/dl between genotypic groups).

**TCF7L2.** To investigate potential interaction of *TCF7L2* with drug therapy, the recently published Go-DARTS (Genetics of Diabetes Audit and Research Tayside) study genotyped 6,516 U.K. participants for *TCF7L2* and found that the T allele was overrepresented in individuals requiring insulin treatment and underrepresented in the patients managed by diet alone. The authors concluded that *TCF7L2* variants may be associated with increased disease severity and therapeutic failure (52). Another recent publication from the same group reported the effect of *TCF7L2* genotypes on therapeutic response in 901 diabetic patients treated with sulfonylurea and 945 patients treated with metformin. Carriers of the risk *TCF7L2* variants were more likely to fail with sulfonylurea but not metformin therapy as measured by A1C  $>7\%$  within

3–12 months after treatment initiation (53). This finding further supports the hypothesis that *TCF7L2* variants are important in  $\beta$ -cell function. Finally, studies from the DPP on participants with impaired glucose tolerance and elevated fasting glucose reveal that the lifestyle preventive intervention was effective in reducing the genetic risk conferred by the high-risk homozygous genotype to the level of their wild-type counterparts (6).

**OCT1.** One new research area involves the variability in medication transport and metabolism. Recently, Shu et al. (54) examined the hepatic transport of metformin and found that organic cation transporter 1 (*OCT1*), which participates in the hepatic uptake of metformin, may contribute to variation in response to metformin. These authors reported a reduced effect of metformin on AMP kinase phosphorylation in *Oct1*-deficient mouse hepatocytes and poor absorption of metformin in *Oct1*-deficient mice. They also showed that the *OCT1* reduced-function allele in healthy human subjects is predictive of higher glucose levels during an oral glucose tolerance test. Thus, this complementary area of pharmacogenetic investigation holds great promise in explaining the human variability in drug response.

**SLCO1B1.** Although there are few studies addressing genetic predisposition to adverse reactions for glycemic-specific drug classes, in clinical practice the majority of type 2 diabetic patients are treated with statins (55). A recent publication provides the first example of diabetes-related gene–side effect associations. These investigators conducted a GWA study using ~300,000 markers in 85 subjects with definite or incipient myopathy and 90 control subjects, all of whom were taking 80 mg of simvastatin daily (56). This analysis identified a single strong association of myopathy with the rs4363657 SNP located within *SLCO1B1*, a gene encoding the organic anion–transporting polypeptide *OATP1B1*, which was previously shown to regulate the hepatic uptake of statins. The OR for myopathy was 4.5 (95% CI 2.6–7.7) per copy of the C allele and 16.9 (4.7–61.1) in CC compared with TT homozygotes. These findings imply that more than 60% of these statin-induced myopathy cases could be attributed to the C variant.

**4) Can individual genetic information change behavior?** Weight loss and increased physical activity are the cornerstones of therapy for patients with diabetes and pre-diabetes. Results from the DPP and other studies have conclusively demonstrated the efficacy of intensive lifestyle modifications to prevent or delay diabetes onset. However, adherence in the highly selected DPP intervention group was suboptimal, with only 38% of patients achieving weight loss goals and 58% maintaining physical activity goal by study end (34). Thus, even in the ideal circumstances of a rigorous clinical trial, consistent adherence to lifestyle modification remains a difficult clinical challenge. At present, it is not known to what extent individual genetic risk information can be applied to patients with pre-diabetes to motivate significant behavior change.

Given the suboptimal effectiveness of current efforts to implement DPP-like lifestyle programs, providing individuals at risk for diabetes with new tools to improve their motivation and adherence, such as their individual diabetes genotype scores, has the potential for substantial clinical impact. To date, no studies have examined the clinical impact of such diabetes-related genetic testing. However, two trials in other areas provide some evidence to support the potential impact of knowing one's personal "genetic risk" status. In a study of 162 patients with a family history of Alzheimer's disease, participants who learned that they were  $\epsilon 4$ -positive (at increased risk for Alzheimer's disease) were significantly more likely than  $\epsilon 4$ -negative participants to report Alzheimer's disease–specific health behavior change (including changes in diet and exercise) 1 year after disclosure (adjusted OR 2.73 [95% CI 1.14–6.54],  $P = 0.02$ ) (57); and among patients with a family history of familial hypercholesterolemia, subjects randomly assigned to receive genetic testing results to confirm their familial hypercholesterolemia diagnosis had increased confidence in the efficacy of medical therapy versus patients diagnosed via traditional testing, suggesting that personal genetic information can have a positive influence on patient perceptions of how to achieve disease control (58).

**CONCLUSIONS** — This is an era of rapid and exciting scientific advancement in type 2 diabetes genetics and genomics. Newly identified diabetes-associated loci

are being discovered and may open new vistas for elucidating the underlying pathophysiology of this complex disease. Understanding the complex interactions among genetic profiles, individual lifestyles, and environmental factors lies at the core of effective diabetes treatment. Attempts to integrate such knowledge into clinical practice are still in the early stages, and as a result many gaps in knowledge about organization, clinician, and patient needs must be filled before the clinical benefit of this advancement can be fully realized (59).

Three points remain to be emphasized: 1) The current set of type 2 diabetes allele variants may explain as little as 5–10% of the genetic basis for type 2 diabetes. The SNPs identified thus far signal important chromosomal "neighborhoods," but future fine-mapping studies and functional gene assessments will be necessary to pinpoint the true underlying causal mechanisms. Moreover, because current genotyping techniques do not address structural variants (e.g., copy number polymorphisms), have not captured rare variants, and have left as much as 20% of common SNPs in the genome suboptimally covered (with a higher percentage of uncovered regions in the more diverse African population), the full genetic architecture of type 2 diabetes remains largely unexplored. 2) Given the relatively large sample sizes of collaborative GWA studies published to date, we are unlikely to find new polymorphisms with effect sizes as large or larger than *TCF7L2* rs7903146 (at least among populations of European ancestry). Nonetheless, as study sample sizes continue to increase, we should expect to find many more SNPs of modest effect sizes in the range of most currently known genes (OR 1.1–1.2). 3) The addition of aggregated genotype information does not substantially improve upon current diabetes prediction tools. Thus, the future clinical application of diabetes genetic testing may lie in predicting downstream complications, tailoring drug therapy, or motivating behavior change, domains for which we currently have a paucity of data.

We are fortunate to practice medicine at the start of a new era (60). Novel biology remains to be discovered in relation to the effects of inherited DNA variation on human phenotypic diversity in general and metabolic traits in particular. However, enthusiasm for the potential of new genetic knowledge must be tempered with the recognition that current findings,

even in the aggregate, provide only modest clinically applicable new information. Just as each person with type 2 diabetes has a unique phenotype that reflects a complex interaction between genetic variation and environmental factors, the effective clinical care of such a patient will require the skillful integration of new genetic risk information with the traditional patient care skills that have been employed for ages.

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Dr. Allan F. Moore passed away on 24 July 2008. This article, to which he contributed his privileged intellect and unwavering enthusiasm, is dedicated to his memory.

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