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**Citation**

**Published Version**
doi:10.2337/dc12-2211

**Citable link**
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Gene-Environment and Gene-Treatment Interactions in Type 2 Diabetes

Progress, pitfalls, and prospects

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Type 2 diabetes has rapidly emerged as a global health crisis. Because population-level genetic changes take many generations to occur, this epidemic is almost certainly primarily a consequence of recent environmental changes; nonetheless, diabetes does appear to occur preferentially in genetically predisposed populations, which suggests that the effects of pre-existing susceptibility genes have been triggered by recent shifts in nongenetic factors.

Predisposition is influenced by the level of certain environmental exposures, personal factors, access to good-quality primary care, and by genotype. Interactions between genetic and nongenetic risk factors are hypothesized to raise diabetes risk in a synergistic manner; reciprocally, health-enhancing changes in behavior, body composition, or medication may reduce the risk of disease conveyed by genetic factors. Defining the nature of these interactions and identifying ways through which reliable observations of gene-environment interactions (GEIs) can be translated into the public health setting might help 1) optimize targeting of health interventions to persons most likely to respond well to them, 2) improve cost- and health-effectiveness of existing preventive and treatment paradigms; 3) reduce unnecessary adverse consequences of interventions; 4) increase patient adherence to health practitioners’ recommendations; and 5) identify novel interventions that are beneficial only in a defined genetic subgroup of the population. In this Perspective, we describe the rationale and evidence relating to the existence of gene-environment and gene-treatment interactions in type 2 diabetes.

We discuss the tried, tested, and often-failed approaches to investigating gene-lifestyle interactions in type 2 diabetes; we discuss some recent developments in gene-treatment interactions (pharmacogenetics); and we look forward to the strategies that are likely to dominate these fields of research in the future. We conclude with a discussion of the requirements for translating findings from these future studies into a form where they can be used to help predict, prevent, or treat diabetes. Here we describe the rationale and evidence concerning GEIs and gene-treatment interactions in type 2 diabetes, provide an interpretation of current findings and strategies, and offer a view for their future translation.

What is GEI?—The definition of GEI varies somewhat depending on the field of diabetes research. In this review, we adopt epidemiological definitions of interaction, also known as effect modification or effect modulation. For binary outcomes, an interaction would be present if the combined risk attributable to genetic and environmental exposures is significantly greater or less than expected if their effects were additive. For quantitative traits, an interaction would be present if the magnitude of the genetic effect estimate differs across the range of an environmental exposure or treatment. Although the word environment when used in the context of GEI can relate to any nongenetic factor to which a person is exposed, extending from the macro (e.g., urban planning) to the micro (e.g., circulating proteins) environment, in the fields of complex disease research, the word environment has most often referred to lifestyle behaviors (e.g., diet or physical activity), although this view is evolving (Fig. 1). The word interaction is sometimes used to describe the joint effects of a genetic exposure and a second factor that is positioned on the causal pathway between the genetic exposure and a disease phenotype; in epidemiology, this process is termed mediation, which differs in meaning from interaction. The term epistasis refers to the interaction between two or more genetic loci.

Why do we think GEIs cause type 2 diabetes?—The evidence supporting the existence of gene-lifestyle interactions in type 2 diabetes comes primarily from 1) the pattern and distribution of diabetes across environmental settings and ethnic groups, 2) family-based intervention studies, in which response to interventions varies less between biologically related individuals than between unrelated individuals; and 3) animal studies in which genetic and environmental factors are experimentally manipulated to cause changes in the expression of metabolic phenotypes. A brief overview of pertinent literature from human studies is given below.

There is considerable global variation in the prevalence and incidence of type 2 diabetes (1). In societies of European origin, the prevalence of type 2 diabetes is generally 10% or less, with the disease confined primarily to overweight and...
Assessment of GEI in type 2 diabetes

Figure 1—The future of research on stratified diabetes medicine: a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human physiome.

Obese older adults. However, in some nonwhite populations, including Native Americans (especially Pima Indians), Alaskan Natives, Micro-Indonesia islanders (especially Nauruans), and some Middle Eastern (especially Saudis and Emiratis) and Canadian First Nation populations (2,3) (www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/index-eng.php), the prevalence of type 2 diabetes is substantially higher than in the rest of the world.

The Pima Indians of Arizona have the highest recorded prevalence of type 2 diabetes, with more than half of the adult population affected by the disease (3), and diagnoses are often made in adolescence and occasionally in childhood (4). The damming of the Salt and Gila rivers around 1911 brought an abrupt end to the Pima’s traditional subsistence farming lifestyle and with it a sharp reduction in occupational physical activity and the consumption of fresh produce. A second group of Pima Indians live in the Sierra Madre Mountains of northern Mexico. Although Arizona and Mexican Pima are phylogenetically similar (5), their lifestyles stand in stark contrast, with the Mexican Pima still living a traditional way of life left behind by Arizona Pima almost a century ago. Probably because of this, the prevalence of type 2 diabetes in Mexican Pima is roughly five-times lower than that seen in their Arizonan cousins, with diabetes prevalence in the Mexican Pima comparable to that of other non-Pima populations of northern Mexico (5). This observation emphasizes how environmental changes can awaken an underlying, possibly genetic, susceptibility to obesity and type 2 diabetes.

A popular yet contentious explanation for why indigenous groups (whose evolution has involved long periods of migration, hunter-gatherer lifestyles, and frequent famine) are so susceptible to the adverse consequences of industrialized environments is termed the “thrifty genotype hypothesis,” first proposed by Neel in the 1960s (6). Whereas the original description of the thrifty genotype hypothesis focused on the over-production of insulin after meals and a corresponding period of hypoglycemia that induces appetite, the idea that efficient storage and utilization of energy in adipose tissue is a selected trait has also been widely discussed and attributed to thrifty genes (7). The hypothesis hinges on the notion that frequent exposure to famine and other physiologically stressful events, such as migration and cold temperatures, over thousands of years of evolution may have enriched certain populations with gene variants that promote metabolic thriftiness, which in turn conveyed a survival advantage during famine or other periods of energetic stress. In the modern world, however, where excessive automation and almost effortless access to energy-dense foods are rife, calorie accumulation and storage may become metabolically deleterious. Of note, however, there is little evidence of positive selection genetic signatures around established type 2 diabetes loci (8), suggesting these diabetes loci at least are not thrifty genes.

Caveats of the literature on gene-lifestyle interactions—A recent simulation study on the role gene-gene and GEIs are likely to play in risk prediction and targeted medicine reached a rather sobering conclusion (9). The authors estimated that the average improvement in predictive accuracy, as defined by the area under the receiver operating characteristic curve, for type 2 diabetes was ~5% when between 4 and 20 interactions were added to a prediction model. To conduct their simulations, Aschard et al. (9) made a series of assumptions about the magnitude and frequency of interaction effects, based on published epidemiological studies that had focused on common diseases, common exposures, and common variants; however, it is possible that as geneticists begin to study lower frequency variants, fairly large magnitude interaction effects may be discovered, albeit affecting relatively few individuals, which would likely increase the value of data on interactions for disease prediction.

Epidemiological studies have been the predominant source of literature on gene-lifestyle interactions in cardiovascular and metabolic disease. Dozens of case-control and cohort studies have been published since the late 1990s purporting to have identified gene-lifestyle interactions in type 2 diabetes or related quantitative metabolic traits. Until recently, however, most of these studies were small and often relied on imprecise estimates of environmental exposures and outcomes. These are prone to error and bias, and exposures may not be assessed at the time when they conveyed their effects; for example, the causative exposures may have occurred very early in life, perhaps even in utero. Moreover, the complexities of modeling interaction effects have forced geneticists to focus primarily on very simple models of interaction, whereas clinically relevant interaction effects likely involve multiple genetic and nongenetic biomarkers. In addition, barely a handful of studies have examined incident type 2 diabetes as an outcome, with most focusing on cross-sectional measures of glucose and others relying
on analyses that include prevalent cases of diabetes; this may introduce labeling bias, where the recall of well-known diabetes-associated behaviors is less likely to be accurate in individuals recently diagnosed with disease than in those who have not been diagnosed with disease.

In a systematic review published in 2006 (10), we found that almost all studies published at that time included fewer than 1,000 participants and none included more than 3,000 participants. Although all studies lacked rigorous replication, we identified four classes of genes harboring loci that showed most consistent evidence of gene-lifestyle interactions in diabetogenic traits: the β2 adrenergic receptor (ADRB2), uncoupling proteins (UCP) 1-3, lipid-related loci (LIPC, LPL, FABP2, APOC3, and APOE), and the peroxisome proliferator-activated receptor-γ (PPARG). Of these, PPARG (at its common missense polymorphism Pro12Ala) was perhaps the most promising candidate, with a number of studies reporting interactions with dietary fatty acids or exercise in relation to insulin concentrations (11–13), adiposity (12,14,15), and type 2 diabetes (16). Studies examining interactions between dietary fats and the Pro12Ala genotype have continued to accrue, and attempts have been made to formally summarize this literature through meta-analysis. These attempts have been unsuccessful, however, owing to the challenges of pooling unstandardized data and the inadequate descriptions of the methods and results in many published studies (17).

Other key caveats to small gene-lifestyle interaction studies include their likelihood to be underpowered and that they are prone to reporting biases (18). The problems with measurement imprecision in studies of gene-lifestyle interaction are eloquently outlined and discussed by Wong et al. (19), where the authors provided estimates of sample-size requirements to detect gene-lifestyle interactions in the presence of varying degrees of environmental exposure assessment and phenotyping measurement error. The authors show that for the detection of fairly large magnitude gene-lifestyle interactions (βGE = 2), a study of ~2,000 individuals in which precise measures of environmental exposure and outcome had been made would be adequately powered (95% power, critical α P = 1 × 10⁻⁴); however, studies that imprecisely estimated environmental exposures and phenotypes, as is often the case in epidemiological studies, would require a sample collection ~50-fold larger to afford comparable power.

Although the expected range of effects that are realistic for gene-lifestyle interactions in type 2 diabetes remains unclear, a doubling of the genetic risk estimate in the group exposed to adverse lifestyle factors compared with those who are unexposed (βGE = 2) is at the upper end of the interaction effect estimate ranges reported for common variants and common exposures (10). It is reasonable to conclude, therefore, that most of the interaction studies published to date report “lucky” true-positive results or false-positive results that may be underpinned by analytical and reporting biases. The replication of few examples of gene-lifestyle interactions in type 2 diabetes suggests that the literature is composed largely of the latter. Despite this, recent developments in the ways genetic association studies are performed, such as adoption of hypothesis-free approaches, the availability of comprehensive genotype arrays in large sample collections, global collaborations, and more rigorous analysis and reporting of data, have led to the emergence of many reproducible genetic association signals for type 2 diabetes and related glycemic traits, which has spurred a number of large-scale studies of gene-lifestyle interactions.

Using genome-wide association studies to inform the selection of loci for studies of gene-lifestyle interactions—The identification of more than 50 genetic loci that are reproducibly associated with type 2 diabetes (20) (Fig. 2) and 53 additional loci for glucose and insulin concentrations (21) has fueled multiple studies in which these loci have been tested for interactions with lifestyle risk factors for type 2 diabetes. One of the first publications of this kind focused on the interaction between the FTO rs9999609 variant and physical activity. Two cross-sectional cohort studies (22,23) and one clinical trial analysis (24), published at approximately the same time, provided nominal evidence that physical activity modifies the effects of the FTO variant on BMI or adipose tissue accumulation. Replication studies achieved mixed results; thus, we sought a definitive answer by conducting a prospective meta-analysis including 45 adult (n = 218,166) and 9 pediatric (n = 19,268) cohorts (25). Although the study yielded a statistically significant interaction summary statistic (Pinteraction = 0.005), which was directionally consistent with the original studies’ findings (22), the effect estimate was heterogeneous (I² = 36%), suggesting the presence of one or more latent effect-modifiers (i.e., unidentified factors that change the magnitude of FTO’s effect on BMI). Further data exploration determined that the source of this heterogeneity was the geographic origin of the cohorts, with the interaction effect being driven almost entirely by the North American cohorts. Although this geographic difference remains unexplained, the observation strongly suggests that physical activity is not the causal effect-modifier; instead, factors that correlate with physical activity in North American but not in European cohorts, such as specific dietary factors, are likely to be the causal modifiers of FTO’s obesogenic effects. It is also important to bear in mind that almost all studies reporting significant FTO-lifestyle interactions are cross-sectional observational studies, from which causal effects and causal direction are almost impossible to ascertain. Thus, even if a causal relationship underlies the results reported above, it is possible that the direction of effect is reversed (i.e., a direct effect of FTO variation on lifestyle behaviors, which is stronger in fatter compared with leaner people). These alternative explanations are important to consider when discussing, as many do, the potential translational implications of studies of gene-lifestyle interactions.

The first large-scale study examining the interaction of established type 2 diabetes loci and physical activity included 16,000 men and women from southern Sweden, of whom 2,200 went on to develop diabetes during the ensuing 25 years of follow-up (27). Of the 17 established diabetes loci examined, the study identified a single locus, the noncoding polymorphism rs4430796 at the diabetes gene HNF1B, that interacted with baseline physical activity levels as estimated by questionnaire (Bonferroni corrected Pinteraction = 0.015). In homozygotes for the nonrisk allele (A), baseline physical activity apparently protected against the development of type 2 diabetes, as one would predict from previous studies of physical activity and diabetes; however, in carriers of the rs4430796 risk allele, the protective effect of physical activity appeared to be diminished in a dose-dependent fashion.
In a separate cohort from southern Sweden of ~25,000, two gene-diet interactions have been reported in relation to type 2 diabetes. Sonestedt et al. (28) reported that dietary fat and dietary carbohydrate intake obtained by questionnaire modified the effect of the rs10423928 variant at GIPR on incident diabetes, such that the odds of diabetes associated with the established diabetes risk allele (A) were highest in individuals who consumed low levels of dietary fat or high levels of dietary carbohydrate. In the second study, Hindy et al. (29) reported that the diabetogenic effect of the TCF7L2 variant rs7903146 was augmented in individuals consuming high levels of dietary carbohydrate. In the Nurses Health Study, where Cornelis et al. (30) reported that dietary fat and dietary carbohydrate intake obtained by questionnaire and a genetic risk score (GRS) consisting of 10 genetic loci that had previously been reproducibly associated with type 2 diabetes (20). Cross-sectional analyses were conducted in a cohort of 1,196 prevalent and incident case participants with diabetes and 1,337 matched control participants from the Health Professionals Follow-up Study (32). The Western diet score was more strongly associated with diabetes risk in the health professionals with a higher GRS and less so in those with a lower GRS (Pinteraction = 0.02). Interaction analyses focusing on specific components of the Western diet score indicated that consumption of red and processed meat underlies the interactions described above and that heme iron intake, in particular, may be the central component of the diet score driving the interaction with the GRS. However, an analysis of ~50,000 nondiabetic individuals by the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium failed to find any evidence that established glucose- or insulin-associated loci modify the effects of Western dietary pattern on fasting insulin or glucose levels (33).

Individual groups and large consortia have embarked on genome-wide association study (GWAS) analyses stratified by potential effect modifiers such as sex and BMI. These studies are often much larger than single-cohort analyses but are restricted to cross-sectional data, which may hinder the interpretation of results for the reasons discussed above. This is particularly when focusing on BMI, because the onset of diabetes can correspond with weight loss as a consequence of lifestyle changes in the immediate aftermath of a diagnosis, treatment, or of the disease process itself. Nevertheless, in an analysis of 2,112 lean type 2 diabetes case subjects, 4,123 obese type 2 diabetes case subjects, and 54,412 unstratified non-diabetic control subjects, Perry et al. (34) identified a LAMA1 variant that conveyed a significantly higher odds of diabetes in lean compared with obese diabetic case subjects. Similar BMI stratum-specific genetic effects were observed for 29 of the 36 type 2 diabetes loci (binomial P = 0.0002) that had been identified previously in unstratified GWAS meta-analyses performed by the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) consortium (20). These results indicate that when diabetes develops in a person...
who is lean, genetic risk factors are more likely to be present than in someone who is obese and develops the disease or that weight loss enhances the genetic risk of diabetes.

Genetic analyses performed in clinical trials involving intensive lifestyle modification provide an important adjunct to the epidemiological literature on gene-lifestyle interactions in type 2 diabetes. On one hand, a major advantage of randomized controlled trials is that interaction effects observed in trials are likely to reflect causal processes, whereas those observed in epidemiological investigations are more prone to confounding and reverse causality. Other advantages of well-designed clinical trials include relatively precise estimates of the environmental exposures (treatments) and of the phenotypes, careful ascertainment of participants, randomization of exposures, close predetermined follow-up, and hypothesis-driven design. On the other hand, trials are often smaller than epidemiologic cohorts, control poorly for changes in behavior outside the intervention sessions, and typically consist of individuals at high risk of diabetes; hence, results may not be generalizable to other population subgroups.

Only two randomized controlled trials, the Diabetes Prevention Program (DPP) from the U.S. (35) and the Finnish Diabetes Prevention Study (DPS) (36), have reported results for gene-lifestyle interactions in relation to diabetes incidence. Both studies focused on people at high risk of developing type 2 diabetes and implemented almost identical lifestyle intervention protocols. The DPP randomized 1,079 participants to an intensive lifestyle intervention, 1,082 to a placebo control arm, and 1,073 to metformin treatment. In the Finnish DPS, 522 participants were randomized to a lifestyle or control intervention. The DPP is well powered (~80%) to detect genetic effects, with a hazard ratio of 1.2, but has appreciably lower power to detect gene-treatment interactions (37,38); statistical power to detect interactions in the Finnish DPS is less than in the DPP owing to its smaller sample size.

Notwithstanding the sample size constraints of the DPP, a number of interesting findings relating to gene-treatment interactions have emerged from the trial. For example, lifestyle intervention offsets the risk conveyed by the diabetogenic alleles at the TCF7L2 rs7903146 (39) and ENPP1 K121Q (40) loci, or by a genetic risk score consisting of 34 type 2 diabetes-associated variants (41). Elsewhere, the DPP investigators reported that the CDK2NA/B rs10811661 variant diminishes the effects of lifestyle intervention on diabetes risk and on estimated insulin secretion ($P_{\text{interaction}} = 0.05$) (37); interestingly a subsequent cohort study of 8,600 nondiabetic Swedish adults reported directionally consistent interactions between the same genotype and physical activity levels on the odds of impaired glucose regulation and on continuous 2-h glucose concentrations ($P_{\text{interaction}} = 0.015$) (27).

**Hypothesis-free discovery of gene-lifestyle interaction effects**—The decision to carry forward findings from conventional GWAS experiments to detect gene-lifestyle interactions is a simple, pragmatic, and relatively cost-efficient strategy. However, of the many loci associated with cardiometabolic traits, few have been reproducibly shown to interact with environmental factors; $FTO$ (physical activity interactions in obesity) (25), chromosome 9q21 variants (prudent diet interactions in cardiovascular disease and myocardial infarction) (42), and an obesity GRS (sugar-sweetened beverages interaction in obesity) (43) are rare examples of gene-lifestyle interactions in cardiometabolic traits that have been robustly replicated.

The paucity of replicated examples of GWAS-derived loci that interact with lifestyle factors may be due to the low prioritization of follow-up studies by investigators and journal editors or that not all GWAS-derived loci have been examined for interactions in well-designed studies. Alternatively, it is possible that the statistical approaches used in conventional GWAS experiments bias against the detection of variants that interact with environmental factors that are reasonably prevalent within the populations in which the GWAS are performed. Indeed, the GWAS ranking system is typically based on the $P$ value derived from the main effect regression model for each single nucleotide polymorphism (SNP). Of note, common, disease-associated variants have relatively small effect sizes (typically odds ratios $<1.4$ per risk allele); thus, for a genetic association signal to exceed the conservative genome-wide probability threshold used in most GWAS ($P = 5 \times 10^{-8}$), the estimates of the genetic effect are relatively consistent in magnitude within and between the populations included in GWAS meta-analyses, as reflected in the narrow CIs for the odds ratios of the top-ranked loci and low heterogeneity estimates. Broadly speaking, one would expect that the larger the magnitude of a GEI or gene-gene effect, the greater the variance associated with the main effects for the genetic and/or environmental components (44). Hence, with some exceptions (25,27), it is likely that the gene variants that are most relevant for GEI are those that rank poorly in most GWAS meta-analyses.

Genome-wide interaction studies have potential to identify gene variants that influence diabetes risk that might not be detected using hypothesis-driven approaches. However, the statistical power limitations of such studies when applying conventional tests of interaction, combined with the challenges of identifying large cohort collections with appropriately characterized environmental, genetic, and phenotypic data, pose challenges that conventional genetic association studies do not face. Several methods have been developed to mitigate these challenges; among the most promising is the joint meta-analysis approach, which is derived from the model with two degrees of freedom popularized by Kraft et al. (45) and developed further by Manning et al. (46). Manning et al. (47) went on to apply the joint meta-analysis approach in a genome-wide study of 52 cohorts in which they tested for SNP main effects and interactions (with BMI) on fasting glucose and insulin levels. The analysis yielded novel experiment-wide association signals for main effects, but none was discovered for interactions.

Recognizing that heterogeneous effect estimates are a signature of loci involved in interactions, Paré et al. (48) and Visscher and Posthuma (49) developed methods that model genetic associations with genotypic variance estimates rather than with phenotypic means, as is the case in conventional GWAS experiments. Both approaches involve two key steps: in step 1, a phenotypic variance estimate is obtained for each of the genotypes at a SNP locus. A statistical comparison of these variance estimates is then made, and a $P$ value obtained. These $P$ values are ranked from lowest to highest, and those that exceed an experiment-wide threshold are carried forward to step 2, where conventional, pairwise tests of GEI are performed for an array of environmental exposures, with the intent of identifying one or more...
that underlie the SNP’s heterogeneous ef-
fect estimate revealed in step 1. In a recent
application of method described by
Visscher and Posthuma, Yang et al. (26)
performed a meta-analysis for height and
BMI in 170,000 samples and identified a
single locus for BMI that met the genome-
wide significance threshold; intriguingly,
this locus was FTO, the most plausible
candidate for GEI in obesity currently
known. There was no genome-wide sig-
nificant discovery for height, which is
perhaps unsurprising given that this trait
is under much tighter genetic control
than weight and varies much less than
weight across the adult life span.

Pharmacogenetics—Pharma-
cogenetics is a specialized example of GEI.
Here, the environmental exposure is drug
treatment; by studying interactions be-
tween gene variants and treatment, inves-
tigators seek to identify variants that are
associated with adequate or inadequate
response to diabetes therapies. The phar-
cogenetics of diabetes therapies have
been extensively reviewed elsewhere (50–
52). However, three examples illustrate
successful approaches and the potential
clinical utility of pharmacogenetics in
diabetes:

Firstly, studies of HNF1A mutations
that cause a form of maturity-onset dia-
betes of the young showed that carriers of
these mutations, who are often misdiag-
nosed as having type 1 or type 2 diabetes,
respond better to sulfonylureas than met-
formin, thus facilitating their transition
off insulin or metformin (53,54).

Secondly, common genetic variation
in the gene that encodes a transporter
responsible for disposing of metformin
(MATE1, encoded by SLC47A1) has been
associated with metformin response in a
retrospective patient cohort (55), a pre-
liminary finding corroborated in the
DPP clinical trial (56).

Finally, in a discovery GWAS of
1,000 metformin-treated patients from
the Genetics of Diabetes Audit and Re-
search Tayside (GoDARTS) study, a locus
including the ATM gene was associated
with metformin response. This discovery
was initially replicated in independent
GoDARTS and UK Prospective Diabetes
Study cohorts (57) as well as subsequent
cohorts that were similarly ascertained
(58); however, it was not reproduced in
the DPP clinical trial, which differs from
the earlier studies by its experimental,
prospective design and its enrollment of
nondiabetic participants in whom
metformin was used for diabetes preven-
tion (56). If ATM is eventually established
as a causal regulator of metformin re-
sponse, this will provide a novel unex-
pected role for this established oncogene
in diabetes treatment. The challenge for
pharmacogenetics is to establish clinical
utility, which in adult diabetes is cur-
rently limited to the HNF1A paradigm.
An elegant example of how pharmaco-
genetics influences therapy in neonatal
diabetes has been reviewed by Greeley et al.
(59).

Future directions—We have em-
phasized GEI in this Perspective because
this is where most of the published re-
search has been focused to date. A com-
plementary set of disease predictors is
being generated with the emergence of
comprehensive metabolomic approaches,
in which circulating small molecules
present in human fluids are assayed in a
high-throughput manner through liquid
chromatography and mass spectroscopy.
These molecules represent metabolic
readouts of cellular states at a systems
level and reflect the output of gene prod-
ucts and also their interactions with the
environment. Using these platforms,
independent groups have established a me-
tabolomic signature of branched chain
and aromatic amino acids as associated
with obesity and insulin resistance (60)
as well as future diabetes (61). How genes
regulate circulating levels of these mole-
cules, what they tell us about gene
function, how much they reflect environ-
mental factors, and to what extent they
provide orthogonal information for dia-
betes prediction and treatment response
is the subject of intense investigation.
The participant-level integrated assessment
of variation in the genome, metabolome,
and other aspects of the physiome (e.g.,
microbiome, transcriptome, and prote-
ome) in large cohorts has not previ-
ously been possible, but with recent
advances in technology and analytical
methods, and cost reductions, this is
now feasible and is evolving into a new
field called systems epidemiology (Fig. 1).
This topic is eloquently reviewed else-
where (62,63).

Although recent genetic discoveries
in metabolic traits have typically illus-
trated novel pathways, pointed toward
fundamental biology, confirmed prior
epidemiological observations, high-
lighted the role of β-cell dysfunction in
type 2 diabetes, and provided possible
targets for pharmaotherapy, their role
in genetic prediction is less clear. This is
partly so because even in aggregate, they
only explain a relatively small fraction
of the disease’s heritability (41,64–66).
The latter is likely due to insufficient sample
sizes to detect small effects, a nearly
exclusive focus on populations of European
descent, an imperfect capture of infre-
quent genetic variants, an incomplete as-
certainment of alternate (non-SNP) forms
of genetic variation, and the limited ex-
ploration of additional genetic models,
including those involving GEI. As the
community embraces complementary
approaches that include systematic fine-
mapping, custom-made replication,
denser genotyping arrays, platforms
that focus on functional variation, next-
generation sequencing techniques, ex-
ansion to non-European populations,
and integration of other global biological
measurements with genetic data, the
coming years will continue to elucidate
the genetic architecture of metabolic
phenotypes and its interaction with the
environment. A more refined characteri-
zation of the molecular basis of type 2
diabetes can then be translated into
more detailed disease nosology, appro-
priate targeting of more effective and
better tolerated therapeutic or preven-
tive strategies, more rational and effi-
ciently designed clinical trials, and
stratification of risk groups so that costly
public health interventions can be de-
ployed intelligently.

We speculate that the future of di-
babetes medicine may involve genetic and
molecular biomarker screening in pa-
tients to inform the prescription of
lifestyle or drug therapy for diabetes
prevention or management. However,
the translation of this vision into clinical
practice will require structured research
programs that combine observational ep-
idemiology to generate relevant hypoth-
eses and experimental studies that test
these hypotheses and demonstrate cause
and effect. When reliable and causal
interactions are discovered, it will be
necessary to conduct studies proving
that the inclusion of this information
into conventional risk prediction algo-
rithms improves predictive accuracy and/
or reclassification, or that stratified med-
icine informed by biomarker data im-
proves treatment outcomes; in addition, it
will also be necessary to show that these
strategies are cost-effective compared
with conventional approaches.

The concept of stratified medicine
(otherwise known as personalized or
environmental conditions. The integration time in biomedical research when systems Conclusions

achieve glycemic control. This large ran- liraglutide, and the basal insulin inhibitor sitagliptin, the GLP-1 agonist and metagenomic data to enable a comprehensive analysis for discovery of stratification and surrogate biomarkers. Biomarker stratified clinical trials will then be done to establish the utility of biomarker led therapeutics over traditional nonbiomarker led studies.

Similar technologies can be applied in the framework of comparative medicine. The National Institutes of Health-sponsored Glycemia Reduction Approaches for Diabetes: A Comparative Effectiveness Study (GRADE) trial will for the first time perform head-to-head comparisons of representative agents from four major drug classes for type 2 diabetes treatment—the sulfonylurea glimepiride, the DPP-4 inhibitor sitagliptin, the GLP-1 agonist liraglutide, and the basal insulin glargine—as adjuncts to metformin in achieving glycemic control. This large randomized clinical trial, planning to enroll 6,000 participants in 40+ centers throughout the United States, will be launched in the spring of 2013 and will collect phenotypes, covariates, end points, and biomaterials on all participants to enable the deployment of omics techniques to examine prediction and response to pharmacological manipulation.

Conclusions—We are witnessing a time in biomedical research when systems can be queried globally to establish the metabolic state of the organism in a single experiment. Such technologies can also be deployed across populations, tissues, and environmental conditions. The integration of all this information and its interpretation into a cogent vision presents enormous challenges, not least of which is the scientific imperative of reproducibility. As rigorous analytical standards are implemented and international collaborations enable the pursuit of these fundamental questions at an adequate scale, we stand on the verge of a true transformation of medicine as applied to the individual patient. While discovering and replicating evidence of GEIs is proceeding, the process of discussing and planning how such data can be translated into the clinical arena should already be underway. Current discoveries should also prompt us to consider the benefits and challenges (e.g., ethical, economic, logistic) that using genetic information in diabetes medicine is likely to present, which may enable the rapid translation of human genetics research into clinical practice.

Acknowledgments—P.W.F. is funded by Excellence in Diabetes Research in Sweden (EXODIAB), Lund University, Umeå University, Region Skåne Health Authority, the Swedish Diabetes Association, the Swedish Heart-Lung Foundation, the Swedish Research Council, the European Union, Novo Nordisk, and the National Institutes of Health (National Institute of Child Health and Human Development). J.C.F. is supported by National Institute of Diabetes and Digestive and Kidney Diseases Grants R01 DK-072041 and R01 DK-088214.A1. P.W.F. has received speaking honoraria from Novo Nordisk and other academic and not-for-profit organizations. J.C.F. has received consulting honoraria from Lilly and Pfizer.

P.W.F. and J.C.F. are DPP investigators. P.W.F. and E.P. are IMI-DIRECT Study investigators. This article is entirely the work of the authors, unless indicated otherwise.

No potential conflicts of interest relevant to this article were reported.

P.W.F. planned and wrote the initial draft of the manuscript, revised and edited its content, and approved its submission. E.P. and J.C.F. wrote key sections of the manuscript, revised and edited its content, and approved its submission.

The authors’ opinions are the result of many past interactions with mentors, colleagues, collaborators, students, and fellows, for which the authors express their thanks. The authors also thank Shaqat Ahmad (Genetic and Molecular Epidemiology Unit, Lund University, Sweden) for assistance with reference formatting.

References

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48. Paré G, Cook NR, Ridker PM, Chasman DI. On the use of variance per genotype as a tool to identify quantitative trait interaction effects: a report from the Women’s Genome Health Study. PLoS Genet 2010;6:e1000981


