Type 2 diabetes, though poorly understood, is known to be a disease characterized by an inadequate beta-cell response to the progressive insulin resistance that typically accompanies advancing age, inactivity, and weight gain. The disease accounts for substantial morbidity and mortality from adverse effects on cardiovascular risk and disease-specific complications such as blindness and renal failure. The increasing global prevalence of type 2 diabetes is tied to rising rates of obesity—in part a consequence of social trends toward higher energy intake and reduced energy expenditure. However, the mechanisms that underlie individual differences in the predisposition to obesity remain obscure.

Failure to understand the pathophysiology of diseases such as type 2 diabetes and obesity frustrates efforts to develop improved therapeutic and preventive strategies. The identification of DNA variants influencing disease predisposition will, it is hoped, deliver clues to the processes involved in disease pathogenesis. This would not only spur translational innovation but also provide opportunities for personalized medicine through stratification according to an individual person’s risk and more precise classification of the disease subtype. In this article, I consider the extent to which these objectives have been realized.

Discovery of Susceptibility Genes

For type 2 diabetes and obesity, the discovery of causal genes (Fig. 1 and 2) has followed three main waves. The first wave consisted of family-based linkage analyses (see the Glossary) and focused candidate-gene studies. These proved effective in identifying genes responsible for extreme forms of early-onset disease segregating as single-gene (mendelian) disorders. Genes underlying several distinct, familial forms of nonautoimmune diabetes—including maturity-onset diabetes of the young, mitochondrial diabetes with deafness, and neonatal diabetes—were characterized (see the review by Waterfield and Gloyn). Similar approaches revealed mutations in genes responsible for rare forms of severe childhood obesity, including the genes encoding leptin, the leptin receptor, and proopiomelanocortin (see the review by O’Rahilly). These discoveries have provided insights into processes critical for the maintenance of normal glucose homeostasis and energy balance and clues to the inner workings of the pancreatic beta cell and hypothalamus. For many families, this information has led to improved diagnostic and therapeutic options (described in more detail below).

Attempts to apply similar approaches to families in which either common forms of diabetes or obesity is segregating have proved to be largely unrewarding, and the second wave of discovery involved a switch to tests of association. Although intrinsically more powerful than linkage analysis, association analysis suffers from the disadvantage that the signal can be detected only if one examines
the causal variant itself or a nearby marker with which it is tightly correlated. Until the advent of methods that enabled genomewide surveys of association, researchers were therefore obliged to direct their attention to specific candidate variants or genes of interest. In retrospect, it is obvious that most such studies were seriously underpowered or focused on inappropriate candidates. Nevertheless, by accruing data over the course of multiple studies, some genuine susceptibility variants were identified. Common coding variants in \textit{PPARG} and \textit{KCNJ11} (each of which encodes a protein that acts as a target for classes of therapeutic agents widely used in diabetes management) were shown to have modest effects on the risk of type 2 diabetes. Resequencing of the gene encoding the melanocortin-4 receptor (MC4R) resulted in the identification of low-frequency coding variants that explain approximately 2 to 3% of cases of severe obesity.9 The third, and most successful, wave of discovery has been driven by systematic, large-scale surveys of association between common DNA sequence variants and disease. The first demonstration that unbiased discovery efforts could reveal new insights into the pathogenesis of type 2 diabetes resulted from identification of the association between type 2 diabetes and variants within \textit{TCF7L2} (encoding transcription factor 7–like 2, a protein not previously identified as a biologic candidate).10 \textit{TCF7L2} has now been shown to modulate pancreatic islet function.11 The number of loci for which there is convincing evidence that they confer susceptibility to type 2 diabetes started to grow in early 2007 with the publication of the first genomewide as-
Together, these studies revealed six new associations, including variants near **CDKAL1**, **CDKN2A**, and **CDKN2B** (which encode putative or known regulators of cyclin-dependent kinases) and **HHEX** (which is transcribed into a homeobox protein implicated in beta-cell development). Typically each copy of a susceptibility allele at one of these loci is associated with a 15 to 20% increase in the risk of diabetes. Since then, the dominant approach to discovery has involved ever-larger aggregations of genomewide association data from multiple samples so as to improve the power to identify variants of modest effect: these studies have revealed more than 20 additional confirmed signals of susceptibility to type 2 diabetes (Table 1 and Fig. 1). Though early studies were restricted to samples obtained from persons of European descent, genomewide association analyses conducted in other ethnic groups are now emerging. The current total of approximately 40 confirmed type 2 diabetes loci includes variants in or near **WFS1** (wolframin) and the hepatocyte nuclear factors **HNF1A** and **HNF1B** (genes that also harbor rare mutations responsible for monogenic forms of diabetes); the melatonin-receptor gene **MTNR1B** (which highlights the link between circadian and metabolic regulation); and **IRS1** (encoding insulin-receptor substrate 1), one of a limited number of type 2 diabetes loci with a primary effect on insulin action rather than on secretion.

![Genomic Locations of Proven Signals of Body-Mass Index (BMI), Obesity, and Related Phenotypes.](image)

Figure 2. Genomic Locations of Proven Signals of Body-Mass Index (BMI), Obesity, and Related Phenotypes.

Signals are shown according to their location on each chromosome. Genes causing monogenic and selected syndromic forms of obesity (red triangles) are shown to the left. Common variants that have significant genomewide associations with BMI or multifactorial obesity are shown to the right: loci implicated in BMI or weight variation at the population level (solid blue triangles), additional loci identified in case–control analyses of extreme obesity (open blue triangles), and variants identified primarily because of their association with waist circumference or waist-to-hip ratio (solid green triangles). For the variants shown to the right, the genes named within the triangles are indicative of signal position, but in most instances, formal proof that these are the specific genes responsible for the association is lacking.
An RNA sequence resulting from transcription of a DNA transcript:

Syndromic disease:

A DNA sequence variant that is located outside the coding sequence; some are likely to be involved in gene regulation.

Noncoding variant:

The part of the genomic DNA sequence that encodes proteins (consisting of approximately 1.5% of the total human genome).

Genomewide association study:

An approach used in genetics research to look for associations between many (typically hundreds of thousands) of specific genetic variations (most commonly, single-nucleotide polymorphisms) and particular diseases or traits.

Homozygous:

Having the same allele on both chromosomes at a particular location in the genome.

Linkage analysis:

An approach to susceptibility-gene discovery that relies on matching family-level patterns of segregation of the disease of interest with genetic markers of known location.

Monogenic disease:

Genetic disease attributable to variants with large effects on disease status. Because of the high penetrance of such variants, the disease typically cosegregates in a classic mendelian fashion (e.g., dominant or recessive).

Next-generation sequencing:

DNA sequencing that harnesses advances in miniaturization technology to simultaneously sequence multiple areas of the genome rapidly and at low cost.

Noncoding variant:

A DNA sequence variant that is located outside the coding sequence; some are likely to be involved in gene regulation.

Syndromic disease:

Syndromes are characterized by the concomitant occurrence of several distinct clinical features. In syndromic forms of diabetes such as Wolfram’s syndrome, a rare mutation of large effect leads not only to diabetes but also to a diversity of other features including optic atrophy and deafness.

Transcript:

An RNA sequence resulting from transcription of a DNA sequence (often a gene).

obesity have been similarly productive, with three main strategies being adopted (Table 2 and Fig. 2). Genomewide association studies of population-based samples to examine the full range of BMI values have identified approximately 30 loci influencing BMI and the risk of obesity. The strongest signal remains the association with variants within FTO (the fat-mass and obesity–related gene). Other signals near BDNF, SH2B1, and NEGR1 (all implicated in aspects of neuronal function) reinforce the view of obesity as a disorder of hypothalamic function. A second approach, focusing on case–control analysis of persons selected from the extremes of the BMI distribution, has delivered a complementary, only partly overlapping, set of loci. Finally, genomewide analyses of patterns of fat distribution, prompted by the particularly deleterious health effects of visceral fat accumulation, have characterized approximately 15 loci that are largely distinct from those influencing overall adiposity: many of the 15 display markedly stronger associations in women than in men.

FROM GENES TO CLINICAL PRACTICE

Despite the growing number of loci discovered, the contribution of genetic discoveries to the clinical management of diabetes and obesity remains limited to the small proportion of cases with monogenic forms of disease. What, then, are the obstacles impeding the clinical translation of the scores of multifactorial variants now defined?

The first is the modest effect size of the implicated variants. The common variants with the greatest effects on the risk of type 2 diabetes (TCF7L2 in Europeans, KCNQ1 in Asians) result in lifetime prevalence rates that are, in persons carrying two copies of the risk allele, roughly double those seen in persons with none. The association signal at FTO accounts for less than 0.5% of the overall variance in BMI, equivalent to a difference of 2 to 3 kg between adults homozygous for the risk allele and those homozygous for the alternative allele. Most other variants associated with type 2 diabetes and BMI have effects considerably smaller than these. More detailed analysis of the associated regions may reveal that some of these associations are driven by causal variants with larger effects, although empirical evidence supporting this assertion is limited. In contrast, the mutations underlying monogenic forms of diabetes and obesity have far more dramatic clinical consequences: in pedigrees segregating these conditions, knowing whether a family member has inherited a given causal allele generally allows for the confident prediction of disease status.

A second obstacle to the translation of variants implicated in multifactorial forms of diabetes and obesity relates to the speed with which risk-allele discovery has led to an improved understanding of the biologic basis of disease. Most alleles implicated in monogenic and syndromic forms of diabetes and obesity alter the coding sequence and therefore have dramatic
Table 1. Major Genomewide Association (GWA) Studies of Type 2 Diabetes.*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample Size</th>
<th>Major Ethnic Groups</th>
<th>Study Type</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sladek et al., 2007</td>
<td>1,363</td>
<td>French</td>
<td>Single GWA study</td>
<td>HHX and SLC30A8 associations with type 2 diabetes</td>
</tr>
<tr>
<td>Scott et al., 2007</td>
<td>2,335</td>
<td>Finnish</td>
<td>Single GWA study</td>
<td>CDKAL1, CDKN2A, and IGF2BP2 associations with type 2 diabetes</td>
</tr>
<tr>
<td>Diabetes Genetics Initiative et al., 2007</td>
<td>2,931</td>
<td>Swedish, Finnish</td>
<td>Single GWA study</td>
<td>CDKAL1, CDKN2A, and IGF2BP2 associations with type 2 diabetes</td>
</tr>
<tr>
<td>Zeggini et al., 2007</td>
<td>4,862</td>
<td>British</td>
<td>Single GWA study</td>
<td>CDKAL1, CDKN2A, and IGF2BP2 associations with type 2 diabetes</td>
</tr>
<tr>
<td>Steinthorsdottir et al., 2007</td>
<td>6,674</td>
<td>Icelandic</td>
<td>Single GWA study</td>
<td>CDKAL1 association with type 2 diabetes and insulin secretion</td>
</tr>
<tr>
<td>Zeggini et al., 2008</td>
<td>10,128</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>Six new loci for type 2 diabetes (NOTCH2, JAZF1, ADAMTS9, TSPAN8, THADA, and CDC123)</td>
</tr>
<tr>
<td>Yasuda et al., 2008</td>
<td>1,691</td>
<td>Japanese, Korean, Chinese</td>
<td>Single GWA study</td>
<td>KCNQ1 association with type 2 diabetes in East Asians</td>
</tr>
<tr>
<td>Unoki et al., 2008</td>
<td>1,752</td>
<td>Japanese, Singaporean</td>
<td>Single GWA study</td>
<td>KCNQ1 association with type 2 diabetes in East Asians</td>
</tr>
<tr>
<td>Rung et al., 2009</td>
<td>1,376</td>
<td>French, Danish</td>
<td>Single GWA study</td>
<td>IRS1 association with type 2 diabetes</td>
</tr>
<tr>
<td>Prokopenko et al., 2009</td>
<td>36,610</td>
<td>European</td>
<td>Follow-up of signals for type 2 diabetes from GWA scan for fasting glucose</td>
<td>MTNR1B association with type 2 diabetes and fasting glucose</td>
</tr>
<tr>
<td>Lyssenko et al., 2009</td>
<td>2,931</td>
<td>Swedish, Finnish</td>
<td>Follow-up of signals for type 2 diabetes from GWA scan for insulin secretion</td>
<td>MTNR1B association with type 2 diabetes and fasting glucose</td>
</tr>
<tr>
<td>Bouatia-Naji et al., 2009</td>
<td>2,151</td>
<td>French, Danish, Finnish</td>
<td>Follow-up of signals for type 2 diabetes from GWA scan for fasting glucose</td>
<td>MTNR1B association with type 2 diabetes and fasting glucose</td>
</tr>
<tr>
<td>Dupuis et al., 2010</td>
<td>46,186</td>
<td>European</td>
<td>Follow-up of signals for type 2 diabetes from GWA scan for fasting glucose</td>
<td>ADCY5, PROX1, GCK, GCKR, and DGKB associations with type 2 diabetes and fasting glucose</td>
</tr>
<tr>
<td>Tsai et al., 2010</td>
<td>1,889</td>
<td>Taiwanese</td>
<td>Single GWA study</td>
<td>SRR and PTPRD associations with type 2 diabetes in Taiwanese</td>
</tr>
<tr>
<td>Qi et al., 2010</td>
<td>5,643</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>RBMS1 association with type 2 diabetes</td>
</tr>
<tr>
<td>Voight et al., 2010</td>
<td>47,117</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>12 New loci for type 2 diabetes including DUSP9, KL14, CENTD2, HMG2A, and HNF1A</td>
</tr>
</tbody>
</table>

* Only studies in which there were significant genomewide associations with type 2 diabetes are listed.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample Size</th>
<th>Major Ethnic Group</th>
<th>Study Type</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frayling et al., 2007</td>
<td>4,862</td>
<td>British</td>
<td>GWA study of type 2 diabetes cohort</td>
<td>FTO association with BMI, obesity, and type 2 diabetes</td>
</tr>
<tr>
<td>Scuteri et al., 2007</td>
<td>4,741</td>
<td>Sardinian</td>
<td>GWA study of large population isolate</td>
<td>FTO association with BMI</td>
</tr>
<tr>
<td>Loos et al., 2008</td>
<td>16,876</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>Association of common MC4R variants with BMI</td>
</tr>
<tr>
<td>Chambers et al., 2008</td>
<td>2,684</td>
<td>South Asian</td>
<td>GWA study of population sample</td>
<td>MC4R association with waist circumference</td>
</tr>
<tr>
<td>Willer et al., 2009</td>
<td>32,387</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>TMEM18, KCTD15, GNPDA2, SH2B1, MTCH2, and NEGR1 associations with BMI</td>
</tr>
<tr>
<td>Thorleifsson et al., 2009</td>
<td>34,416</td>
<td>Icelandic</td>
<td>GWA study of large population isolate</td>
<td>Nine new associations with BMI (NEGR1, TMEM18, ETV5, BDNF, FAIM2, KCTD15, SH2B1, and SEC16B) or weight (NCR3)</td>
</tr>
<tr>
<td>Meyre et al., 2009</td>
<td>2,796</td>
<td>French</td>
<td>GWA study of morbidly obese adults vs. normal-weight controls</td>
<td>Associations of signals near NPC1, MAF, and PTER with extreme obesity (from case–control analyses)</td>
</tr>
<tr>
<td>Lindgren et al., 2009</td>
<td>38,580</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>Associations near TFAP2B and MSRA with waist circumference and near LYPLAL1 with waist-to-hip ratio</td>
</tr>
<tr>
<td>Heard-Costa et al., 2009</td>
<td>31,373</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>Associations of NRXN3 variants with waist circumference</td>
</tr>
<tr>
<td>Scherag et al., 2010</td>
<td>2,258</td>
<td>European</td>
<td>GWA study of persons with extreme early onset obesity vs. lean controls</td>
<td>SDCCAG8 and TNKS–MSRA associations with childhood obesity</td>
</tr>
<tr>
<td>Speliotes et al., 2010</td>
<td>123,865</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>18 New loci (including POMC, GIPR, and HMGAL1) influencing BMI</td>
</tr>
<tr>
<td>Heid et al., 2010</td>
<td>77,167</td>
<td>European</td>
<td>GWA meta-analysis</td>
<td>13 New loci (including VEGFA, TBX15, and HOXC13) influencing waist-to-hip ratio independent of BMI</td>
</tr>
</tbody>
</table>

* Only studies in which there were significant genomewide associations with BMI, waist circumference, waist-to-hip ratio, or obesity are listed.
and largely predictable effects on the function of the gene. The use of molecular diagnostics to derive clinically useful prognostic and therapeutic information relies on this relatively straightforward assignment of functional significance. In multifactorial disease, however, most susceptibility variants lie outside the coding regions of genes and are assumed to influence transcript regulation rather than gene function.

Characterization of the downstream consequences of these “noncoding” variants is difficult, given our rudimentary knowledge of the mechanics of gene regulation. Detailed functional studies are required to translate these genomic “signposts” into biologic knowledge that can spur translational development, and there have been relatively few successes. Indeed, at most susceptibility loci, it remains far from clear even which transcripts mediate the susceptibility effects that have been observed.

The time required to achieve clinical translation is often underestimated, and most of the discoveries in multifactorial disease have simply been too recent for their full translational potential to be realized. That potential lies in three main areas: the characterization of disease mechanisms that provide new targets for treatment and prevention, improved risk prediction and differential diagnosis, and personalized treatment and prevention.

**From Genetics to Biology**

An improved understanding of pathophysiology achieved through genetic discovery provides new opportunities for treatment, diagnosis, and monitoring. Studies of risk variants for type 2 diabetes in healthy populations have shown that most variants act through perturbation of insulin secretion rather than insulin action, establishing inherited abnormalities of beta-cell function or mass (or both) as critical components of the progression to type 2 diabetes (Fig. 3). (An interactive graphic depicting proposed mechanisms of...)

![](https://www.nejm.org/doi/fig/3598534241010238/762355/1207187f3.png)
functions have roles in the maintenance of normal islet function. Beyond that, efforts to identify key processes in the pathogenesis of type 2 diabetes — for example, by showing that genes encoding members of particular pathways are overrepresented at susceptibility loci — have not been particularly rewarding. Either type 2 diabetes is highly heterogeneous, or those fundamental disease processes are poorly captured by existing biologic knowledge.

Efforts to achieve therapeutic modification of weight have had little success. The identification of new pathways amenable to safe and effective weight manipulation would be a valuable “deliverable” from genetic-discovery efforts. However, the transition from association signal to causal mechanism has not been straightforward, especially when the disease involves tissues as inaccessible to direct study as the human hypothalamus. Consider the example of FTO. Although the association signal maps to a clearly defined region of the gene, and the effect is comparatively large, there is still some doubt as to whether FTO itself is responsible for the weight phenotype, rather than one of the nearby genes such as RPGRIP1L (also expressed in the hypothalamus, with responses to alterations in nutritional and hormonal status similar to those of FTO). Studies of mice with disruptions of Fto sequence are consistent with the hypothesis that FTO mediates the BMI effect in humans, whereas studies of human FTO mutations have been less clear-cut. Notwithstanding these data, the story emerging from the growing number of loci supports the view of overall obesity as a disease of hypothalamic dysregulation. In contrast, variation in patterns of fat distribution is associated with variants within genes that influence adipocyte development and function. How best to use this information to effect early translation into new therapeutic or preventive approaches remains uncertain.

One characteristic of metabolic disease is the cluster of traits referred to as the metabolic syndrome. However, the genetic evidence to date provides limited support for the metabolic syndrome as a defined pathophysiological entity, perhaps indicating that this clustering is driven by environmental factors. Though BMI-associated variants such as FTO modulate the risk of type 2 diabetes and hyperlipidemia, and loci altering lipid levels have secondary effects on the risk of coronary artery disease, there is little suggestion that the variants implicated in individual components of the metabolic syndrome overlap. At some loci, the patterns of association actually run counter to the broader correlative patterns of the metabolic syndrome. At the glucokinase regulator gene GCKR, for example, one common variant allele increases triglyceride levels yet lowers glucose levels. The complexity of the relations that can exist at the genetic level between closely related phenotypes is further illustrated by the observation that alleles associated with similar degrees of fasting hyperglycemia in healthy populations have highly variable effects on the risk of type 2 diabetes later in life.

In cases of monogenic disease, genetic information can provide powerful diagnostic and predictive value for selected patients. Since subtypes of monogenic diabetes and obesity vary in their prognostic implications and therapeutic recommendations, a definitive molecular diagnosis is an important component of clinical management (Table 3). To date, the use of molecular diagnostic tools has been limited by the expense of using conventional sequencing technologies to screen known causal genes for mutations that are often specific to a given family. Next-generation sequencing technologies are likely to be transformative in the medium term, though distinguishing pathogenic mutation from incidental variation will remain a challenge. In the meantime, improved biomarkers of diabetes subtypes that enable the more precise targeting of diagnostic resequencing would be valuable. For ex-
ample, patients with maturity-onset diabetes of the young caused by \textit{HNF1A} mutations have recently been shown to have C-reactive protein (CRP) levels well below those of patients with other subtypes of diabetes, suggesting that CRP could form the basis of a useful diagnostic test.\textsuperscript{63} This observation also exemplifies the early translation of genetic discoveries, since it came directly from genomewide association studies showing that CRP levels are influenced by common variants near \textit{HNF1A}.\textsuperscript{22,43}

The effect sizes of the known, common variants influencing the risk of type 2 diabetes and variation in adult BMI are modest, and the proportion of overall predisposition explained is small: approximately 5 to 10\% for type 2 diabetes and 1\% for BMI.\textsuperscript{22,43} As a result, the ability to perform individual-level prediction with respect to these traits is limited. By combining data from multiple loci, one can identify persons who have inherited especially high or low numbers of risk alleles: the risk of type 2 diabetes differs by a factor of approximately 4 between persons in the top 1\% and those in the bottom 1\% of the “risk-score” distribution.\textsuperscript{64-67} However, the risk profiles of many such persons are already discernible on the basis of conventional risk factors (e.g., BMI or family history), and there is limited evidence to suggest that information about genetic predisposition can be used effectively to guide the modification of long-term behavior. The discriminative accuracy of genetic profiling of known type 2 diabetes risk variants (as measured by means of receiver-operating-characteristic curves) is only approximately 60\%,\textsuperscript{64-67} well below the threshold required for clinical usefulness and the degree of prediction achievable on the basis of nongenetic risk factors.\textsuperscript{68} Furthermore, estimates of risk can depend crucially on exactly which variants are included in the risk profile.\textsuperscript{69} The key to improved performance will be the identification of risk variants with greater effect sizes than those discovered so far. Since existing genomewide association studies have most likely captured any common variants of large effect, the search is now focused on less-common variants.

A person’s risk of type 2 diabetes or obesity reflects the joint effects of genetic predisposition and relevant environmental exposures. Efforts to determine whether these genetic and environmental components of risk interact (in the statistical sense that joint effects cannot be predicted from main effects alone)\textsuperscript{70} face challenges associated with measuring relevant exposures (diet and physical activity being notoriously difficult to estimate) and the effect of imprecision on statistical power.\textsuperscript{71} Although claims that statistical interactions reflect shared mechanisms (i.e., that the interacting factors act

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Diabetes Subtype} & \textbf{Causal Genes} & \textbf{Optimal Treatment} \\
\hline
Type 1 diabetes & About 40 known (genes in HLA region, \textit{INS}, \textit{PTPN22}, and others) & Lifelong insulin \\
\hline
Type 2 diabetes & About 40 known (\textit{TCF7L2}, \textit{CDKAL1}, and others) & Metformin as primary treatment; also sulfonylureas, glitazones, or insulin \\
\hline
LADA & Genes in HLA region, \textit{INS}, and \textit{PTPN22} (as in type 1 diabetes) & Early recourse to insulin therapy \\
\hline
GCK-MODY & \textit{GCK} & Diet modification \\
\hline
HNF1A MODY & \textit{HNF1A} & Sulfonylureas (low dose) \\
\hline
Mitochondrial diabetes & \textit{MTTL1} & Early recourse to insulin therapy \\
\hline
Lipodystrophies & \textit{LMNA}, \textit{PPARG}, \textit{AGPAT2}, \textit{CAV1}, \textit{BSCL2}, \textit{LMNB2}, and \textit{AKT2} & Uncertain; thiazolidinediones for some subtypes \\
\hline
Neonatal diabetes & \textit{KCNJ11}, \textit{ABCC8} & Sulfonylureas (high dose) \\
\hline
Neonatal diabetes & \textit{INS} & Insulin \\
\hline
\end{tabular}
\caption{Initial Treatments for Various Diabetes Subtypes.}\textsuperscript{6}
\end{table}

\textsuperscript{*} GCK denotes glucokinase, LADA latent autoimmune diabetes in adults, MODY maturity-onset diabetes of the young, and tRNA transfer RNA.
through the same pathways) are probably overstated, understanding the relative contributions of genetic and environmental components to risk is important. After all, environmental factors can be modified more readily than genetic factors.

Genetic discoveries have provided a molecular basis for the clinically useful classification of monogenic forms of diabetes and obesity. Will the same be true for the common forms of these conditions? Probably not: as far as the common variants are concerned, each patient with diabetes or obesity has an individual “barcode” of susceptibility alleles and protective alleles across many loci. It is possible to show that the genetic profiles of lean subjects with type 2 diabetes and obese subjects with type 2 diabetes are not identical, but these differences appear to be inadequate for clinically useful subclassification. If efforts to uncover less prevalent, higher-penetrance alleles are successful, more precise classification of disease subtypes may become possible, particularly if genetic data can be integrated with clinical and biochemical information. For example, in persons presenting with diabetes in early adulthood, there are several possible diagnoses: various subtypes of maturity-onset diabetes of the young or mitochondrial diabetes, for example, as well as type 1 or type 2 diabetes. Assigning the correct diagnosis has both prognostic and therapeutic benefits for the patient (Table 3).

**SUMMARY**

Given the substantial time it takes to translate basic biomedical discoveries into clinical tools, any current assessment of the clinical value of recent advances in the genetic basis of common diseases is probably an underestimate. An improved understanding of fundamental disease mechanisms is already emerging; this will underpin future therapeutic advances. But the expansion of personalized medicine beyond monogenic forms of disease awaits a more complete description of predisposition. The boundaries of personalized medicine will be much clearer in a few years, after large-scale genomewide resequencing efforts (now under way) provide a systematic, comprehensive description of the relations between genome sequence variation and major clinical phenotypes.

Dr. McCarthy reports receiving consulting fees from Prosidion Pharmaceuticals and lecture fees from Novo Nordisk. No other potential conflict of interest relevant to this article was reported. Disclosure forms provided by the author are available with the full text of this article at NEJM.org.
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