NIH working group report—using genomic information to guide weight management: From universal to precision treatment

Review

Obesity

NIH Working Group Report—Using Genomic Information to Guide Weight Management: From Universal to Precision Treatment

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Objective: Precision medicine utilizes genomic and other data to optimize and personalize treatment. Although more than 2,500 genetic tests are currently available, largely for extreme and/or rare phenotypes, the question remains whether this approach can be used for the treatment of common, complex conditions like obesity, inflammation, and insulin resistance, which underlie a host of metabolic diseases.
Methods: This review, developed from a Trans-NIH Conference titled "Genes, Behaviors, and Response to Weight Loss Interventions," provides an overview of the state of genetic and genomic research in the area of weight change and identifies key areas for future research.
Results: Although many loci have been identified that are associated with cross-sectional measures of obesity/body size, relatively little is known regarding the genes/loci that influence dynamic measures of weight change over time. Although successful short-term weight loss has been achieved using many different strategies, sustainable weight loss has proven elusive for many, and there are important gaps in our understanding of energy balance regulation.
Conclusions: Elucidating the molecular basis of variability in weight change has the potential to improve treatment outcomes and inform innovative approaches that can simultaneously take into account information from genomic and other sources in devising individualized treatment plans.

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Introduction

The prevalence of overweight and obesity in the United States and other Western countries has seen sharp increases, and worldwide obesity prevalence is increasing at alarming rates, including in populous nations, such as India and China (1). The precipitous rise in obesity prevalence, coinciding with the abundance of palatable, highly processed, energy-dense foods and reduced physical activity levels, demonstrates the substantial contribution of environmental factors to obesity. Nevertheless, a sizeable proportion of the population remains of normal weight despite living in obesogenic settings, suggesting that the extent to which people or populations respond to influences in their surroundings may be determined by innate factors, such as genetic makeup. The heritability of body mass index (BMI) has been consistently estimated at approximately 40-70% (2-5), suggesting that about half of the interindividual variance in body size can be attributed to genes, whereas the other half is due to environmental influences. Both experimental and epidemiological studies have provided extensive evidence for an intricate interplay between genes and environment in the regulation of body weight and energy balance (6,7).

Although a genetic basis for obesity and body composition has been well established (8), family and twin studies also provide evidence that a person's genetic makeup plays a role in response to weight loss or gain. In classic genetic studies of energy balance in which body weight was manipulated via overfeeding or exercise in monozygotic (MZ) twins, Bouchard et al. reported a high concordance between the twin pairs for both weight gain ($r_{\text{within-pair}} = 0.55$; $F = 3.4$) (9) and weight loss ($r_{\text{within-pair}} = 0.74$; $F = 6.8$) (10). These investigators later reported

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that a variant in the resistin gene (*RETN*, IVS2 + 39C>T) was associated with increases in both abdominal visceral and total fat following overfeeding in MZ twins, with individuals with the TC genotype having significantly higher values of both measures compared with TT homozygotes (11). Using a similar MZ twin design but inducing a daily energy deficit via a 400 kcal/day energy-restricted diet, Hainer et al. (12) observed 12.8 times more variation in weight loss between pairs than within twin pairs ($r_{\text{within-pair}} = 0.85$; $F = 12.8$). In another study of MZ and dizygotic twins, Keski-Rahkonen et al. (13) reported the heritability of intentional weight loss of ≥5 kg to be 38% (95% confidence interval [CI], 19%-55%) in men and 66% (95% CI, 55%-75%) in women. More recently, Hatoum et al. (14) found that a patient's genetic makeup was a strong determinant in weight loss after gastric bypass surgery; first-degree relatives lost a similar amount of weight following surgery (9% difference; intraclass correlation coefficient [ICC] = 70.4%), which was not observed between co-habiting individuals (26% difference; ICC = 0.9%) or other unrelated individuals (25% difference; ICC = 14.3%) following surgery. Taken together, these twin and family studies indicate that response to weight change interventions varies widely between individuals and that this may be under some degree of genetic control.

To date, large-scale genome-wide association studies (GWAS) have identified nearly 150 genetic variants that have been significantly associated with cross-sectional measures of BMI, waist circumference, or obesity risk, many in multiple populations (15,16). Among the most consistent findings are those for pathways affecting central nervous system processing and neural regulation of feeding (e.g., *BDNF*, *MC4R*, *NEGR1*), as well as genes associated with fasting insulin secretion and action, RNA binding/processing, energy metabolism, lipid biology, and/or adipogenesis (e.g., *FTO*, *TCF7L2*, *IRS1*, *FOXO3*, *RPTOR*, *PTBP2*, *MAP2K5*, *MAPK3*) (15). For many GWAS variants, the underlying biology that links the variant to body weight regulation is unclear. Many of these loci lie in regulatory and/or other noncoding regions and may play important roles in gene regulation, but not necessarily for the gene to which they have been attributed (17,18). For example, variants within the *FTO* gene, which have been consistently associated with obesity traits in multiple GWAS, have recently been shown to reside within enhancer elements that regulate expression of the *IRX3* and *IRX5* genes, which appear to influence adipocyte development, thermogenesis, and lipid storage (19). Importantly, the combined contribution of all variants associated with body size measures to date is less than 5%, with *FTO* having one of the largest effects at 0.34% (20). Using an approach called genome-wide complex trait analysis (GCTA), which estimates the combined effect of all genomic variation on complex outcomes, the genomic heritability of cross-sectionally measured BMI has been estimated to be between 16% and 30% (21,22). Although the GCTA approach is likely to underestimate heritability, as it only reflects variation captured on the genotyping array, these estimates suggest that environmental context, gene-gene, gene-environment, epigenetic, and/or other types of interaction/regulation may be critical to consider in assessing the genetic underpinnings of a complex outcome, such as energy balance. As an example, Winkler et al. (23) recently identified 21 novel loci with significant age- or gender-specific associations with BMI or body shape.

It remains unclear whether variants associated with cross-sectional measures of overall or abdominal obesity traits also contribute to dynamic measures of body weight, as the genetic determinants of weight change may differ from those associated with BMI (24). Few studies have been performed to assess the role of genetic variation within the context of weight change *a priori*, either in free-living populations or in clinical trials involving specific behavioral, dietary, or other types of interventions. Despite substantial evidence for a genetic component contributing to the regulation of body mass/composition, only a limited number of genes (described later) have been associated with body weight change in response to changes in the environment.

Defining Weight Change Phenotypes

It is important to consider that changes in body weight and BMI, although commonly used in large epidemiologic and clinical trials because of their ease of measurement, may not fully capture genetic associations with weight-related phenotypes. For example, in a 1-year controlled trial of moderate exercise, variation in the cytochrome p19 (*CYP19*) gene was associated with significant decreases in total body fat (−3.1 kg vs. −0.5 kg, respectively for those with two vs. no copies of the *CYP19* 11-repeat alleles, $P < 0.01$) and percent fat (−2.4% vs. −0.6%, respectively, $P < 0.001$) but not change in BMI, suggesting that genes may act upon body fatness without significantly influencing body weight *per se* (25). Measures of body circumferences following weight loss may indicate important changes in fat distribution and lean body mass, and more refined measures of visceral versus subcutaneous fat using computed tomography or magnetic resonance imaging may also provide measures that are more closely correlated with gene function than BMI or body weight.

Weight change is a complex outcome, as both the degree and pattern of weight change impact health. For example, in the Diabetes Prevention Program (DPP; described in more detail later), both short- and intermediate-term weight loss were associated with reduced diabetes risk and intermediate cardiometabolic risk factor levels, whereas weight cycling (defined as number of 5 lb [2.25 kg] weight cycles) raised diabetes risk, fasting glucose levels, insulin resistance, and systolic blood pressure. Initial (baseline to 1 month) and late (last 6 months of the 2-year intervention period) weight loss had no discernable impact of diabetes risk (26). Similar results have been reported in people with pre-existing diabetes who underwent lifestyle intervention as part of the Look AHEAD (Action for Health in Diabetes) trial (27). These studies point to alternative phenotypes that may be informative for genetics studies of weight loss/maintenance/regain.

Genetic Predictors of Obesity Treatment Response

Given the small effects of BMI loci identified to date, it is possible that genetic effects may be more closely aligned with dynamic, rather than static, phenotypes. In a recent GWAS of weight change trajectories from age 1-17 years, Warrington et al. (28) identified a novel variant in the *FAM120AOS* gene and confirmed three known adult BMI-associated loci (*FTO*, *MC4R*, and *ADCY3*) and one childhood obesity locus (*OLFM4*) with significant genome-wide association ($P_{\text{Wald}} < 1.13 \times 10^{-8}$) with BMI at 8 years and/or change over time. The analysis of short-term change in response to weight loss interventions may also reveal novel genes/loci and biology associated with treatment response.

Behavioral strategies for weight loss, involving kilocalorie restriction and physical activity, are currently the frontline treatment for common forms of obesity (29). Randomized controlled trials of lifestyle interventions for behavioral weight loss reliably produce initial weight losses of 7% or more, resulting in clinically important health benefits (30,31). Two of the largest obesity-treatment randomized controlled trials to date have focused on energy intake, dietary fat, and physical activity to support weight loss goals. The DPP randomized 3,234 individuals with obesity or overweight and at risk for diabetes to metformin treatment, lifestyle intervention, or a placebo control arm (30,32). In the Look AHEAD study, 5,145 individuals with obesity or overweight who had Type 2 diabetes (T2D) were randomized to intensive lifestyle intervention (ILI) or a diabetes support and education (DSE) control without an active weight loss program (33). Both weight loss interventions produced significant weight losses as compared with the control groups (e.g., Look AHEAD, Year 1 percent weight change, ILI: $-8.6\% + 6.9\%$, DSE: $0.7\% + 4.8\%$) (6). Partial weight regain was nonetheless common (e.g., Look AHEAD, Year 4 percent weight change: ILI: -6.15% vs. DSE: -0.88%; percent weight change at a median of 9.6-year follow-up: ILI: -6.0% vs. DSE: -3.5% (31,34)).

The largest study to date to address the role of genetic variation in weight loss response examined the association between 91 established obesity-predisposing loci, derived from the comprehensive results of GWAS available in 2015 (15), and weight loss or weight regain in the DPP and Look AHEAD cohorts (35). The combined genetic sample included 5,730 participants randomly assigned to either behavioral weight loss treatment or a control condition. Of the 91 loci, one was consistently associated with weight loss over 4 years in meta-analysis. Each copy of the minor G allele for the rs1885988 variant at *MTIF3* was significantly associated with a mean 1.14 kg lower weight in the lifestyle arm versus a nonsignificantly higher weight of 0.33 kg in the comparison arm. These effects produced a statistical interaction of gene × treatment arm reaching experiment-wide significance at Year 3 and nominal significance across the 4 years. Nevertheless, no other obesity-associated loci predicted weight loss, and no loci predicted weight regain. The *MTIF3* gene encodes a protein that is essential for ATP synthesis and energy balance in the mitochondria (36). The minor G allele has previously been associated with higher BMI (37,38) and hip circumference (39). Thus, carriers of the *MTIF3* obesity-inducing allele seem to benefit more from ILIs than noncarriers. This locus has also begun to emerge in epidemiologic gene × environment interactions studies of BMI, with *MTIF3* genotype associated more strongly with BMI for those eating a healthy dietary intake pattern compared with those in the nonhealthy diet group (40).

No studies to date have searched for novel genetic loci associated with behavioral weight loss leveraging a genome-wide approach. The only exploratory study to date comes from Look AHEAD, in which single nucleotide polymorphism (SNP) variation across the IBC chip (Illumina, San Diego, CA), a gene-centric assay of roughly 50,000 SNPs covering early candidate genes for cardiovascular disease, was examined in relation to magnitude of weight loss after 1 year (41). Two novel regions of significant array-wide association with Year 1 weight loss in ILI were identified. *ABCB11/G6PC* rs484066 was associated with 1.16 kg less weight loss per minor allele at Year 1, whereas *TNFRSF11A*, or *RANK*, rs17069904 was associated with 1.70 kg greater weight loss per allele at Year 1. *ABCB11*, or *BSEP*, is a bile salt export pump and the primary mediator of bile salt secretion and fat transport from the gut. *G6PC* is a primary regulator of glucose homeostasis with mutations related to hypoglycemia; this locus has previously been identified as a predictor of high density lipoprotein cholesterol and glucose in GWAS (42,43). *RANK*, along with the *RANK* ligand, are members of the tumor necrosis factor (*TNF*) family of genes and are expressed in adipose tissue (44). Although provocative, these exploratory analyses await confirmation in independent samples. Smaller trials have tested whether genetic variants may predict differential response to diets varying in macronutrient composition. For example, the Pounds Lost trial (45) found individuals carrying obesity-associated alleles at the *FTO* locus to differentially benefit from a high-protein, calorie-restricted diet in losing weight (46). Variation in the *FTO* locus has also been shown to be associated with weight loss following bariatric surgery (47,48). This interesting research awaits further replication.

Taken together, this emerging evidence indicates that genetic variation may impact the efficacy of behavioral weight loss interventions. Initial results indicate that agnostic genetic association studies focused on treatment response may yield new insights into genetic predictors of weight loss, but larger trials or a consortium of weight loss trial will be required to achieve the larger samples size necessary to test these hypotheses with statistical certainty.

Complex Systems That Influence Energy Balance

Epigenetic mechanisms in energy homeostasis and obesity

Interactions between the environment and the genome that modulate the risk for obesity can happen through direct chemical alterations, including DNA methylation and histone modifications (49). Methylation, an epigenetic mechanism that can both positively and negatively regulate gene expression, plays a critical role in driving many cell-specific and tissue-specific functions. It is now well established that some epigenetic modifications of DNA may also occur in response to changes in the environment, including nutrition and exercise, which can alter gene expression in a stable and heritable manner that may influence metabolism, behavior, and ultimately overall health. These features make epigenetics a potentially important pathogenic mechanism in complex disorders, such as obesity.

Recent epigenome-wide association studies have shown that physical activity and high-fat diets may alter the DNA methylation pattern in tissues of importance for energy homeostasis such as skeletal muscle and adipose tissue (50-52); these epigenetic changes may affect weight loss and/or weight gain. In support of this hypothesis, a 6-month exercise intervention was associated with altered DNA methylation patterns of numerous candidate genes for obesity, such as *FTO*, *GRB14*, and *TUB* in adipose tissue, as well as of genes regulating adipogenesis, and was associated with decreased waist circumference in sedentary middle aged men (50). Additionally, obesity has been associated with altered DNA methylation compared to individuals without obesity in numerous human studies (49,53-55). *HIF3A* has shown consistent differential DNA methylation in relation to obesity in several studies (56,57). Epigenetic mechanisms may also affect a person's response to weight increase, weight loss,

and maintenance by controlling genes that regulate energy homeostasis. For example, Demerath et al. (55) found that the degree of methylation of eight different CpG sites, including one site near *CPT1A*, was associated with a change in BMI in participants who gained weight over a 30-year period. Additionally, when Dahlman et al. (58) compared the methylome in adipocytes from women who formerly had obesity and had lost weight following gastric bypass surgery with women who had never had obesity, they found differential DNA methylation of genes involved in adipogenesis.

Weight loss associated with roux-en-Y gastric bypass surgery, which is commonly used to treat morbid obesity, was recently shown to alter the epigenome in adipose tissue, skeletal muscle, and blood (59-61). Interestingly, maternal weight loss by gastric bypass surgery was also found to influence the methylation pattern of offspring born after, versus before, weight loss (62). In a separate study, Nicoletti et al. (63) compared epigenetic changes in relation to two different weight loss strategies: an energy-restricted diet and gastric bypass surgery, and they reported that baseline methylation of *SERPINE1* may predict weight loss after gastric bypass surgery. Together, these studies support an important role for epigenetic mechanisms in controlling energy homeostasis and obesity. However, further studies are needed to fully dissect the role of epigenetics in the growing incidence of obesity and to establish whether epigenetic markers may be used to guide weight management.

The microbiome and weight change

The human microbiome may play a significant role in the etiology of obesity in both humans and animal models (64). Hosted in the gastrointestinal tract, the gut microbiome is part of a large endocrine organ that regulates not only nutrient sensing and metabolism but also satiety and energy homeostasis. The millions of microorganisms comprising the complex intestinal "superorganism" perform a number of functions for host health, including food processing, breakdown and metabolism of indigestible nutrients, pathogen displacement, synthesis of vitamins, and regulation of body weight (65). They play such an important role that we now know that microbiota disruptions in early life can have long-lasting effects on body weight in adulthood (66). The host bacterial composition has been shown to adapt in response to dietary factors and in response to weight loss. Diet or surgically induced weight loss promote alterations in the gut that can impact the efficacy of the treatment strategies (67,68). Specific bacterial species can have influences by themselves. For example, the archaeon *Methanobrevibacter smithii*, has an enhanced ability to metabolize dietary substrates or end products of the metabolism of other bacteria, thereby increasing host energy intake and weight gain (69).

Experiments in animal models, particularly rodents, show specific reproducible changes in the microbiota because of the ability to control factors such as genetics, diet, and environment. However, in humans, these effects have been less consistently demonstrated. With weight loss, there is a decrease in the ratio of Firmicutes to Bacteroidetes phyla (68). Damms-Machado et al. (70) demonstrated that surgical weight loss interventions like laparoscopic sleeve gastrectomy seem to improve the obesity-associated gut microbiota toward a lean microbiome phenotype. They described a reduction of the energy-reabsorbing potential of the gut microbiota following surgery indicated by the Firmicutes/Bacteroidetes ratio. The interaction of a community depends on a balanced microbial diversity, and each group has different tasks and different qualities, which together compose a "healthy" microbiome (71). Manipulation of gut microbiota could reduce intestinal low-grade inflammation and improve gut barrier integrity, ameliorating metabolic balance and promoting weight loss (71). The use of prebiotics and probiotics as potential aids in weight loss/gain interventions has great potential, but further evidence is needed to better understand the real clinical potential of studies of the gut microbiome.

Behavioral Phenotypes Underlying BMI and Body Weight Change

Of the known genes underlying Mendelian forms of severe obesity (see Table 1), one consistent underlying feature is hyperphagia, suggesting that ingestive *behavior* may be the prime driver of weight gain or loss. Many of the loci associated with obesity in GWAS are also expressed in the brain and often specifically in hypothalamic eating regulatory pathways (15). Physical activity is a second prominent health behavior known to prevent weight gain and promote weight loss maintenance (72-75). Both eating and physical activity behaviors have been shown to have substantial genetic underpinnings (76,77) and may directly or indirectly mediate the association between genetic/genomic variation and measures of body mass/size.

Genetics of food preferences and ingestive behavior

Many of the loci associated with obesity in GWAS are located in or nearby genes expressed in brain eating regulatory pathways, highlighting a potential role in the central nervous system and eating behavior for these genetic associations (78). Consistent with this hypothesis, the *FTO* locus rs9939609, for example, has been shown to predict preferences for and consumption of palatable, calorie-dense foods (79,80) and reduced satiety (81) in laboratory paradigms, and greater total caloric and total fat intake assessed by dietary recall (80,82). In recent GWAS of dietary intake, *FTO* emerged as associated with a greater percentage of calories from protein (83,84) and fat (85), although inconsistently so.

Although monogenic obesity is often associated with abnormal appetite and excessive food consumption, more subtle types of feeding behavior, such as food preferences, have also been shown to have a substantial genetic component (86,87). The *TAS2R38* gene is associated with the perception of the bitter-tasting thiourea compounds, and genotype at this locus defines three taster groups: supertasters, medium tasters, and nontasters, with nontasters having a higher BMI compared with the other taster groups; differences in dietary patterns were also observed (88). Taster status at another locus, 6-n-propylthiouracil (*PROP*), was associated with significantly greater reduction in energy intake for super-tasters during two randomized control dietary interventions focused on lowering energy density or changing eating frequency (89). Taken together, these studies suggest that genetic associations with body weight or BMI may be modulated by more direct links between food preferences, eating behavior, and genes.

Genetics of physical activity

Multiple studies have demonstrated that physically active individuals are less likely to gain weight over time (75,90,91), and physical

TABLE 1 Single genes associated with Mendelian forms of human obesity

Gene	Dominant (D)/ recessive (R)/ imprinted (I)	Early onset morbid obesity	Hyperphagia	Hypogonadism	Hormonal alterations	Altered growth/ dysmorphia	Altered glucose/ insulin metabolism	Elevated precursor proteins	Pigmentation alterations	Cognitive impairments
Leptin (*LEP*)	R	X	X	X	X		X			
Leptin receptor (*LEPR*)	R	X	X	X	X		X			
Pro-opiomelanocortin (*POMC*)	R	X	X		X				X	
Melanocortin 4 receptor (*MC4R*)	D	X	X			X	X			
Single-minded homolog 1 (*SIM1*)	R	X	X		X	X	X			
Proprotein convertase subtilisin/ kexin type 1 (*PCSK1*)	R	X	X	X	X		X	X		
HBII-85 snoRNA (associated with Prader–Willi syndrome)	I	X	X	X		X				X
Brain-derived neurotrophic factor (*BDNF*; associated with WAGR syndrome)	R	X	X							X

exercise has also been shown to facilitate both weight loss and weight maintenance (92). In studies of twins and other related individuals, physical activity has been shown to aggregate in families, with reported heritability estimates for physical activity behavior ranging from 9% to almost 80% (93-96). In animal models, the strongest genetic predictors of spontaneous physical activity include the dopamine receptor 1 (*Drd1*) and nescient helix loop helix 2 (*Nhlh2*) genes, which have also been implicated in feeding behavior (97-100). In humans, variation in the leptin receptor (*LEPR*) and melanocortin 4 receptor (*MC4R*) genes was associated with physical inactivity (101-103), which appears to be driven by genetic pathways that are distinct from those encoding activity. A limited number of genes have been identified that may influence exercise adherence and/or exercise tolerance, with small effects that await replication (104,105). Change in body weight, waist circumference, hip circumference, and BMI have been shown to be significantly associated with adherence status both before and after an aerobic exercise intervention (105), suggesting a plausible pathway by which genes that influence adherence may ultimately influence weight change.

Personalizing Weight Loss Interventions

Although ongoing efforts are elucidating the genetic underpinnings of obesity and weight change, a different question is whether these discoveries can be implemented in the clinical setting to personalize weight loss interventions. The success of such interventions would rely not only on an understanding of the pathophysiological mechanisms linking genotype and weight but also on the ability to communicate a personalized strategy to patients and motivate behavior change.

A few studies have examined whether communicating genetic risk information to patients motivates weight-related health behavior change. In a recent trial, 1,016 university students were randomized to receive simple weight control advice with and without their *FTO* rs9939609 genotype (106). Of the 279 participants who completed the 1-month follow-up survey, those in the genotyped group were more likely to be in a contemplation or action stage of readiness to control weight, compared with those receiving advice only (odds ratio 1.77, 95% CI, 1.08-2.89, $P = 0.023$). The researchers observed an interaction of study group with body weight; the effect of *FTO* genotype information on readiness for change was greater among individuals with overweight/obesity (only 9% of the respondents) than among those of normal weight (106). Perhaps most relevant to the present discussion, the researchers also observed an interaction between study group and genotype; compared with control participants, participants learning they carried the higher-risk AT or AA *FTO* genotype, but not those learning they carried the low-risk TT genotype, were more likely to be in an advanced stage of change after 1 month (106). The groups did not differ, however, in the proportions reporting they had actually followed any of the weight control advice, suggesting that additional information may need to be given to motivate actual behavior change.

Two trials in the field of T2D have assessed weight change in response to genetic testing. In the Genetic Counseling and Lifestyle Change for Diabetes Prevention Study (107), 177 patients with metabolic syndrome were randomized to receive genetic testing for T2D susceptibility based on 36 T2D-associated SNPs plus brief genetic counseling versus no genetic testing. Diabetes risk for genotyped

TABLE 2 Future directions

Research needed	Examples
Discovery research	Leverage genome-wide genetic and genomic technologies to explore novel genetic loci for intentional weight loss or weight change
	Develop advanced statistical approaches designed to concurrently examine the effects of phenotypic and genotypic data from multiple sources
Genetic variation	Design large randomized control trials of behavioral weight loss interventions designed to examine genetic variation in weight loss/maintenance/regain
	Convene behavior weight loss intervention consortia to leverage resources
	Replication of smaller studies examining genetic variation
Measurement	Examine measures of body composition, other than BMI (e.g., functional vs. static phenotypes, visceral and subcutaneous fat using computed tomography or magnetic resonance imaging)
Mechanisms	Examine epigenetic and microbiome mechanisms involved in controlling energy homeostasis and weight management
	Examine indirect and direct genetic pathways of health behaviors (diet, physical activity) on weight loss/maintenance/regain
Personalized weight loss	Examine whether genetic discoveries and technological advances can be implemented in a clinical setting to motivate behavior change/adherence to weight loss interventions
	Examine whether baseline characteristics, including genetics and genomics, predict change in weight, weight loss maintenance, or change in obesity-related comorbidities with sufficient precision to permit tailored treatment guidelines

participants was summarized with a risk score categorizing their genetic risk as low, average, or high. All patients were then enrolled in a 12-week lifestyle medication program modeled on the evidence-based DPP (108). The lifestyle intervention was effective: the group overall lost a mean of 8.5 ± 10.1 pounds, with 31% losing at least 5% of their body weight. Communicating genetic risk did not change this effectiveness, however. The genotyped and control arms did not differ with respect to weight loss, attendance at the 12 DPP sessions, or motivation or confidence to make health behavior changes (107). In a second randomized trial, 601 patients with obesity or overweight received T2D risk estimates based on family history, BMI, and fasting plasma glucose, followed by either T2D genetic susceptibility results from four T2D-associated SNPs or eye disease counseling as a control (109). All participants received brief lifestyle counseling but were not otherwise enrolled in a weight loss program. Although the group receiving genetic risk information reported lower calorie and fat intake after 3 months, the two groups did not differ in these behaviors or in physical activity, weight loss, insulin resistance, or perceived risk after 6 months.

Personalizing genetic risk information is only one component of a genotype-informed approach to weight loss. A clear deficit of the trials to date is that the genetic risk information provided to participants was not connected to personalized weight loss strategies but, rather, to uniform interventions, be they simple advice or an intensive 12-week program. To advance the field of precision weight loss, the combination of an individual's genotype, along with the unique underlying pathophysiology it suggests, should be used to develop dietary and physical activity recommendations that target the metabolic derangements specific to each person.

Future Directions

Although a genetic basis for obesity and even response to alterations in energy balance has been clearly established, few studies (24,110) have examined whether the same genes and/or processes that influence obesity when assessed cross-sectionally also influence weight loss, weight maintenance, and/or weight regain following weight loss interventions. By taking into account the influence of genetic variation on these disease processes, precision medicine in behavioral weight loss may present several new avenues to tackle the obesity epidemic. For example, identifying subgroups of populations with obesity who are genetically prone to respond well to a given weight loss intervention might be targeted accordingly. Similarly, genetic information might prove valuable when seeking to identify people who are unlikely to respond well to a given weight loss therapy or who might experience adverse events. There are many compelling examples of the use of genomic data in clinical settings, such as screening for *BRCA1*/*BRCA2* gene mutations to aid treatment decisions for familial breast cancer and genetic screening for drug metabolizing genes like *CYP2D6* to inform the prescription and dosing of codeine for pain relief. To optimize the use of genetic information, clinicians, patients, and their relatives would all benefit from an improved level of medical literacy when exchanging genetic information (111).

Although complex diseases and outcomes pose the biggest challenge for precision medicine, improving treatment for such outcomes also has the potential to impact the greatest number of people. Technology exists today to characterize individuals in a highly comprehensive manner that includes 24-h assessment of heart and respiratory rate, physical movement, exposure to changes in light/sound/temperature, sleeping patterns, eating patterns, and a host of other measures. Portable, wearable monitors can be used to upload patient data remotely and automatically, and Web-based, computerized devices, like scales and bioimpedance instruments, can monitor fluid balance and body composition without the need for the participant or patient to interact directly with researchers or health care providers. These devices can be linked to environmental monitors in the home, and GPS tracking systems can document the location and physical setting of the wearer. In addition to monitoring devices, it is now feasible and affordable to sequence an entire genome in as little as 10 days. Next-generation sequencing and advanced mass spectrometry have paved the way for the fast and complete characterization of the transcriptome, proteome, epigenome, and metabolome. Classic information about family and medical history can be combined with a

host of behavioral, psychological, and demographic data to completely account for a multitude of factors that may influence both disease processes and response to treatment.

Acquiring data is the easy part. What is direly needed are innovative approaches for mining multiple levels of "omics" and other data to discern patterns of data-disease relationships that may then be used for decision-making in clinical treatment. Although the statistical approaches lag behind the technology and our ability to gather data, the potential is great to make substantial progress in this area. This article highlights the importance of developing a model that combines genes with established phenotypes in order to bring us closer to personalized treatment. Table 2 outlines future research directions to advance the science and potentially inform personalized gene-based interventions for successful weight loss, maintenance, and regain.

With advances in technology comes a demand for more innovative studies. There are several large, multimillion-dollar prospective studies that have been recently initiated in Europe and the United States, including the Innovative Medicines Initiative DIRECT Study in Europe (112) and the Google Baseline Study in the United States (https://www.dtmi.duke.edu/news/duke-and-stanford-assist-google-x-defining-health); both studies involve repeated intensive phenotyping and objective long-term measures of behavior assessed with wearable devices, from which much will be learned about the genetic and environmental influences on weight change and metabolic health. Although interrogating existing trials for gene-intervention interactions is pragmatic and should be done, new trials that are specifically designed to assess the combined effects of genotypes and interventions are needed. Genotype-based recall trials, in which the power to detect differences in response to treatment between participants with a high and low degree of genetic burden is maximized, provide one such opportunity. With innovation at every level, from data acquisition to statistical analysis to study design, recent and future scientific discoveries may help move obesity prevention and treatment from universal to precision approaches.O

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