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Viewpoint: Toward Precision Approaches for the Prevention and Treatment of Obesity

Susan Z. Yanovski, MD[1] and **Jack A. Yanovski, MD, PhD**[2]

[1]Co-Director, Office of Obesity Research, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 6707 Democracy Blvd, Rm 6025, Bethesda, MD, 20892-5450, sy29f@nih.gov, Phone: 301-594-8882, Fax: 301-480-8300.

[2]Chief, Section on Growth and Obesity, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, 10 Center Dr, Room 1-3330 MSC 1103, Bethesda, MD 20892-1103, jy15i@nih.gov, Phone: 301-496-0858, FAX: 301-402-0574

Obesity, defined as a body mass index of 30 or greater for adults and 95th percentile or more for age and sex among youths, affects almost 40% of adults and 19% of youths in the United States and has increased substantially over the past 40 years.[1] Easy availability of inexpensive, energy-dense, palatable foods; higher costs of, and insufficient access to, more healthful foods; reduced need for physical activity; and plentiful opportunities to engage in rewarding sedentary behaviors create an ideal environment for obesity to emerge. The significant differences in obesity prevalence among genetically similar Pima American Indians living in Arizona (>60%) and in Mexico (<20%) — groups with marked differences in access to food and obligate physical activity[2] — provide a clear example of how important environment can be for obesity.

Nevertheless, even under obesity-promoting conditions, not everyone develops obesity; there is variability in response to the environment. Important differences among individuals in obesity susceptibility may be due to psychosocial, cultural, and economic factors, but also can be caused by genetic sequence variations, epigenetic events, and other factors, including gene-environment interactions. There are, for example, an increasing number of identified single gene defects sufficient to cause severe, childhood-onset obesity. Individuals with rare inactivating mutations of genes in the hypothalamic leptin-signaling pathway (such as those with complete deficiencies of leptin, its receptor, and several downstream effectors of leptin) develop obesity. Heterozygous mutations affecting some genes in the same pathway, including the melanocortin 4 receptor (MC4R), also lead to obesity. MC4R heterozygous inactivating mutations are reported to be found in as many as 1% to 4% of individuals with severe, early-onset obesity.[3]

Correspondence: Address correspondence to Dr. S. Yanovski or Dr. J. Yanovski.

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Additionally, many single-nucleotide polymorphisms (SNPs) and copy number variations throughout the genome that are not directly linked to leptin are associated with BMI; in many cases, each change has a relatively minor contribution to body weight. The most well-known of these are intronic SNPs of the FTO gene (a gene linked with common obesity), for which presence of 2 risk alleles increases adults' body weight by a mean of approximately 3 kg and increases odds for obesity 1.67-fold.[4] Some SNPs (including those of FTO) show evidence for gene-environment interactions, including interactions with physical activity and even socioeconomic status.[5]

Concordant with the individual heterogeneity in circumstances that leads to variability in weight gain, when people with obesity try to lose weight, they also demonstrate substantial individual differences both in the amount of weight lost during intervention and in the amount of weight regained thereafter. Such variability is seen for behavioral,[6] pharmacotherapeutic,[7] and surgical[8] approaches. Although there have been myriad attempts to characterize predictors of response for behavioral and pharmacologic approaches for weight management, the only consistently identified predictors of later response appear to be early responses to the intervention (e.g., weight lost during the first few weeks of intervention) and adherence to the weight loss program.[9] However, most studies attempting to predict weight loss involve relatively small cohorts. Furthermore, because similar measures of potential predictors are infrequently collected by different investigators, results are difficult to combine through meta-analysis. As a result, initial choices for obesity prevention or treatment usually do not consider predictors of variability in response. Instead, factors such as availability, cost, and patient or physician preferences take precedence over a more targeted approach.

Advances in the understanding of the genetics of obesity have begun to change this situation, and some patients with monogenic obesity can receive treatment specifically directed at their disorders. For the rare individual with leptin deficiency, treatment with leptin induces a remarkable and sustained improvement in adiposity. In 2 patients with proopiomelanocortin (POMC) deficiency, substantial weight losses in response to injections with an α-melanocyte-stimulating hormone analogue have been recently reported.[10] As the understanding of the most important genes regulating body weight increases and additional patients with monogenic disorders are identified, more treatments targeted to underlying mechanisms can be developed and deployed.

Because most people with obesity do not have a monogenic cause, but rather have multiple genetic risk variants (each with small effects), a solitary "magic bullet" seems unlikely to materialize. Nevertheless, it remains possible that identification of genetic, metabolic, behavioral, and environmental factors that make people susceptible to (or protected from) obesity, accompanied by a better elucidation of the factors that account for variability in success of different obesity treatments, will allow development of approaches for obesity prevention and treatment that pinpoint the interventions most likely to be effective for many more individuals. Better phenotyping in very large numbers of people with obesity will be required. A phenotype is a set of observable characteristics that are measurable, distinct, and arise from an interaction between genes and environment. Phenotypes may be behavioral as well as physiological, and may explain individual variation in susceptibility to obesity

development or response to treatment. There are active investigations to identify underlying behavioral or psychological characteristics, such as differences in satiety, sensitivity to reward, impulsivity, food cue reactivity, neural and humoral responses to foods, and affective response to exercise that can be tested as potential targets for intervention. Physiological characteristics, including composition of the gut microbiome, metabolic or metabolomic differences at baseline or in response to acute changes in energy balance, gastrointestinal motility, and epigenetic modifications in histone acetylation or DNA methylation could help identify both prevention and treatment efforts targeted to underlying causal pathways (Box).

Personalized approaches based on better genetic and phenotypic characterization would not necessarily involve medications, devices, or surgery. Interventions targeting behavior change, nutrition, or physical activity all have the potential to be more effective with better understanding of individual factors that predict response. Although identifying predictive phenotypes might initially require sophisticated technologies, a goal would be the development of a standardized set of accessible diagnostic tools that could include biosamples, behavioral tasks, and patient-reported measures that clinicians could employ to guide therapeutic recommendations. Even the most sophisticated individual approaches for obesity prevention and treatment are less likely to be effective in an environment that is obesity-promoting. As research moves toward precision prevention and treatment, parallel efforts are needed to make environments conducive to healthy eating and physical activity—making the healthy choice the easy choice. Precision approaches for obesity prevention and treatment, in concert with efforts to improve population health, have the potential to reduce the burden of illness and disability due to obesity and its related disorders.

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Box: Examples of Approaches to Investigate Targeted Strategies for Obesity Prevention and Treatment

Patient-reported measures
Measures of food preferences, hunger, and satiety
Neurocognitive testing
Physiological and psychological response to activity
Functional neuroimaging
Gastrointestinal physiology and microbiome
Metabolomics
Sequence and copy number variants
Epigenetic modifications
Nutrigenomics
Pharmacogenomics