

Precision medicine in adult and pediatric obesity: a clinical perspective

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Abstract: It remains largely unknown as to why some individuals experience substantial weight loss with obesity interventions, while others receiving these same interventions do not. Person-specific characteristics likely play a significant role in this heterogeneity in treatment response. The practice of precision medicine accounts for an individual's genes, environment, and lifestyle when deciding upon treatment type and intensity in order to optimize benefit and minimize risk. In this review, we first discuss biopsychosocial determinants of obesity, as understanding the complexity of this disease is necessary for appreciating how difficult it is to develop individualized treatment plans. Next, we present literature on person-specific characteristics associated with, and predictive of, weight loss response to various obesity treatments including lifestyle modification, pharmacotherapy, metabolic and bariatric surgery, and medical devices. Finally, we discuss important gaps in our understanding of the causes of obesity in relation to the suboptimal treatment outcomes in certain patients, and offer solutions that may lead to the development of more effective and targeted obesity therapies.

Keywords: anti-obesity agents, bariatric surgery, obesity, obesity etiology, precision medicine, weight loss

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Introduction

Obesity remains at epidemic proportions in the United States (US), affecting nearly 40% of adults and 19% of children.¹ There is significant evidence to support the complex and multifactorial etiology of this disease.² While numerous interventions for the treatment of obesity are associated with overall mean weight loss, the degree of weight loss attained on an individual level can be highly variable. For example, in the Satiety and Clinical Adiposity Liraglutide Evidence (SCALE) Obesity and Prediabetes Trial of nondiabetic adults with obesity, the mean weight loss achieved with liraglutide was 8.4 kg; however, the standard deviation was nearly as high at 7.3 kg.³ Similar findings have been reported in the pediatric literature across various obesity interventions.⁴ Such variability in individual response suggests that obesity is a heterogeneous disease and that person-specific characteristics may be important determinants of treatment effectiveness. Given

both the degree of heterogeneity in the etiology of obesity and the variability in individual responsiveness to treatment, personalized medicine strategies have the potential to be more effective than current approaches that often apply treatment modalities broadly without accounting for individual patient-level differences.⁵

The National Institutes of Health defines precision medicine as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.”⁶ The goal of precision medicine is to optimize therapeutic benefit and minimize risk by targeting an individual's specific needs based on their phenotype, genotype, or psychological factors. Optimizing therapeutic benefit includes finding the most effective treatment for an individual as efficiently as possible, especially as a patient's willingness to follow up and continue in management may be

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affected by whether or not they perceive a benefit from the initial treatment.⁷

In this review, we discuss precision medicine as it applies to the clinical care of adults and youth with obesity. Following a brief review of the biopsychosocial determinants of obesity in general, we present data on what is currently known about the individual variability in the effectiveness of interventions for obesity, focusing on characteristics associated with or predictive of treatment responsiveness. We selected studies based upon a review of published literature from *PubMed* and *Google Scholar* using the following keywords: ('Predictor' OR 'Predictors') AND ('Weight Loss' OR 'Weight Loss Response' OR 'Weight Reduction') AND ['body mass index (BMI)' OR 'Weight'] AND ('Intervention' OR 'Treatment' OR 'lifestyle' OR 'lifestyle modification' OR 'pharmacotherapy' OR 'medication' OR 'bariatric surgery' OR 'metabolic surgery' OR 'device' OR 'medical device'). We additionally performed searches on the specific pharmacotherapies, metabolic and bariatric surgeries, and device therapies mentioned. We included randomized controlled trials (RCTs), retrospective and prospective cohort trials, and observational studies. Given the broad scope of this review, our intent was to discuss general trends and not to include every article published in this field. Finally, we identify important gaps in the literature and offer potential solutions in an effort to accelerate the development of more effective and targeted treatments for obesity.

The biopsychosocial determinants of obesity

Obesity is a multifactorial disease with individual, environmental, and socioeconomic determinants (Table 1).^{4,8} Fully understanding the complexity of the general factors contributing to obesity makes one appreciate how difficult it is to develop individualized treatment plans. The role of many of these factors as predictors of response to obesity interventions have yet to be explored. In this section, we present a brief overview of biopsychosocial contributors to the development and progression of obesity as a framework for understanding the challenges of applying precision medicine approaches to this complex disease.

A significant portion of BMI is heritable.⁹ A Genetic Investigation of ANthropometric Traits consortium (GIANT) meta-analysis identified 97

BMI-associated loci in adults of European descent accounting for 2.7% of the variability in BMI.¹⁰ In total, more than 250 BMI-associated loci have been discovered among adults of African, east Asian, and European descent,¹¹ with many of these same loci also identified in children.¹² The GIANT consortium additionally uncovered 941 near-independent single nucleotide polymorphisms (SNPs) associated with BMI among adults with European ancestry accounting for 6% of the variance in BMI.¹³ These findings suggest that, while a multitude of loci and SNPs play a role in BMI heritability, the majority of the genetic sources for the variability in BMI remain unknown. Certainly, ethnic and population differences underlie the genetic predisposition to obesity development.¹⁴

Numerous genetic mutations have been associated with the development of severe monogenic obesity [e.g. brain-derived neurotrophic factor, leptin, leptin receptor, melanocortin 4 receptor, proopiomelanocortin (POMC)].¹⁵ Moreover, several genetic syndromes, including Prader–Willi, Alstrom, and Bardet–Biedl syndromes, are implicated. For some of these rare forms of obesity, accounting for fewer than 5% of all cases,¹⁶ targeted therapies have been discovered (e.g. leptin for congenital leptin deficiency,¹⁷ alpha-melanocyte stimulating hormone analog for POMC deficiency¹⁸ and Bardet–Biedl syndrome¹⁹). However, true monogenic obesity with targeted therapies is rare. Most cases of obesity are polygenic in origin, and targeted therapies for these cases are not currently available and will be substantially more difficult to establish. Further, the mechanisms by which genetic variants contribute to the development of obesity are largely unknown.

Peptide hormones [e.g. insulin, ghrelin, glucagon-like peptide-1 (GLP-1)] and neurotransmitters (e.g. dopamine, serotonin, gamma-aminobutyric acid) play a significant role in the regulation of appetite, satiety, food reward, and addiction. Pharmacotherapies developed for the treatment of obesity target the actions of these specific hormones and neurotransmitters, and perhaps are influenced by certain genotypes.^{20,21} The interaction of these pharmacotherapies with endogenous gut–brain hormones and neurotransmitters, along with inter-individual differences in the functionality of receptors upon which these hormones interact, represent additional sources of variability in drug response.

Table 1. Proposed causes and risk factors for the development of obesity.^a

Category	Examples
<i>Individual</i>	
Genetics and epigenetics	Congenital leptin deficiency, Bardet–Biedl syndrome
Gut–brain hormones	Ghrelin, leptin, insulin
Eating behaviors	Binge eating, loss of control eating, hunger, food addiction
Disease states	Cushing’s disease, hypothyroidism
Medications	Steroids, atypical antipsychotics, insulin
Psychological conditions/mood	Depression, anxiety
Physical activity	Sedentary lifestyle, increased screen time
‘-omics’	Microbiome, metabolome, transcriptome, proteome
Pre- and perinatal exposures	Prenatal weight gain, gestational diabetes in mother
Adverse life events	Adverse childhood experiences
<i>Environmental</i>	
Commercial messaging	Advertising for calorically dense foods
Cultural norms	Portion sizes, body image norms
Built environment and area deprivation	Walkability, green spaces
<i>Socioeconomic</i>	
Poverty	‘Food desert’, ‘food swamps’
Education status	Low education level
^a Nonexhaustive.	

In addition to genetic and physiologic factors, environmental and psychosocial determinants also play significant roles in obesity development and progression. For example, individuals of low socioeconomic status are more likely to live in neighborhoods with fewer physical fitness resources,²² and such adverse surroundings increase the odds of being overweight by 20–60% in children.²³ In a study examining exposure to ‘healthy’ fast food meal advertising, a child’s fondness for fast food increased after such exposure; however, healthier dietary choices did not.²⁴ The home environment also impacts an individual’s likelihood of developing obesity, and may impact his or her response to therapeutic interventions.^{25,26} In addition, psychological factors must also be considered. For example, Sutaria and colleagues found that children with obesity compared with those with normal weight were significantly more likely to have

depression.²⁷ Attention deficit–hyperactivity disorder has similarly been linked to obesity.²⁸

One potentially important link between these genetic, physiologic, and environmental determinants of obesity is epigenetics, or the heritable changes that influence gene expression without affecting the DNA sequence.²⁹ The recent development of epigenome-wide association studies (EWASs) allows for the investigation of such interactions.³⁰ For example, in a study of 2097 African-American adults, 37 methylation variants in blood were associated with BMI.³¹ In another study, paternal obesity was associated with insulin-like growth factor-2 (IGF-2) hypomethylation among 628 newborns.³² Indeed, those who are genetically predisposed to obesity development may be more susceptible to doing so when placed in increasingly obesogenic environments.

It is important to note that the potential causes of obesity listed above is not exhaustive, and numerous other factors have been associated with its development. These include prenatal weight gain and the presence of gestational diabetes in the mother, gestational weight, medications associated with weight gain, environmental toxins, and an individual's microbiome, transcriptome, and proteome.^{33–35}

Heterogeneity in the effectiveness of interventions for the treatment of obesity

While numerous studies have identified the characteristics associated with or predictive of weight loss response to obesity interventions, the most reliable predictors appear to be degree of adherence to the intervention, and early weight loss as a predictor of later or sustained weight loss (which is important to consider when determining whether to continue therapy).^{36–40} Most studies reporting person-specific characteristics associated with weight loss response were performed in adults; however, a few have examined these factors in children. In this section, we review the evidence on the characteristics associated with weight loss response to lifestyle modification therapy (LMT), pharmacotherapy, metabolic and bariatric surgery (MBS), and medical devices.

Lifestyle modification therapy

Table 2 summarizes studies identifying characteristics associated with weight loss response to LMT. Not surprisingly, a higher degree of adherence to various components of LMT and early weight loss have both been associated with better long-term outcomes.^{40–44} Psychosocial factors associated with improved weight loss response in adults include greater social support;⁴⁵ higher baseline exercise self-efficacy,⁴⁶ dietary restraint,⁴⁷ flexible cognitive restraint,⁴⁸ and motivation (in men);⁴⁸ lower levels of psychopathology (in women),⁴⁹ emotional eating,⁴⁸ and disinhibition;⁴⁷ and fewer exercise barriers⁴⁸ and previous dieting attempts.⁴⁶ In children, higher levels of global self-worth have positively predicted weight loss response,⁵⁰ while higher levels of disordered eating in the child and the presence of psychopathology in the mother have been identified as negative predictors.^{39,50,51}

Whether baseline weight status and age predict weight loss response to LMT remains unclear. In

children, while Braet and Moens found that higher baseline weight predicted increased weight loss following inpatient and outpatient interventions, respectively, Madsen and colleagues showed that a higher baseline BMI *z*-score predicted a decreased weight loss to an outpatient intervention.^{39,50,59} In adults, both Heiner and colleagues and Azar and colleagues showed that higher baseline BMI was associated with greater weight loss to LMT programs.^{56,61} As for age, Moens and colleagues found that older age during an outpatient intervention positively predicted weight loss 8 years later in children, while Danielsson and colleagues showed that younger children were more likely to achieve clinically significant weight loss during a 3-year outpatient intervention.^{50,54} In adults, while Apolzan and colleagues and Funk and colleagues found that older age was associated with greater short and long-term weight loss to LMT programs, respectively, Bachar and colleagues found that younger age was associated with a higher odds of achieving 5% or greater weight loss at 6 months.^{43–45}

Several studies have examined the hormonal characteristics associated with weight loss response to LMT. For example, in a 12-week prospective trial assessing weight loss predictors after energy restriction followed by weight maintenance, adults with decreased weight loss during restriction and rapid weight gain during maintenance had higher baseline insulin, interleukin-6, and adipose tissue inflammation markers compared with adults with increased weight loss during restriction and continued weight loss or stabilization during maintenance.⁵⁸ In a 4-week women-only inpatient intervention involving calorie restriction, supervised activity, and cognitive behavioral modification, baseline c-peptide, growth hormone, pancreatic polypeptide, and free T3 concentrations were associated with increased weight loss, while insulin-like growth factor-1, cortisol, adiponectin, and neuropeptide Y levels correlated with decreased weight loss.⁵⁶ In a 2-year longitudinal study assessing the association between baseline leptin levels and weight loss to an educational based program in children, the odds of weight loss increased with greater leptin concentrations.⁵⁵ Combined, these studies suggest that higher levels of inflammation (as expressed by such factors as adipose tissue inflammation, cortisol, adiponectin, and leptin) appear to be associated with a worse weight loss response to LMT.^{55,56,58}

Table 2. Predictors of weight loss response to lifestyle and behavioral interventions.

Author	Inclusion criteria	n	Study design	Predictors of response
Aller and colleagues ⁵²	Adults, BMI ≥ 30 kg/m ² , participating in a lifestyle modification program	587	Prospective cohort study assessing the association between genotype and 3- and 12-month weight loss among patients enrolled in a weight loss program	G/G genotype of PLIN1 (rs2289487) and PLIN1 (rs2304795); T/T genotype of PLIN1 (rs1052700), and C/C genotype of MMP2 predicted $\geq 5\%$ weight loss at 3 months. C/G-G/G genotype of PPAR γ (rs1801282) and T/C genotype of TIMP4 (rs3755724) predicted $\geq 5\%$ weight loss at 12 months. Those with combination of PPAR γ (rs1801282) C/G-G/G and TIMP4 (rs3755724) T/C had even greater weight loss
Apolzan and colleagues ⁴³	Adults, BMI ≥ 24 kg/m ² (≥ 22 kg/m ² in Asian descent), FPG 95–125, FPG 140–199 mg/dl after 2 h oral glucose load	3234	Retrospective analysis of data from the Diabetes Prevention Program (compared weight loss with metformin, intensive lifestyle intervention, and placebo) to identify predictors of long-term (15 year) weight loss	Greater weight loss in first year, older age, and continued metformin use in the metformin group; older age and absence of either DM or family history of DM in the intensive lifestyle group; and higher baseline FPG levels in the placebo group independently predicted greater long-term weight loss
Bachar and colleagues ⁴⁴	Adults, BMI ≥ 25 kg/m ² , attending outpatient clinics	11,482	Retrospective analysis of electronic health records examining factors associated with 5% weight loss at 6 months and weight maintenance at 1 year	Higher BMI, younger age, increased visits with a dietician, and not treated with insulin associated with greater odds of $\geq 5\%$ weight loss at 6 months. In those with $\geq 5\%$ weight loss at 6 months, more frequent weighing associated with improved weight maintenance at 1 year
Balantekin and colleagues ⁵¹	Children (7–11 years), BMI ≥ 85 th percentile, participating in family-based behavioral weight loss treatment	241	Retrospective study assessing if children with distinct eating disorder patterns differed in eating disorder pathology and BMI-for-age z-score (zBMI) change	Children with highest eating disorder pathology did not achieve clinically significant weight loss (defined as zBMI ≥ 0.25 unit loss)
Braet ³⁹	Children (7–17 years), BMI >95 th percentile	122	Cross-sectional study examining predictors of treatment outcomes 2 years after completion of 10-month inpatient treatment program	Higher baseline weight, age, and weight loss during inpatient treatment predicted greater weight loss; higher eating disorder characteristics predicted lower weight loss
Chan and Raffa ⁴²	Adults in MOVE! Weight Management Program	237,577	Retrospective study assessing association between participation in lifestyle intervention program and weight loss	Increased participation with MOVE! Program increased odds of $\geq 5\%$ weight loss
Chen and colleagues ⁵³	Adults females with obesity	34	Prospective study assessing neural activation to palatable food receipt and genetics; compared those receiving 12-week BWL intervention with those not receiving intervention	Among BWL participants, baseline to 12-week reduction in frontostriatal activation to milkshake predicted greater weight loss at 12, 36, and 60 weeks; possessing A/A or T/A genotype of FTO variant rs9939609 predicted greater weight loss at 12 and 36 weeks

(Continued)

Table 2. (Continued)

Author	Inclusion criteria	n	Study design	Predictors of response
Danielsson and colleagues ⁵⁴	Children (6–16 years), followed in weight management program	643	Retrospective analysis assessing if degree of obesity and age predict efficacy of long-term behavioral treatment	6–9 year olds with severe pediatric obesity (BMI-SD ≥ 3.5) more likely to achieve ≥ 0.5 unit BMI-SD reduction than adolescents with severe pediatric obesity
Di Stefano and colleagues ⁵⁵	Children (8–15 years), BMI > 95 th percentile	418	Prospective 2-year cohort study assessing association between baseline serum leptin and response to educational based weight loss program	Odds ratio of weight loss response significantly increased by greater quintile of serum leptin concentration
Funk and colleagues ⁴⁵	Adult veterans, BMI ≥ 40 kg/m ² or ≥ 35 kg/m ² with ≥ 1 obesity-related comorbidities	206	Retrospective analysis of participants in a 4-month weight loss program examining predictors of weight loss	Greater social support and older age associated with greater weight loss
Grave and colleagues ⁴⁷	Adults, BMI ≥ 30 kg/m ²	500	Prospective 12-month cohort study of participants entering weight loss programs, assessing psychological predictors of weight loss	Increased baseline dietary restraint and decreased disinhibition predicted increased likelihood of achieving $\geq 5\%$ weight loss at 12 months
Gross and colleagues ⁴⁰	Children (4–18 years), followed in weight management programs	687	Retrospective analysis of the Pediatric Obesity Weight Evaluation Registry (POWER)	$\geq 3\%$ BMI reduction at 1 month associated with increased BMI reduction at 6 and 12 months
Hainer and colleagues ⁵⁶	Adult females with obesity exhibiting stable weight on a 1 week normocaloric diet	67	Prospective 4-week inpatient weight reduction program assessing psycho-behavioral and hormonal factors as predictors of weight loss	Baseline free T3, c-peptide, GH, PP associated with higher reduction in weight; baseline IGF-1, cortisol, adiponectin, NPY correlated with lower reduction in weight
Horth and colleagues ⁵⁷	Adults, BMI 30–40 kg/m ²	307	Retrospective analysis of a clinical trial in which patients with obesity randomized to ad libitum low-carbohydrate or low-fat diet for 2 years	Pre-DM (FPG 100–125 mg/dl) and high fasting insulin levels associated with greater weight loss to low-fat <i>versus</i> low-carbohydrate diet at 2 years. Pre-DM and low fasting insulin levels associated with greater weight loss to low-carbohydrate <i>versus</i> low-fat diet at 2 years.
Kong and colleagues ³⁷	Adults, BMI ≥ 27 kg/m ² with pre-DM or metabolic syndrome	51	Retrospective analysis of lifestyle modification weight loss trial, assessing predictors of retention after 1 year of intervention with $\geq 5\%$ weight loss	Lower response rate to question “I am capable of doing more physical activity” and weight loss $< 0.5\%$ at 6 weeks after intervention initiation predicted lower retention and $< 5\%$ weight loss at 1 year
Kong and colleagues ⁵⁸	Adults, BMI 25–38 kg/m ²	50	Prospective 3-month cohort study assessing predictors of weight loss through 6 weeks of energy restriction followed by 6 weeks of weight maintenance	Participants with lower weight loss and rapid weight had highest baseline plasma insulin, IL-6, and adipose tissue inflammation (HAM56+ cells); plasma insulin, IL-6, leukocyte number, and adipose tissue (HAM56) together predicted weight trajectory

(Continued)

Table 2. (Continued)

Author	Inclusion criteria	<i>n</i>	Study design	Predictors of response
Madsen and colleagues ⁵⁹	Children (8–19 years), followed in a weight management clinic	214	Retrospective cohort study of children undergoing clinic-based lifestyle modification program, assessing efficacy and predictors of weight loss	Higher baseline BMI z-score predicted poor response at first (mean 4.1 months) and ultimate (mean 12.1 months) follow-ups; fasting insulin explained 6% response variance at first follow up; baseline BMI z-score plus change in BMI z-score at first visit explained up to 50% of response at ultimate visit
Moens and colleagues ⁵⁰	Children with obesity followed in a weight management program	90	Prospective 8-year cohort study assessing child and familial variables associated with long-term weight regulation	Age, degree of overweight at baseline, global self-worth positively predicted, and psychopathology in mother negative predicted weight loss after 8 years
Rotella and colleagues ⁴⁹	Adults with obesity referred to weight management clinic	270	Prospective 6-month cohort study assessing psychological/psychopathological features associated with better treatment response to a lifestyle modification program	In women, higher psychopathology associated with worse outcomes. In men, higher motivation was associated with increased likelihood achieving $\geq 5\%$ weight loss
Samblas and colleagues ⁶⁰	Adults, WC >94 cm (males) and >80 cm (females) with metabolic syndrome	47	Case-control study assessing transcriptomic and epigenomic patterns; compared high weight loss responders ($>8\%$ body weight) with low responders ($<8\%$ body weight) following 6-month dietary modification program	<i>CD44</i> showed higher expression and lower DNA methylation levels in low responders <i>versus</i> high responders
Stotland and Larocque ⁴¹	Adults, BMI ≥ 25 kg/m ²	344	Prospective 9-month cohort study assessing if early treatment response and change in eating behavior predicted ongoing weight loss to low/very low-calorie diets	Very low-calorie diet, BMI change, number of weigh-ins, and change in uncontrolled eating in first 5 weeks predicted ongoing weight loss at 9 months
Teixeira and colleagues ⁴⁶	Adults, BMI 25–38 kg/m ²	158	Prospective 16-month cohort study comparing behavioral/psychosocial differences between those with $\geq 5\%$ weight loss and those with $<5\%$ weight loss 1 year after a 6-week weight management program	Higher accepting dream weight, lower level of previous dieting, higher exercise self-efficacy, and smaller waist-to-hip ratio predicted increased likelihood of achieving $\geq 5\%$ weight loss at 16 months
Teixeira and colleagues ⁴⁸	Adults, female BMI 25–40 kg/m ²	225	Retrospective 2-year cohort study assessing mediators of weight loss and weight loss maintenance during/after 1-year weight loss intervention	Lower emotional eating, increased flexible cognitive restraint, and fewer exercise barriers mediated 1-year weight loss; flexible restraint and exercise self-efficacy mediated 2-year weight loss
Yank and colleagues ³⁸	Adults, BMI ≥ 25 kg/m ² with pre-DM or metabolic syndrome	72	Retrospective 15-month cohort study assessing weight loss patterns and predictors of response to primary care-based lifestyle intervention	Participants with moderate and steady, and substantial and early, weight loss achieved $\geq 5\%$ short-term weight loss and maintained this at 15 months

BMI, body mass index; BWL, behavioral weight loss; DM, diabetes mellitus; FPG, fasting plasma glucose; FTO, fat mass and obesity-associated protein; GH, growth hormone; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; NPY, neuropeptide Y; PP, pancreatic polypeptide; PPAR γ , peroxisome proliferator-activated receptor gamma; RCT, randomized controlled trial; SD, standard deviation; WC, waist circumference.

Finally, a few studies have examined neural, genetic, and epigenetic predictors of weight loss response to LMT in adults. For example, Chen and colleagues studied neural activation to palatable food receipt and genetics in women who underwent a 12-week behavioral weight loss program. A greater reduction in frontostriatal activation to a milkshake from baseline to 12 weeks predicted increased weight loss at 12, 36, and 60 weeks, and possessing the A/A or T/A genotype of the fat mass and obesity-associated protein (FTO) variant rs9939609 predicted greater weight loss at 12 and 36 weeks.⁵³ Aller and colleagues found that polymorphisms in genes related to the regulation of fat storage and adipocyte structure adaptation predicted 3- and 12-month weight loss to an LMT program.⁵² Samblas and colleagues showed that, among adults undergoing a 6-month dietary modification program, baseline CD44 in white blood cells showed lower expression and higher DNA methylation levels in those who achieved 8% or greater weight loss compared with those achieving less than 8%.⁶⁰ This suggests that CD44 gene transcription and methylation may be a useful biomarker for weight loss prediction.⁶⁰ Gardner and colleagues showed that, among adults with overweight and obesity prescribed either a healthy low-fat or low-carbohydrate diet, SNP multilocus genotype patterns were not associated with the dietary effects on weight loss for either diet.⁶²

Pharmacotherapy

There are five US Food and Drug Administration (FDA)-approved medications for the long-term management of obesity in adults: orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, and liraglutide. Phentermine is approved for short-term weight loss, and studies also have shown topiramate monotherapy^{63,64} and exenatide^{65,66} to be effective. In adolescents 16 years of age or younger, orlistat is the only US FDA-approved medication for weight loss; however, many of the medications used in adults are also used in pediatric weight management clinical settings.⁶⁷ It is important to note that our understanding of the underlying mechanisms leading to weight loss for many of these medications continues to remain incompletely understood.

Review of the RCTs leading to US FDA approval of the available obesity pharmacotherapies largely show a similar pattern: overall mean weight loss

with considerable response variability on an individual level.^{2,68-70} Person-specific characteristics likely contribute to the heterogeneity in weight loss response seen in these large-scale RCTs. To date, numerous studies have examined characteristics associated with weight loss response to obesity pharmacotherapies (Table 3). A majority of these investigations involve orlistat⁷¹⁻⁷⁶ and GLP-1 receptor agonists (GLP1-RAs)⁷⁷⁻⁸⁵ in individuals with overweight/obesity, or topiramate in individuals with seizure disorders with or without obesity.⁸⁶⁻⁸⁹ Studies evaluating hormonal, genotypic, and neuronal predictors of weight loss response are rare.^{78,90,91}

Early weight loss is the most commonly described predictor of sustained weight loss in response to obesity pharmacotherapies. Rissanen and colleagues and Toplak and colleagues both found that weight loss of 5% or greater at 3 months predicted sustained weight loss with orlistat at 1 and 2 years, respectively.^{74,75} Smith and colleagues analyzed pooled data from the Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) trials and reported similar results with lorcaserin.⁹² In analyses of pooled data from the Contrave Obesity Research (COR) and SCALE trials, Fujioka and colleagues found that those with 5% or greater weight loss at 4 months were more likely to maintain clinically significant weight loss 1 year after starting liraglutide⁷⁹ and naltrexone/bupropion,⁹⁷ respectively. In a study of adolescents and adults with epilepsy prescribed topiramate, 3-month weight loss predicted greater BMI reduction at 6 months.⁸⁹

Increased hunger and food intake, as well as decreased satiety, are commonly identified baseline eating behavior characteristics associated with increased weight loss response to obesity pharmacotherapies. Such findings have been noted in analyses involving exenatide,⁸⁵ topiramate,⁸⁹ phentermine,⁹³ and topiramate/phentermine.⁹⁵ For example, in a prospective trial of adults prescribed phentermine, Thomas and colleagues found that increased desire to eat and lower cognitive restraint at baseline were more common in those experiencing 5% or greater weight loss after 2 months compared with those with less than 5% weight loss.⁹³ In an analysis of pooled data from the COR trials, Dalton and colleagues showed that those with the greatest improvement in craving control at 8 weeks had

Table 3. Predictors of response to obesity pharmacotherapies.

Author	Inclusion criteria	n	Study design	Predictors of response
ORLISTAT				
Chanoine and Richard ⁷¹	Adolescents (12–16 years), BMI ≥ 2 kg/m ² above the 95th percentile (excluded BMI ≥ 44 kg/m ² ; weight > 130 kg of < 55 kg)		Retrospective analysis of a multicenter 1-year RCT (orlistat 120 mg 3 times daily <i>versus</i> placebo); assessed if 3-month weight loss predicted 12-month weight loss	Greater weight loss at 3 months correlated with greater weight loss at 1 year.
Elfhag and colleagues ⁷²	Adults, BMI ≥ 30 kg/m ²	148	Retrospective analysis of self-reported data	Men experienced greater weight loss than women; 'order' and 'deliberation' facets of conscientiousness positively correlated with weight loss
Hollywood and Ogden ⁷³	Adults prescribed orlistat	566	Retrospective analysis of a 6-month open-label study of participants prescribed orlistat; only those completing baseline and 6-month surveys included in analysis	A decrease in unhealthy eating, increase belief in treatment control, increased belief that the unpleasant side effects of orlistat are both due to eating behavior and just part of the drug, and baseline greater endorsement of medical solutions predicted those most likely to reduce BMI at 6 months
Rissanen and colleagues ⁷⁴	Adults, BMI 28–43 kg/m ²	220	Retrospective analysis of pooled data from two 2-year multicenter RCTs (orlistat 120 mg 3 times daily <i>versus</i> placebo) comparing those who lost $\geq 5\%$ <i>versus</i> < 5% weight at 3 months	Weight loss $\geq 5\%$ at 3 months predicted sustained weight loss at 2 years
Toplak and colleagues ⁷⁵	Adults, BMI 30–43 kg/m ² , body weight ≥ 90 kg, WC ≥ 88 cm (female) or ≥ 102 cm (male)	430	1 year, open-label, randomized, parallel group trial with all participants receiving 120 mg orlistat three times daily; compared 500 kcal <i>versus</i> 1000 kcal energy deficit diet; orlistat discontinued in participants who did not achieve $\geq 5\%$ weight loss at 3- and 6-month assessment	$\geq 5\%$ weight loss at 3 months associated with long-term weight loss at 1 year in both diet groups
Ullrich and colleagues ⁷⁶	Adults, BMI 30–40 kg/m ²	62	Retrospective analysis of open-label 72 week trial (orlistat 120 mg three times daily <i>versus</i> placebo)	Low fat and carbohydrate intake predicted increased weight loss
Lorcaserin				
Farr and colleagues ⁹⁰	Adults, BMI > 30 kg/m ² or > 27 kg/m ² with ≥ 1 comorbidities	48	Prospective 1-month RCT comparing lorcaserin 10 mg twice daily with placebo; assessed neuronal activation with fMRI at baseline, 1 week, and 1 month	Activations in amygdala, parietal, and visual cortices at baseline correlated with decreases in caloric intake, weight, and BMI at 1 month
Smith and colleagues ⁹²	Adults, BMI 30–45 kg/m ² or 27–29.9 kg/m ² with ≥ 1 comorbidities	6897	Retrospective analysis of pooled data from three trials (BLOOM, BLOSSOM, and BLOOM-DM) comparing lorcaserin + LMT with placebo + LMT; assessed if weight loss response at 3 months predicted response at 1 year	$\geq 5\%$ weight loss at 3 months predicted greater weight loss at 1 year

(Continued)

Table 3. (Continued)

Author	Inclusion criteria	n	Study design	Predictors of response
PHENTERMINE				
Thomas and colleagues ⁹³	Adults, BMI 30–40 kg/m ²	35	Prospective 8-week trial of participants receiving phentermine comparing those with ≥5% versus <5% weight loss	Participants with ≥5% weight loss had higher pre-breakfast hunger, desire to eat, prospective food consumption and lower baseline cognitive restraint; higher home prospective food consumption and lower baseline cognitive restraint predicted increased weight loss
Topiramate				
Ben-Menachem and colleagues ⁸⁶	Adults with epilepsy	49	Prospective open-label trial adding topiramate to existing anticonvulsant regimen, assessing change in weight from baseline to 3- and 12-months after topiramate initiated	3-month weight loss correlated with reduced caloric intake; 1-year weight loss correlated with higher baseline BMI despite caloric intake returning to baseline levels; participants with obesity lost more weight than participants without obesity
El Yaman and colleagues ⁸⁷	Children and adults with epilepsy	120	Prospective cohort study of participants started on topiramate	Participants with higher baseline BMI and younger age lost more weight at year 2; higher average topiramate dose (>6 mg/kg/day) associated with larger decrease in BMI from baseline
Iwaki and colleagues ⁸⁸	Adults with epilepsy	78	Prospective, open-label study assessing weight loss 1, 6, 12, 18 months after starting topiramate; compared those with no versus mild intellectual disability (ID)	Participants with no/mild ID lost more weight compared with those with moderate/profound ID
Kazerooni and Lim ⁹⁴	Adults, BMI ≥25 kg/m ²	767	Retrospective cohort study examining weight loss outcomes 1 year after topiramate initiated (for any indication)	Higher prevalence of females lost ≥5% compared with males; adherent participants more likely to lose ≥5% BW compared with nonadherent participants
Klein and colleagues ⁸⁹	Children (≥12 years) and adults with epilepsy	22	Prospective study assessing 3 week, 3 month, 6 month, and long-term weight loss after starting topiramate	Weight loss, reduction of appetite, and amount of intake at 3 months predicted BMI decrease at 6 months; high initial BMI and body fat predicted lower BMI reduction at 6 months
Li and colleagues ⁹¹	Adults, BMI 30–50 kg/m ² or 27–50 kg/m ² with ≥1 comorbidities	1004	Retrospective study of DNA samples from participants previously completing clinical trials, assessing efficacy of topiramate for obesity	Carriers of haplotype T-C-A in INSR had greater weight loss than noncarriers; Rs55834942 SNP from HNF1A associated with increased weight loss response
Phentermine/topiramate				
Acosta and colleagues ⁹⁵	Adults, BMI 30–40 kg/m ²	24	2-week RCT assessing effects of phentermine/topiramate on weight and quantitative traits	Higher intake at baseline buffet meal satiety test associated with greater weight loss at 2 weeks

(Continued)

Table 3. (Continued)

Author	Inclusion criteria	n	Study design	Predictors of response
Naltrexone/bupropion				
Dalton and colleagues ⁹⁶	Adults, BMI 30–45 kg/m ² or 27–45 kg/m ² with ≥1 comorbidities	2,046	Retrospective analysis of four 56-week RCTs (COR-I, COR-II, COR-BMOD, COR-DM) comparing NB32, NB16, and placebo	Participants with the greatest improvement in craving control at 8 weeks had greater weight loss after 56 weeks
Fujioka and colleagues ⁹⁷	Adults, BMI 30–45 kg/m ² or 27–45 kg/m ² with ≥1 comorbidities	3362	Retrospective analysis of four 56-week RCTs (COR-I, COR-II, COR-BMOD, COR-DM) comparing NB32, NB16, and placebo	Participants with ≥5% weight loss at 4 months more likely to maintain clinically significant weight loss at 1 year
Liraglutide				
Ard and colleagues ⁷⁷	Adults, BMI ≥30 kg/m ² or ≥27 kg/m ² with ≥1 comorbidities	5325	Retrospective analysis of data from five RCTs (liraglutide 3.0 mg <i>versus</i> placebo) comparing weight loss by race/ethnicity	No significant weight loss response differences by race/ethnicity
Dahlqvist and colleagues ⁷⁸	Adults, BMI 27.5–45 kg/m ² , HbA1c 7.5–11.5%, c-peptide ≥10 nmol/L, treated with multiple daily injection insulin for ≥6 months	124	Retrospective analysis of a 24-week RCT comparing liraglutide 1.8 mg with placebo as adjunct to multiple daily injection insulin regimen with or without metformin	Lower HbA1c and mean glucose level predicted greater weight loss response to liraglutide
Fujioka and colleagues ⁷⁹	Adults, BMI ≥30 kg/m ² without DM or BMI ≥27 kg/m ² with ≥1 comorbidities not including DM (SCALE Obesity and Prediabetes), or BMI ≥27 kg/m ² with DM (SCALE Diabetes)	4577	Retrospective analysis of data from SCALE Obesity and Prediabetes and SCALE Diabetes trials	Greater proportion of those with ≥4% weight loss at 4 months achieved ≥5%, ≥10%, and ≥15% weight loss at 56 weeks compared with those with <4% weight loss at 4 months
Gomez-Peralta and colleagues ⁸⁰	Adults with T2DM on liraglutide	799	Retrospective chart review of electronic medical records	Higher baseline weight and longer treatment duration predicted improved weight loss response
Halawi and colleagues ⁸¹	Adults, BMI ≥30 kg/m ² or ≥27 kg/m ² with ≥1 comorbidities	40	Prospective 4-month RCT assessing effect of liraglutide <i>versus</i> placebo on gastric motor function, satiety, and weight	Delayed gastric emptying at 5 weeks correlated with increased weight loss with liraglutide at 4 months
Wilding and colleagues ⁸²	Adults, BMI ≥30 kg/m ² without DM or BMI ≥27 kg/m ² with ≥1 comorbidities not including DM (SCALE Obesity and Prediabetes), or BMI ≥27 kg/m ² with DM (SCALE Diabetes)	4372	Retrospective analysis of data from SCALE Obesity and Prediabetes and SCALE Diabetes trials	Increased drug exposure correlated with increased weight loss

(Continued)

Table 3. (Continued)

Author	Inclusion criteria	n	Study design	Predictors of response
EXENATIDE				
Anichini and colleagues ⁸³	Adults with T2DM and therapeutic failure on oral therapy (metformin or metformin + SU)	315	Retrospective analysis of participants prescribed exenatide 10 µg twice daily	Longer DM duration in males, lower baseline A1c in females predicted those most likely to lose ≥8.5% weight at 1 year
Gorgojo-Martínez and colleagues ⁸⁴	Adults, T2DM, BMI ≥ 30 kg/m ²	148	Retrospective analysis of participants prescribed exenatide 2 mg weekly	Higher BMI, previous use of DPP4 inhibitors predicted weight loss ≥3% after 6 months
Nathan and colleagues ⁸⁵	Children (12–19 years), BMI ≥1.2 times 95th percentile or BMI ≥35 kg/m ² , without DM	32	Retrospective analysis of 2 RCTs comparing exenatide 10 µg twice daily <i>versus</i> placebo	Higher baseline appetite, female sex predicted greater BMI loss at 3 months

BMI, body mass index; DM, diabetes mellitus; DPP4, dipeptidyl peptidase-4; fMRI, functional magnetic resonance imaging; HbA1c, hemoglobin A1c; HNF1A, hepatocyte nuclear factors 1-alpha; INSR, insulin receptor; LMT, lifestyle modification therapy; NB16, 16 mg naltrexone SR/360 mg bupropion SR; NB32, 32 mg naltrexone SR/360 mg bupropion SR; RCT, randomized controlled trial; SCALE, Satiety and Clinical Adiposity Liraglutide Evidence; SNP, single nucleotide polymorphism; SU, sulfonylureas; T2DM, type 2 diabetes mellitus; WC, waist circumference.

increased weight loss 56 weeks after starting naltrexone/ bupropion, which is not surprising given naltrexone's mechanism as an opiate receptor agonist.⁹⁶

Whether sex predicts weight loss response to obesity pharmacotherapies remains unclear. In a retrospective analysis of adults prescribed orlistat, self-reported weight loss was significantly greater in males than in females; however, compliance, which can be challenging with this medication due to gastrointestinal side effects, was not formally assessed.⁷² In contrast, Kazerooni and Lim examined weight loss outcomes after topiramate initiation in a Veteran population and found that the prevalence of 5% or greater weight loss after 1 year was 14% higher in females than in males.⁹⁴ Similarly, female sex predicted a greater BMI reduction 3 months following exenatide initiation in adolescents with severe obesity, a finding also described in adolescents with insulin resistance receiving metformin.^{85,98} Sex differences in weight loss response to obesity pharmacotherapies may be related to medication-hormonal interactions known to be different between sexes, including leptin which is present in higher concentrations in females compared with males at all BMI levels.^{85,99}

Only a few studies have explored physiologic, pharmacokinetic, and genotypic predictors of

weight loss response to obesity pharmacotherapies. For example, Halawi and colleagues showed that delayed gastric emptying at 5 weeks correlated with increased weight loss with liraglutide at 4 months, suggesting that gastric emptying may be a biomarker of responsiveness to determine those suitable for prolonged treatment with this medication.⁸¹ Wilding and colleagues performed a retrospective analysis of pooled data from RCTs involving liraglutide and found that increased drug exposure (assessed by area under the concentration-time curve) was associated with greater weight loss.⁸² In a 4-week trial using functional magnetic resonance imaging (fMRI) to assess neuronal activation to lorcaserin, Farr and colleagues demonstrated that baseline amygdala, parietal, and visual cortex activations correlated with decreased caloric intake and BMI among adults with obesity.⁹⁰ Additionally, in a study of DNA samples from participants who completed RCTs assessing topiramate for obesity treatment, carriers of a haplotype T-C-A in the INSR gene, and the SNP rs55834942, had greater weight loss compared with noncarriers.⁹¹

Specifically, in adults with type 2 diabetes mellitus (T2DM) prescribed GLP1-RAs, a lower hemoglobin A1c level seems to predict an improved weight loss response.^{78,83} Further, a higher baseline weight status,^{80,84} longer duration of treatment,⁸⁰ and previous use of dipeptidyl peptidase

4 inhibitors⁸⁴ have also been associated with better weight loss outcomes. Overall, while some predictors of weight loss response to obesity pharmacotherapy have been uncovered, there is a myriad of others yet to be elucidated.

Metabolic and bariatric surgery

Table 4 summarizes studies identifying characteristics associated with weight loss response to MBS. A majority of these studies involve Roux-en-Y gastric bypass (RYGB),^{100–113} with a few evaluating vertical sleeve gastrectomy (VSG),¹¹⁴ laparoscopic adjustable gastric banding (LAGB),^{115–117} biliopancreatic diversion (BPD),¹¹⁸ sleeve gastropasty,¹¹⁹ or a pooling of data from multiple procedures.^{120–124} Overall, studies exploring predictors of weight loss response to MBS in adolescents are rare.^{108,116}

Similar to the other interventions, early weight loss predicts sustained weight loss, as noted in studies of adults who underwent sleeve gastropasty, RYGB, and VSG.^{119,122} The most commonly identified predictor of worse response appears to be a higher baseline BMI as seen with RYGB,^{100–101,109,111} LAGB,¹¹⁵ and VSG.¹²⁰ Older age, fasting glycemia, and the presence of T2DM have additionally been associated with worse outcomes as seen in studies examining RYGB,^{100,101,104,111} LAGB,¹¹⁵ VSG,^{111,120} and BPD.¹¹⁸ Al-Khyatt and colleagues, Lent and colleagues, and Sillen and Andersson all showed that the presence of diabetes at baseline predicted worse weight loss response to RYGB, while Dixon and colleagues showed that baseline insulin resistance was associated with decreased weight loss 1 year following LAGB.^{100,104,109,115}

Numerous investigations have examined psychosocial and eating behavior determinants of weight loss response to MBS. For example, the perception of social support has been associated with better response to RYGB,¹¹² and decreased binge eating appears to predict greater weight loss to LAGB in adults.¹¹⁷ Among adolescents who underwent RYGB, greater weight-related quality of life was associated with weight maintenance 5 or more years after MBS.¹⁰⁸ Factors that have been associated with worse weight loss response to MBS include the presence of emotional food craving (with VSG¹¹⁴), food addiction symptoms (with VSG or RYGB¹²³), loss of control eating (with LAGB¹¹⁶), and higher levels of eating in

response to anger, frustration, or depression (with VSG or RYGB¹²³). Lower physical activity and self-esteem, and higher eating disinhibition, have been associated with long-term weight regain following RYGB.¹⁰⁵

A few studies have explored the genetic predictors of weight loss response to MBS, specifically to RYGB. For example, a longitudinal study by Hatoum and colleagues comparing first-degree relatives, nongenetically related cohabiting pairs, and nonrelated pairs undergoing RYGB found that, while first-degree relatives had a similar weight loss response to surgery (only a 9% difference in excess weight loss between members of each pair), no similarities were seen between cohabiting and unrelated individuals.¹⁰³ Carrying the I125L allele variant of MC4R,¹⁰⁵ the 5-HT2C gene polymorphism rs3813929 (TT genotype),¹⁰⁷ and a G to T substitution in rs696217 (preproghrelin gene),¹¹³ have all been associated with improved weight loss response, while carrying the rs1126535 C allele (CD40L gene)¹¹³ and increasing numbers of SNP alleles near FTO, insulin-induced gene 2 (INSIG2), MC4R, and PCSK1 have been associated with worse response to RYGB.¹¹⁰

Medical device therapy

Studies examining predictors of weight loss response to medical devices are rare, and all have involved adults undergoing intragastric balloon therapy (Table 5).^{125–127} Consistent with other treatment modalities, early weight loss appears to predict sustained weight loss response.^{126,127} In two separate studies, older age was associated with greater weight loss.^{125,126} As for psychosocial factors, higher education level and social relationship scores, a strict exercise commitment, and increased number of follow-up visits have all been predictive of increased weight loss 6 months after intragastric balloon placement.^{125–127} Future studies are needed to explore the factors predictive of weight loss response to other medical devices, including vagal blockade and aspiration therapies.

Gaps and opportunities for future research in the development of targeted therapies for obesity

It was 30 years ago that the American Diabetes Association proposed two classes of diabetes mellitus (DM): insulin-dependent (type 1) and

Table 4. Predictors of response to metabolic and bariatric surgery.

Author	Inclusion criteria	n	Study design	Predictors of response
Roux-en-Y gastric bypass				
Al-Khyatt and colleagues ¹⁰⁰	Adults, receiving RYGB	227	Retrospective cohort study assessing predictors of 1-year EWL	Higher BMI, older age, presence of DM, and preoperative weight gain predicted lower 1-year EWL
Faria and colleagues ¹⁰¹	Adults, receiving RYGB	163	Prospective cohort study assessing fasting glycemia as predictor of weight loss	Baseline BMI and fasting blood glucose >100 mg/dl inversely correlated with probability of achieving >80% EWL or >35% weight loss after 1 year; effect not detectable in participants on oral antidiabetic medications following RYGB
Guajardo-Salinas and colleagues ¹⁰²	Adults, BMI ≥ 40 kg/m ² receiving RYGB	75	Retrospective study examining predictors of weight loss following RYGB, comparing Whites and Hispanics	No difference in EWL and BMI between Whites and Hispanics after 1 year; higher HDL and lower SBP pre-RYGB significantly predicted EWL at 12 months in Whites; lower Fibrospect score pre-RYGB predicted higher EWL at 12 months in Hispanics
Hatoum and colleagues ¹⁰³	Patients, receiving RYGB	848	Prospective study to determine if there is a significant genetic contribution to weight loss following RYGB through genotyping; first-degree relatives, nongenetically related cohabiting pairs, and nonrelated pairs were compared	First-degree relative pairs had similar response to surgery; similarity not seen in cohabiting or unrelated individuals
Lent and colleagues ¹⁰⁴	Patients, receiving RYGB	3125	Retrospective study examining weight trajectories of patients receiving RYGB to identify clinical, behavioral, and demographic features of patients by weight loss trajectory	Those with below average weight loss trajectory more likely to be male and have DM, and less likely to have a smoking history or taking sleeping medications. Lower initial weight loss post-surgery associated with greater chance of poorer weight outcomes
Livhits and colleagues ¹⁰⁵	Patients, receiving RYGB	197	Retrospective cohort study assessing predictors of weight regain (≥15% from lowest weight to weight at survey completion, average 45 months after RYGB)	Low physical activity and self-esteem, and higher eating disinhibition, associated with weight regain
Mirshahi and colleagues ¹⁰⁶	Patients, receiving RYGB	1433	Prospective cohort study assessing MC4R genotype and its relationship with weight loss and clinical phenotypes during a 4-year period before/after RYGB	1125L allele carriers lost 9% more weight compared with noncarriers, continued rapid weight loss longer, regained less weight, and had a lower presurgery HOMA
Novais and colleagues ¹⁰⁷	Adult females, receiving RYGB	351	Prospective cohort study assessing association between 12 gene polymorphisms and 1-year %EWL	5-HT2C gene polymorphism rs3813929 (TT genotype) predicted greater 1-year %EWL
Ryder and colleagues ¹⁰⁸	Adolescents, receiving RYGB	50	Retrospective study assessing psychosocial factors associated with long-term weight loss maintenance	Greater quality of life at 5–12 years associated with better weight loss maintenance at 5–12 years

(Continued)

Table 4. (Continued)

Author	Inclusion criteria	<i>n</i>	Study design	Predictors of response
Sillen and Andersson ¹⁰⁹	Patients, receiving RYGB	281	Retrospective analysis, assessing preoperative factors predictive of successful weight loss (EWL \geq 60%) 1–3 years following RYGB	Earlier onset of obesity and higher preoperative BMI associated with unsuccessful weight loss at 1 year; preoperative psychiatric disorders, DM, hypertension, and higher BMI associated with unsuccessful weight loss at 2 years
Still and colleagues ¹¹⁰	Caucasian adults, BMI \geq 35 kg/m ² , receiving RYGB	1001	Prospective cohort study assessing relationship between SNPs in/near FTO, INSIG2, MC4R, and PCSK1 and weight loss	Increasing numbers of SNP alleles near FTO, INSIG2, MC4R, and PCSK1 associated with decreased weight loss
Still and colleagues ¹¹¹	Patients, receiving RYGB	2365	Retrospective analysis of a prospectively recruited cohort study assessing clinical factors associated with weight loss	Higher baseline BMI and preoperative weight loss, iron deficiency, use of any DM medications, nonuse of bupropion, no history of smoking, age $>$ 50 years, and presence of fibrosis on liver biopsy associated with poorer long-term ($>$ 36 month) weight loss
ter Braak and colleagues ¹¹²	Adults, \geq 1 year follow-up data available, receiving RYGB	112	Retrospective, case-control study comparing nonresponders (% alterable weight loss $<$ 10th percentile) to responders (% alterable weight loss 25–75th percentile) in perceived social support and stressful life events	Perceived social support able to classify 84% of participants correctly as responders <i>versus</i> nonresponders; stressful life events not related to weight loss
Vitolo and colleagues ¹¹³	Adults with severe obesity, receiving RYGB	100	Prospective cohort study assessing relationship between SNPs rs2241766 for adiponectin gene, rs490683 for ghrelin receptor, rs696217 and rs27647 for the preproghrelin/ghrelin gene, and rs1126535 for the CD40L gene and weight loss at 6, 26, and 52 weeks following RYGB	Carrying G to T substitution in rs696217 (preproghrelin gene) associated with improved weight loss response; carrying rs1126535 C allele (CD40L gene) associated with worse weight loss response
Biliopancreatic diversion, adjustable gastric banding, sleeve gastropasty, sleeve gastrectomy				
Dixon and colleagues ¹¹⁵	Adults, BMI \geq 35 kg/m ² , significant medical, physical, or psychosocial disabilities, attempted weight loss by other means for \geq 5 years	440	Prospective cohort study assessing preoperative predictors of weight loss 1 year after AGB	Older age; higher BMI; insulin resistance; and diseases associated with insulin resistance, poor physical activity, and pain associated with decreased EWL at 1 year
Janse Van Vuuren and colleagues ¹¹⁴	Adults, receiving SG	106	Prospective cohort study assessing if post-surgery food cravings predict weight loss outcomes at 6–8 months	Emotional food cravings experienced 4–6 weeks following SG predicted poorer weight loss outcomes at 6 months
Lopez-Nava and colleagues ¹¹⁹	Adults, receiving sleeve gastropasty	248	Retrospective analysis assessing long-term outcomes, reproducibility, and predictors of weight loss response	Percent weight loss at 6 months predicted percent weight loss at 24 months

(Continued)

Table 4. (Continued)

Author	Inclusion criteria	n	Study design	Predictors of response
Sysko and colleagues ¹¹⁶	Adolescents (14–18 years), receiving AGB	101	Prospective cohort study assessing presurgical psychological predictors of 1 year weight loss after AGB	Baseline loss of control eating and higher family conflict predicted decreased weight loss rate over 1 year
Valera-Mora and colleagues ¹¹⁸	Adults, receiving BPD	107	Prospective cohort study assessing predictors of weight loss and reversal of comorbidities at 2 years	Older age and presence of DM negatively predicted, and initial fat mass positively predicted, weight loss at 2 years
Wood and Ogden ¹¹⁷	Adults, receiving AGB	49	Prospective cohort study assessing if pre- and postoperative binge eating behaviors predict weight loss	Decrease in binge eating as a consequence of having AGB predicted postoperative weight loss
Studies involving multiple surgical procedures				
de Hollanda and colleagues ¹²⁰	Adults, ≥30 month follow-up data available, receiving RYGB or SG	658	Retrospective analysis comparing participants experiencing EWL ≥ 50% versus <50%	EWL < 50% at 1 year associated with higher baseline BMI and presence of presurgical T2DM
Kontinen and colleagues ¹²¹	Adults, BMI ≥ 34 kg/m ² (males) or BMI ≥ 38 kg/m ² (females), receiving gastric banding, vertical banded gastroplasty, gastric bypass	3926	Prospective matched interventional trial comparing participants undergoing bariatric surgery with conventional weight loss intervention	Pretreatment eating behaviors unrelated to weight changes after bariatric surgery; participants with lower levels of 6-month and 1-year disinhibition and hunger and who experienced larger 1-year decreases in these behaviors lost more weight 2, 6, and 10 years after surgery
Manning and colleagues ¹²²	Adults, BMI ≥ 40 kg/m ² or ≥ 35 kg/m ² with ≥1 obesity-related comorbidities, receiving RYGB or SG	1456	Retrospective cross-sectional study assessing if early postoperative weight loss predicts maximal weight loss	Weight loss velocity from 3–6 months independent predictor of maximal percent weight loss
Miller-Matero and colleagues ¹²³	Adults, receiving RYGB or SG	101	Retrospective analysis assessing if preoperative problematic eating behaviors predicted 1-year weight loss	Higher levels of eating in response to anger/frustration and depression correlated with decreased weight loss; higher number of food addiction symptoms increased likelihood participants experienced less weight loss
Subramaniam and colleagues ¹²⁴	Adults, receiving RYGB, SG, or one anastomosis gastric bypass-mini gastric bypass	57	Prospective cohort study assessing pre- and postsurgical predictors of weight loss following bariatric surgery	Older age, higher BMI, and greater emotional eating and external eating predicted less weight loss

AGB, adjustable gastric banding; BMI, body mass index; BPD, biliopancreatic diversion; DM, diabetes mellitus; EWL, excess weight loss; FTO, fat mass and obesity-associated protein; HDL, High-density lipoprotein; HOMA, homeostatic model assessment; INSIG2, insulin-induced gene 2; MC4R, melanocortin 4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; RYGB, Roux-en-Y gastric bypass; SBP, systolic blood pressure; SG, sleeve gastrectomy; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

Table 5. Predictors of response to device therapy.

Author	Inclusion criteria	n	Study design	Predictors of response
Kotzampassi and colleagues ¹²⁵	Adults, BMI < 35 kg/m ² with comorbidities; BMI ≥ 35 kg/m ² resistant to LMT for 6 months; or BMI ≥ 50 kg/m ² , receiving 6-month intragastric balloon	583	Retrospective analysis comparing successful (%EWL ≥ 50%) and poor (%EWL < 20%) responders	Older age, females, higher education level, single/divorced participants, and strict exercise commitment predicted success
Madeira and colleagues ¹²⁶	Adults, BMI ≥ 30 kg/m ² and metabolic syndrome without DM, receiving 6-months intragastric balloon	50	Prospective 6-month study assessing predictors of weight loss response	Baseline advanced age and higher social relationship score associated with weight loss > 10% at 6 months; weight loss > 5% at 2 and 4 weeks and higher intensity of dyspepsia at 2 weeks predicted weight loss > 10% at 6 months
Vargas and colleagues ¹²⁷	Adults, BMI > 30 kg/m ² , receiving intragastric balloon	321	Retrospective analysis assessing safety, efficacy, and factors associated with intolerance and response to intragastric balloon	Greater number of follow-up visits and weight loss at 3 months associated with increased weight loss at 6 months

BMI, body mass index; DM, diabetes mellitus; EWL, excess weight loss; LMT, lifestyle modification therapy.

insulin-independent (type 2).¹²⁸ Over time, new subgroups were discovered, including latent autoimmune diabetes in adults and mature onset diabetes in the young (MODY). A recent cluster analysis suggested five DM subtypes in adults, each with different patient characteristics and risks for complications.¹²⁹ Moreover, it has become clear that the treatments for DM, including therapy type (e.g. sulfonylureas for HNF1A- or HNF4A-MODY) and efficacy, differ depending on the underlying cause. Our understanding of the etiologies underlying obesity may not be far ahead of where our understanding of the etiologies underlying DM were not long ago. Similar to DM, the substantial degree of heterogeneity seen in individual response to weight loss interventions is likely due to an equally large degree of heterogeneity in the cause. Without a clearer understanding of the specific etiology or distinct phenotypes, which may be complex and are unlikely based upon single features, the development of directed treatments will be challenging.

While targeted treatments for several forms of monogenic obesity have emerged, most cases of obesity are polygenic in origin. In polygenic obesity, groups of alleles at different gene loci have variants each contributing a small additional effect towards body weight regulation. It may be

that every individual with obesity carries his or her own specific polygenic variants.^{130,131} While precision medicine, as an approach, may be presently better suited for the treatment of monogenic obesity, continued advancements in genetics, pharmacogenetics, and epigenetics may eventually elucidate pharmacotherapeutic options for polygenic forms.

The rise of electronic health records (EHRs) and the subsequent creation of EHR-enabled clinical discovery cohorts may provide a valuable tool for examining person-specific characteristics associated with weight loss to interventions in the real-world setting. EHRs can be combined across multiple institutions to increase sample size and statistical power.¹³² This is especially helpful for exploring outcomes to interventions in smaller groups of individuals, or for evaluating rare medication side effects. Integrating ‘-omic’ data (e.g. genomic, metabolomic) into the EHR will improve the capacity for identifying additional sources of variability in drug-response relationships that are too challenging to identify from smaller-scale studies. Further, large-scale observational studies combining EHR data with machine learning statistical techniques may allow us to better determine phenotypic characteristics associated with weight loss response to obesity interventions. That said, the heterogeneity in the

approach to medical weight management and the inconsistent timing of patient evaluations leads to missing or flawed data, thereby limiting the amount of aggregated data that can be collected from EHR studies. Further, while correlation can be determined from such observational studies, causation cannot be, and compliance often cannot be readily assessed.

Similar to the way that combining meta-analyses has increased our identification of the loci and SNPs contributing to the development of obesity and the metabolic syndrome,^{10,11} combining data from obesity interventional trials may help us better identify subgroups of responders to various treatments. This is especially pertinent in pediatric obesity, where most studies are small and subgroup analyses are therefore limited. Fortunately, attempts are underway to standardize these processes, at least in the adult realm. The Accumulating Data to Optimally Predict obesity Treatment (ADOPT) Core Measures project was designed to provide investigators with tools to generate evidence through the use of common measures following four domains: behavioral, biological, environmental, and psychosocial.¹³³ Accumulating data on these factors will help inform the design and delivery of effective, tailored obesity treatments.¹³⁴

As mentioned previously, several phenotypic predictors of weight loss response have already been elucidated. The most consistently identified predictors of later response to an intervention are early response and higher adherence,³⁶ which should be reported in clinical trials. Increased baseline appetite and decreased satiety predict better response, while the presence of disordered eating and psychopathology predict worse response to several interventions.^{47–49,51,85,95,105,123} While these identified ‘primordial’ predictors represent the beginning of our understanding into person-specific characteristics predictive of weight loss response, many are not specific enough to help us tailor therapy. For example, given that increased hunger predicts greater weight loss response to exenatide,⁸⁵ topiramate,⁸⁹ and phentermine,⁹⁴ adding this variable to a pharmacotherapy selection algorithm may not help in the decision-making between these three options. In order to differentiate between which therapies to consider for each patient, we need to uncover personalized predictors that are specific to each intervention. Incorporating neuroimaging (e.g.

fMRI), biobanks, and data repositories into studies evaluating characteristics associated with weight loss will help us discover predictors that are more precise.

Finally, future studies should also examine predictors of weight loss response to mobile health technologies, such as smartphone applications. Presently, evidence showing that these tools improve weight loss is mixed;^{135–138} however, as with other interventions improved adherence appears to predict greater weight loss response.^{139,140} Studies should also examine the optimal timing for treatment interventions. Such investigations should focus on determining the window of opportunity for when an intervention should be initiated in order to achieve the best possible response. Given that, among adolescents who develop obesity the most rapid weight gain appears to occur between the ages of 2 and 6 years, earlier interventions are likely needed.¹⁴¹ The time course for beginning, discontinuing, or intensifying treatment in any population remains elusive and will require further investigation.

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