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The Accumulating Data to Optimally Predict Obesity Treatment (ADOPT): Recommendations from the Biological Domain

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Abstract

Background: The responses to behavioral, pharmacological, or surgical obesity treatments are highly individualized. ADOPT provides a framework for how obesity researchers, working collectively, can generate the evidence base needed to guide the development of tailored, and potentially more effective, strategies for obesity treatment.

Objective: The objective of the ADOPT Biological Domain subgroup is to create a list of high priority biological measures for weight loss studies that will advance understanding of individual variability in response to adult obesity treatments. This list includes measures of body composition, energy homeostasis (energy intake and output), brain structure and function, and biomarkers, as well as biobanking procedures, which could feasibly be included in most, if not all, studies of obesity treatment. The **recommended** high priority measures are selected to balance needs for sensitivity, specificity, and/or comprehensiveness with feasibility to achieve a commonality of usage and increase the breadth and impact of obesity research.

Significance: The accumulation of data on key biological factors, along with behavioral, psychosocial, and environmental factors, can generate a more precise description of the interplay and synergy among them and their impact on treatment responses, which can ultimately inform the design and delivery of effective, tailored obesity treatments.

Keywords

ADOPT; Body Composition; Energy Homeostasis; Biomarkers; Biobanking; Brain Structure; Brain Function

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INTRODUCTION

Weight loss provokes coordinated changes in multiple energy homeostatic systems, which culminate in disproportionately increased energy intake and decreased energy expenditure (1, 2). The extensive inter-individual variability in responses to weight loss (3) and treatments differentially targeting these systems (4, 5) suggests that treatment could be improved via better understanding of the biological factors mediating energy balance (6, 7).

The NIH-sponsored Accumulating Data to Optimally Predict obesity Treatment (ADOPT) Core Measures Project (8) aims to advance adult obesity medicine in the face of this individual variability in treatment responses (9). ADOPT is designed to provide investigators with tools to generate an evidence base consisting of common measures across four domains: Behavioral, Biological, Environmental, and Psychosocial, that can enhance interdisciplinary research and advance understanding of the sources of response variability, depicted in the ADOPT working model.

The biological domain subgroup of the ADOPT Working Group was tasked with recommending core measures relevant to the "constructs" of body composition, energy homeostasis, biomarkers, brain structure and function, and biobanking, as previously designated by the full ADOPT Working Group. The uniform reporting of common measures can increase the impact and generalizability of the combined research body. Further information regarding each construct and measure described below is available at the ADOPT Core Measures Workspace in the Grid-Enabled Measures (GEM) database (www.gem-measures.org), which is also a venue for discussions that help to build consensus around common measures.

IDENTIFICATION OF BIOLOGICAL MEASURES

Selection Criteria.

In an effort to create a list of measures of relevant biological constructs that could be employed across most, if not all, clinical human obesity studies, several factors were considered in the selection of the methods (designated as "measures") best designed to evaluate each construct, given the constraints of human weight loss trials. These included: 1) the strength of the current evidence relating each measure to relevant constructs and weight loss outcomes; 2) the measure's validity and reliability; 3) the feasibility of widespread use of the measure; 4) the measure's burden to investigators (cost, administration, availability) and subjects (time and invasiveness); and 5) the measure's applicability to small (<50 participants), moderate (50–200 participants), and large (>200 participants) studies.

In many cases, the "gold standard" measures were not the most practical, within the feasibility constraints of many weight loss trials. Recognizing the frequent dichotomy between precision and practicality, we provide two classifications of measures within constructs. "**Recommended" measures, highlighted in bold**, are those that should be feasible and cost-effective in all obesity-related clinical trials. "Suggested*" measures, italicized*, are those that should be feasible and cost-effective in many, if not most, clinical trials and, if possible, should be performed in addition to the **recommended** measures.

Except as otherwise noted (e.g., for targeted genetic studies), all measures outlined below should be obtained at baseline and at other time points (e.g., during and after an intervention) in each study.

ADOPT CORE MEASURES FOR THE BIOLOGICAL DOMAIN

Construct: Body Composition

Within the construct of body composition, we included both anthropometric and bioelectrical impedance measures to allow assessment of body fat content, central versus peripheral, and visceral versus subcutaneous fat distribution, in a manner that can be integrated across previous and future studies (10). It is likely that this recommendation will change going forward, as more investigators use **recommended** measures of body fat content (see below).

Anthropometry—Anthropometry includes assessment of **height, weight**, and calculated **body mass index** (BMI), as well as central fat mass and of the relative distribution of fat in central and peripheral fat depots by **waist and hip circumferences** and calculated **waist-to-hip ratio** (WHR). The feasibility of anthropometry permits easy frequent measurement (at least every 1–3 months in the initial phases of weight loss trials), which is necessary to document early responses (1–2 months) to surgical (11, 12) and non-surgical (13, 14) interventions as predictors of long-term success.

However, together, BMI, sex, and age, explain approximately 50–60% of the variance in percent body fat, as measured by *dual energy x-ray absorptiometry (DXA)*, which is the "gold standard" (15) and anthropometry is clearly less accurate than bioelectric impedance spectroscopy (BIS), DXA, MRI, and BodPod (see below). The accuracy of BMI is further diminished in participants with increased fractional lean body mass, such as athletes with very high muscle mass, (e.g., weightlifters) (16), or increased fractional fat mass, such as the elderly. BMI does not assess fat mass (FM) and fat-free mass (FFM), both of which are important determinants of energy expenditure (EE) and intake (EI), and different interventions may differentially affect body composition (fat mass and fat-free mass) and weight (16).

It is **recommended** that both **waist circumference** and **WHR** are collected in all adult studies (17), since both the absolute amount of central fat (17, 18) and the relative amount of fat distributed in central vs. peripheral fat depots (19, 20) have been shown to be predictive of multiple adiposity-related co-morbidities and may affect intervention response (21–23). Both these measures have been reported to correlate closely with visceral and subcutaneous adipose tissue measured by *DXA* or MRI (24, 25). To minimize variability in WHR, it is critical that investigators utilize uniform landmarks, with waist circumference measured at the iliac crest and hip circumference measured at the level of the trochanters as utilized by the National Center for Health Statistics in NHANES studies (26). It should be noted the abdominal circumference measured at the midpoint between the inferior border of the ribcage and the superior aspect of the iliac crest has been reported to be a better correlate of central adiposity in some studies (27). However, the NIH method is recommended to allow better comparisons with existing NHANES and other data.

Anatomic Fat Storage—Anthropometry fails to distinguish subcutaneous from visceral fat, which has been reported to be correlated with risk of metabolic syndrome, cardiovascular disease, and several malignancies (28), and the relative distribution of visceral and subcutaneous fat varies significantly by gender and between ethnic/racial groups (29), Specifically, it is **recommended** that all studies include more direct measures of fat mass by **Bioelectrical Impedance Spectroscopy (conventionally denoted as BIS)** (30), which is a non-invasive and inexpensive type of bioimpedance to assess body composition that can be utilized in studies of any size or duration. BIS is comparable to the single frequency devices used in Bio-impedance Analysis (conventionally denoted as BIA) in terms of subject burden and cost. The multi-segmental, multi-frequency BIS device allows identification of more components of bioimpedance (capacitance, resistance, etc.,.) than single frequency BIA devices and BIS measures of extracellular/intracellular resistance have been reported to be significantly correlated with intraabdominal fat mass measures by CT scan (31). BIS has also been reported to correlate better with fat mass than BMI and better with visceral/intraabdominal fat (measured by MRI) than waist circumference or WHR (32). Overall, BIS has been reported to explain 80–90% of the variance in fat mass and visceral fat and 50–55% of the variance in intraabdominal fat by *DXA* and/or *magnetic resonance imaging (MRI)* (32, 33). Despite the advantages of BIS, it has been reported to underestimate FM and overestimate FFM, especially in males (33), and BIS can be less reliable when hydration status of FM and FFM are uncertain (e.g., in children, individuals with edema, and post-bariatric surgery patients). In addition, there are multiple BIS systems available which have not been cross-validated. It is therefore essential to always report the exact BIS system utilized.

The addition of BIS will allow for integration of data from multiple studies and further validation of this approach. While BIS provides the best option for the assessment of body composition, when balancing the value of the data with the cost and participant burden in large clinical trials, this recommendation does not preclude the use of more accurate or precise suggested measures of body composition such as *DXA, MRI, or quantitative magnetic resonance spectroscopy (QMRS).* It is anticipated that the acquisition of BIS data along with other suggested measures of body composition in some studies will provide a large dataset that can be utilized to better define the precision of BIS in different populations.

Construct: Energy Homeostasis

The relative long-term constancy of body weight and overall lack of success of non-surgical interventions in long-term weight reduction suggests that, at usual weight, energy intake and output are “coupled” and vary directly to maintain energy stores; once weight is perturbed, this coupling is lost, and energy intake and output now vary inversely to “defend” previous body energy stores (2, 34).There is large inter-individual variability in energy intake (EI) and expenditure (EE) (including cardiorespiratory fitness, which is an important determinant of exercise recommendations) and, of course, adherence before, during, and after weight change (3, 23, 35–37). A better understanding of this variability is likely to identify certain energy homeostatic phenotypes that are predictive of individualized best practice recommendations.

Energy Expenditure—Total energy expenditure (TEE) is comprised of resting energy expenditure (REE), the thermic effect of feeding (TEF), and non-resting energy expenditure (NREE) (38), each of which is likely to change in weight loss studies. Direct and indirect objective measures for these variables presents challenges for large clinical weight loss trials because of their expense, participant burden, and feasibility. Because of these limitations, it is **recommended** that measures of TEE and its components be calculated.

Calculated REE should be acquired with the **Mifflin St.-Jeor equation** (39), which is best correlated (R^2=0.80–0.85) with calorimetric measures of REE (39) and superior to other less studied or more population-specific equations (40). The Mifflin St.-Jeor equation is provided below:

$$\text{Males}: \text{REE}\,(\text{kcal/day}) = 10 \times \text{weight}\,(\text{kg}) + 6.25 \times \text{height}\,(\text{cm}) - 5 \times \text{age}\,(\text{y}) + 5$$

$$\text{Females}: \text{REE}\,(\text{kcal/day}) = 10 \times \text{weight}\,(\text{kg}) + 6.25 \times \text{height}\,(\text{cm}) - 5 \times \text{age}\,(\text{y}) - 161$$

It should be noted that the Mifflin-St. Jeor equation may also have limitations in its generalizability. Equations for individuals who are transgender, intersex, have abnormal numbers of X or Y chromosomes, or who have undergone or are undergoing surgical or hormonal therapy relevant to gender have not as yet been derived (41). The increasing attention to gender medicine and gender-specific biological variation in human metabolic disease should yield an expanded list of calculations going forward.

In lieu of directly measuring NREE, it is **recommended** that a questionnaire-based assessment of **Physical Activity Level (PAL)** be acquired (42). PAL is defined as TEE/REE, and the questionnaire-derived PAL was chosen because of its simplicity, its validation by correlation with PAL measured by calorimetry, and its applicability across multiple studies. This questionnaire provides a self-evaluation of physical activity during work and leisure activities. The calculated REE and PAL can then be used to derive a **Calculated TEE**: TEE = PAL × REE.

The working group readily acknowledges that other direct and indirect measures can provide more accurate and precise measures of TEE, its components, and metabolic adaptation in response to treatment (43) but are not feasible in many weight loss trials due to the expense and required specialized equipment (38, 44). If possible, calorimetric measurement of *REE in the overnight fasted state using a metabolic cart or room indirect calorimeter* to measure rates of carbon dioxide production (VCO_2) and oxygen consumption (VO_2) is suggested. The VCO_2/VO_2 ratio provides an index of the relative mixture of metabolic fuels being utilized. Similarly, doubly-labeled water can be used to measure TEE in the free-living environment, and whole-room indirect calorimetry chambers can be used to provide robust objective estimates of TEE, NREE, and REE. While these approaches can also be utilized to acquire TEF with the appropriate feeding study design, TEF is neither **recommended** nor *suggested* across all studies because of the necessary complexity of these designs coupled with the relatively small contribution of TEF to TEE and adaptive thermogenesis (3).

Energy Intake: Under static conditions of body weight and composition stability, EI must be equal to TEE. **Energy Intake – Steady State** refers to energy intake when body composition and mass are not changing over time and can be presumed equal to calculated TEE (45). It should be noted that this does not include or account for variations in diet composition or the possible effects on partitioning of stored calories (see Construct: Body Composition) that might occur for example, as a result of weight loss with a resistance training component (increased partitioning of stored calories as FFM) versus aerobic training (46). During dynamic periods of weight change (EI≠EE), measuring EI is more difficult. Self-reported EI measures have been shown to be inaccurate (47) but **Changes in EI** during such periods can be mathematically modeled with measures of EE and body composition dynamics (33). This model has recently been validated against the intake-balance method in a two-year calorie restriction experiment in 140 people of varying age and BMI (48) and requires only baseline anthropometric and demographic information along with repeated body weight measurements over the course of the intervention. There are assumptions underlying this model, such as the stability of REE and PAL. More frequent body weight measurement increases the precision of the calculated changes in EI over time, and physical activity time course data (e.g., from actigraphy measurements) can also be incorporated to account for changes in NREE. The full description of this calculation, including MatLab Code information, can be found at the GEM measures Biological Domain website (https://www.gem-measures.org/Public/wsmeasures.aspx?cat=8&aid=1&wid=25).

Estimation of the average EI over an extended duration is ideally calculated using the intake-balance method involving body composition measurements, along with repeated TEE measurements using doubly labeled water (49); these procedures are, unfortunately, impractical for larger weight loss studies. Depending upon the duration and types of weight loss intervention, and participant age and gender, **calculated EI** based on TEE and weight or body composition change has been reported to account for between 20 and 60% of the variance in EI calculated using the *intake-balance method* as described above (48).

Cardiorespiratory Fitness—Cardiorespiratory fitness (CRF) varies significantly between individuals and may modify response to obesity treatment either directly or via compliance with exercise recommendations (50). CRF is also significantly correlated with mortality and co-morbidity risk, independent of body fatness (51). While the gold standard for cardiorespiratory fitness is an ergometric VO_{2max} test, an approximation can be made from **resting heart rate (RHR)** or an alternative submaximal fitness test. RHR was selected as a **recommended** measure because it is easy and inexpensive to perform and has been reported to explain about 20% of the variance in CRF (52), using multiple different equations and calculations. The *3-minute step test* has been reported to explain 50–90% of the variance in fitness by treadmill testing but may not be practical for larger studies and so is *suggested* rather than recommended (53, 54). For subjects who are unable to perform the step test, due to orthopedic or fitness issues, a simpler version using a corridor walk may be substituted (55).

Construct: Brain Structure and Function

Obesity-associated alterations in brain structure and function (56, 57) are correlated with weight loss and regain in behavioral and bariatric surgery trials (56, 58), with limited data regarding other treatments. Incentive motivation, reward learning, and executive function (including working memory) (58) are the neurocognitive constructs most predictive of treatment outcomes. These functions are largely mediated by the dopaminergic fronto-striatal (reward/motivation), fronto-parietal (executive function), and hippocampal-amygdala (learning and memory) systems, which operate as both independent and interdependent networks (59). Emerging data also indicated related neural systems (interoceptive and salience networks) could be important for weight outcome prediction (60).

This manuscript focuses on brain structure and function rather than the affected neurocognitive constructs discussed in the ADOPT Psychosocial Domain (61). The current gold standard measures are magnetic resonance imaging (MRI) to assess structure and blood oxygen-dependent functional MRI (fMRI) to assess function. FMRI can identify the 1) neural substrates that execute behaviors in response to environmental demands and 2) functionally-linked intrinsic neural networks that can be assessed in the absence of external, environmental demands (i.e., *resting state fMRI*). Measurement of resting state connectivity is feasible in large multi-site studies and, when integrated with other measures (e.g., cognitive, psychosocial, other biomarkers), can define mechanisms and neuropsychological subtypes that may predict response to treatment (62) even though correlations of resting state fMRI in specific single brain regions with behaviors are relatively low (63–69).

Because of the cost and burden to both the participants and researchers, *resting state fMRI* scans are only only suggested when feasible. Analyses of these fMRI data should include the assessment and comparison across several networks representing the neural systems described above. The *suggested MRI/fMRI protocol* includes: 1) anatomical MRI for structure (volume, density, shape, cortical thickness) and to aid in preprocessing of the fMRI data, 2) diffusion MRI (white matter tractography or structural connectivity), and 3) resting state functional connectivity (RSFC) MRI. Given that RSFC MRI may be sensitive to internal state, collecting data about the participant's last meal and the subjective experience of internal state (hunger, satiety) is *suggested* (61). Resting state studies in fasting and fed states will provide insights into brain areas related to meal initiation and cessation. The value of fMRI is significantly increased through integration with neurocognitive and psychosocial measures (61) and biomarkers of energy intake (e.g., gut peptides) and expenditure (e.g., leptin and thyroid hormones) described below.

Construct: Biomarkers

Biomarkers can provide information about the potential mechanisms by which information regarding nutreint availability, energy stores, and energy balance are communicated to central nervous system tracts regulating energy homeostasis, as well as providing valuable insights into adiposity-related comorbdities. Biomarker significance is influenced by whether subjects are at weight homeostasis, are weight-reduced, or in the process of weight gain or loss. Some of the **recommended** biomarkers (e.g., leptin) predictably and coordinately change in response to calorie-restricted weight loss in a manner that would

elevate appetite and suppress energy expenditure (1). Baseline measures for some **recommended** biomarkers (e.g., leptin, total ghrelin) are predictive of weight regain (70, 71) in some, but not all studies (72). The potential value/cost of these measures at baseline, after weight loss, and after a period of weight maintenance, is considered high, given the low subject burden (i.e., a blood draw) and commercial availability of the assays.

Biomarkers – Energy Homeostasis.—A number of adipocyte-derived hormones yield valuable data regarding factors that may affect or represent energy stores and balance. As exemplified by **leptin** (73), response to any intervention may depend upon whether the participant is being treated to promote weight loss or prevent weight regain. Therefore, biochemical assessments relevant to energy balance and/or affecting energy intake and output are extremely relevant,

Leptin is secreted by adipose tissue, reflects both adipose tissue stores and energy balance, and is **recommended**. At baseline weight, circulating leptin concentrations are directly proportional to FM, while during caloric restriction, the leptin/FM ratio may be severely decreased, versus only mildly diminished, following weight loss (73). A low ratio of leptin-to-fat mass may therefore be an indicator of undernutrition, while an unusually high ratio may suggest leptin resistance.

Measurement of fasting levels of the pancreatic peptide **amylin** is **recommended** not only for its effects on nutrient utilization by inhibition of post-prandial glucagon but also because it reduces energy intake by promoting satiation and attenuates the disproportionate decline in energy expenditure that typically occurs during and following weight loss and thus serves as a marker of weight response (74). In rodent studies, amylin receptors are located within the brainstem, as well in multiple other organs, and exogenous amylin acts synergistically with leptin as well as GLP-1, $PYY_{3–36}$, and other anorexiant molecules (75) and in human studies co-administration of amylin with leptin has been shown to enhance weight loss during caloric restriction (76)..

Adiponectin, particularly **high molecular weight (HMW) adiponectin**, is **recommended** because of its positive association with cardiovascular fitness and insulin sensitivity and its negative association with secretion of multiple pro- inflammatory cytokines. During caloric restriction, adiponectin levels increase disproportionately to the decrease in fat mass. The multi-functional nature of adiponectin and its potentially pivotal role in mediating co-morbidity risk, make it a worthwhile and relatively inexpensive test to perform; analyses of HMW and low molecular weight adiponectin is recommended in all studies (77, 78).

Measures of key components of **thyroid hormones** (**thyroid stimulating hormone (TSH), thyroxine (T4), the free T4 Index (fT4I)** are **recommended** because of their known role in regulating energy balance. Diet-induced weight loss is accompanied by a decline in TSH, T3 and T4 similar to “sick euthyroid syndrome” (79, 80), and thyroid hormone repletion in weight-reduced individuals has recently been reported to resolve some of the peripheral adaptive responses thought to drive weight regain (81) in a manner similar to what is seen following thyroid repletion in hypothyroid individuals (82, 83). Other factors commonly measured when assessing thyroid status (*T3, rT3)* present a significant burden for

researchers because of the expense of these assays and are *suggested* only when resources are available.

Hunger/satiety hormone levels change in response to meals and collectively provide surrogate signals for nutrient availability. A number of gut-derived peptides, including ghrelin, GLP-1, $PYY_{3–36}$, affect appetite (84) and coordinately change in response to calorie-restriction (1). Baseline total ghrelin levels are predictive of weight loss (70), and meal responses of $PYY_{3–36}$ and GLP-1 have been associated with successful reduced weight maintenance (85). Such studies provide examples of how these peptides could be valuable in modeling treatment outcomes. While postprandial responses of these hormones are considered to provide the most pertinent information for predicting treatment responses, meal challenges were judged too great a burden on both participants and the researchers. Measurement of fasting total **ghrelin, GLP-1, and $PYY_{3–36}$** is **recommended** for all weight loss studies as the best compromise between feasibility and informational value. Other gut peptides with similar actions were considered for predicting treatment outcomes, including cholecystokinin (CCK) and glucagon inhibitory peptide (GIP) but the added value was deemed insufficient because of the greater assay difficulty and expense and the likelihood of collinearity with those already recommended. *Plasma AgRP* has been *suggested* as a biomarker of hypothalamic melanocortin activity, which could reflect downstream activity of the hunger and satiety signals though there is only limited evidence for it as a biomarker. AgRP is linked to insulin sensitivity during and after weight loss (86), suggesting that this molecule may provide insights relevant to other biomarkers as well as brain function. For these reasons, measures of *CCK, GIP, AgRP*, and *postprandial responses of total ghrelin, GLP-1, and $PYY_{3–36}$* were suggested only when it is feasible and resources are available. It should also be noted that properly processed and stored samples can be biobanked (see below) for future analyses if cost limitations are prohibitive in a given study.

Nutrient sensing systems in peripheral tissues and in specific regions of the hypothalamus exist that convey signals of nutrient availability for appetite regulation and therefore serve as indices of nutrient status – **fasting levels of glucose, non-esterified fatty acids (NEFA), and triglycerides (TG)** are **recommended** at baseline, during weight loss and after weight loss. Glucose, non-esterified free fatty acids (NEFA), and triglycerides (TGs) are the primary nutrients in circulation, and all three respond to calorie-restricted weight loss (1). TGs are also thought to affect the sensitivity of the brain to peripheral hormones through their effects on blood brain barrier transport. These metabolites consistently change with diet-induced weight loss in a manner that could elevate appetite (1), and the assays are relatively inexpensive and commonly used in clinical research. As with the gut peptides, of measuring postprandial responses of these molecules is not feasible in all studies. For these reasons, acquiring *postprandial responses in glucose, NEFAs, and TGs* is *suggested* only when resources are available.

Metabolic (anabolic and catabolic) function, insulin sensitivity, and glucose control could serve as mediators or moderators of treatment responses and have been shown to influence patterns of weight loss and weight loss maintenance (71, 87). Some studies suggest that diet macronutrient content may influence weight loss intervention efficacy according to the level of insulin sensitivity (88). The group **recommends** that **fasting levels**

of insulin, glucagon, and glycosylated hemoglobin (Hba1C) be measured before, during, and after weight loss. Along with the metabolite data, these measures can be utilized to calculate indices of insulin sensitivity and secretion (**HOMA-IR and HOMA-B**) (89). There was some discussion that an *oral glucose tolerance test (OGTT)* should also be included to provide a more accurate assessment of glucose control. However, there was insufficient evidence that the OGTT would provide sufficient added value over the other surrogate biomarkers of metabolic function for weight loss outcomes, and it is *suggested* only when resources are available. There are more invasive measures of insulin secretion and sensitivity (hyperinsulinemic-euglycemic clamp, intravenous glucose tolerance test, etc.) and more comprehensive measures of key aspects of metabolic flexibility, but these tests are not feasible for all large scale clinical weight loss trials.

We also recommend assessment of the inflammatory markers **tumor necrosis factor-alpha (TNF-α)**, **C-reactive protein (CRP)**, and **interleukin 6 (IL-6)** in the fasted state before, during, and after weight loss. These inflammatory factors could mediate or moderate the impact of metabolic dysfunction on treatment outcomes. TNF-α is a true adipokine and is elevated in obesity (90). CRP is made in the liver, largely in response to IL-6, which is produced in liver and skeletal muscle. These molecules represent three different sources of inflammatory markers and all are associated with the subsequent risk of type 2 diabetes (91) and cardiovascular disease (92). Using network modeling that combined biological, gut microbiota, and environmental factors relevant to weight trajectories, baseline levels of IL-6 and plasma insulin most accurately classified individuals who did or did not lose weight and maintain weight loss (93). Global inflammatory status could be assessed by larger panels, but these biomarkers should be sufficient at present to examine the strength of the link between inflammation and treatment outcomes.

Biobanking Tissues

The molecular mechanisms underlying the physiological opposition to weight loss and reduced weight maintenance (2), and the possibility that they mimic the “pre-obese” state in which someone is genetically and physiologically “at risk” for weight gain, have not been comprehensively elucidated. A uniform methodology across weight loss studies for collecting and storing biological samples to measure RNA and DNA from cells in the blood as well as exosomal and free RNAs would provide a valuable resource for interrogating the molecular underpinnings of weight gain, weight loss, and weight regain. For reasons discussed below, **biobanking of whole blood** and its components (plasma, serum, etc.,) with appropriate stabilization (e.g., protease inhibitors) is **recommended** as the best balance of feasibility, cost, participant burden, expertise/equipment needed to collect and process the samples, and relevance to weight loss physiology.

Though many different kinds of bodily fluids and tissues can be collected with varying degrees of difficulty, expense, and value (Figure 1), whole blood gives the greatest advantages for ease and the potential amount of relevant information it can provide. Though sample collection is invasive and can be challenging for individuals with obesity, participant burden and the need for expertise to collect whole blood samples is offset by the ability to use samples to interrogate circulating proteins, metabolites, and noncoding RNAs, which

have been identified as relevant to energy homeostasis or which may one day be identified. In addition, both red and white cells can be used to examine cellular processes related to a host of outcomes, including glycosylation, immune response, and metabolism.

In addition to the assessment of the biomarkers described above, both RNA and DNA can be extracted from whole blood for a global assessment of genomic variation, gene expression, and epigenetic modification to ultimately allow a uniform characterization of the contribution of genes across weight loss studies. This genetic screening would comprise a powerful resource for understanding the genetic and epigenetic molecular underpinnings of variability in weight loss. This type of screening is suggested at present due to resource limitations but, as its feasibility and cost becomes more reasonable, we fully expect that it will become a recommended assessment. The biobanking recommendation of whole blood will ensure that tissues will be available to pursue future genetic studies, even if resources are not immediately available. Sequence variations in multiple genes have been tied to energy balance and treatment outcomes in weight loss studies, which could serve to focus the analysis. These genes include *BDNF, DRB3, FTO, GNPDA2, LYPLA, MC4R, MTCH2, and MTIF3*, while other less-studied genes (*NEGR1, PLIN, and RANK. LEP and LEPR*) may also provide relevant information about the variability in treatment response. Studies demonstrating significant intra-pair correlations (r=0.75–0.85) in response to weight loss interventions among identical twins (94) and genetic predictors of weight loss response to various interventions in large clinical trials (95, 96) suggest that different SNPs may be predictive of the magnitude of weight loss versus regain depending upon the nature of the intervention and subject population. In the future, the use of array-based chips with highly-informative, dense single nucleotide polymorphism (SNP) content, including genome-wide tag SNPs found across diverse world populations and customizable markers for use in large weight loss studies, can be used as a cost-effective means of creating a well-powered cohort of individuals in which the genetic underpinnings of weight loss can be examined for multiple traits and outcomes.

Biobanking of other tissues is also *suggested* depending upon resource availability. *Buccal (cheek) cells* are easy and inexpensive to collect via cytobrushes, which involves simply swabbing the cheeks and gutters of the mouth to collect sloughed cells. Both DNA and RNA can be extracted from buccal cells (97), though there is a limited range and relevance of markers that can be measured (97). Similar limitations are inherent in the use of *saliva* samples. *Urine and stool samples* are relatively easy and inexpensive to obtain; though the relevance of urinary biomarkers to weight loss may be limited. Stool (98) can be used to examine the gut microbiome, gut absorption, and markers of metabolism. While transplantation of the microbiome from obese or lean mice or humans to gnotobiotic (germ-free mice) clearly affects somatotype, the role of the microbiome as a cause or potential therapeutic target in human obesity is not clearly established (99). Current research in the NIH Human Microbiome Project (HMP) (100) directly addresses these issues, and investigators are *suggested* to contact the NIH directly for microbiome banking information.

Tissue biopsies allow unbiased genomic, epigenetic, and proteomic interrogation of key metabolic tissues (skeletal muscle, adipose) involved in the regulation of energy balance. Due to burdens placed on subjects and investigators, *the collection of specific tissue biopsies*

is *suggested* for studies with specific objectives directed at elucidating molecular mechanisms or generating the evidence as to how these tissues could serve as mediators or moderators of treatment outcomes.

CONCLUSIONS

The ADOPT Biological Domain Subgroup was tasked with identifying feasible measures of biological constructs (body composition, energy homeostasis, brain structure and function, blood biomarkers, and biobanking tissues) that, when used consistently in weight loss trials, could serve to explain the variability in treatment outcomes and lay the foundation for genetic, epigenetic, and –omic based analyses. Selections (see Table 1) were made with the underlying goal of maximizing the potential to address knowledge gaps in obesity treatment, in conjunction with the other ADOPT Domains. It is the intent of the ADOPT Project that these recommendations and suggestions and the GEM website will be updated as new information becomes available.

It should be emphasized that the recommended measures are not always the “gold standard” but they are the ones that are most feasible across numerous different study sizes and population. When integrated across studies and with the other ADOPT domains, the recommended measures will facilitate development of a large, comprehensive database that could be mined to evaluate, propose, and implement current and future obesity treatments with maximal efficacy. The **recommended** and *suggested* measures are intended to augment weight loss intervention studies, rather than replace planned measures.

The strengths and weaknesses of the ADOPT Biological Domain are closely intertwined. The main strength is the practicality of measures that can be implemented in most, if not all, studies going forward at little additional expense and inconvenience to investigators and participants. An additional strength is the intentional malleability of the ADOPT recommendations and suggestions. Regular modifications of the ADOPT domain manuscripts are anticipated based on new data and techniques that become available and on input from the scientific community through the GEM website. The weaknesses of the **recommended** and *suggested* measures are that, to achieve necessary fiscal and feasibility goals, numerous more sensitive or specific measures are not included. To address these issues, we would encourage biobanking of serum, plasma, and buffy coats on as many participants as possible in anticipation of the decreasing costs and increasing understanding of relevant future assays.

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What is already known about this subject?

- Biological adaptations to weight loss interventions contribute to the high rates of obesity recidivism.
- Key aspects of this biological response may explain, in part, the high level of individual variability in the response to obesity treatments.
- We lack an evidence base with a broad range of biological factors or a consensus on a list of measures that, when used in weight loss trials, could inform the development of tailored treatments.

What does our study add?

- The ADOPT Core Measures Project suggests an initial list of common core biological constructs and associated measures related to body composition, energy homeostasis, brain structure and function, biomarkers, and biobanking approaches, which could be feasibly employed in small, medium, and large weight loss trials.
- In order to reliably identify complex interactions among multiple factors influencing energy balance, the **recommended** and *suggested* measures will significantly enhance the value of future studies by facilitating the integration of multiple data sets to deepen our understanding of the individual variability in treatment responses.
- The consistent use of ADOPT Biological Domain measures in weight loss trials, along with key measures from psychosocial, behavioral, and environmental domains, could help to identify predictors of treatment responses and inform precision-medicine oriented interventions.

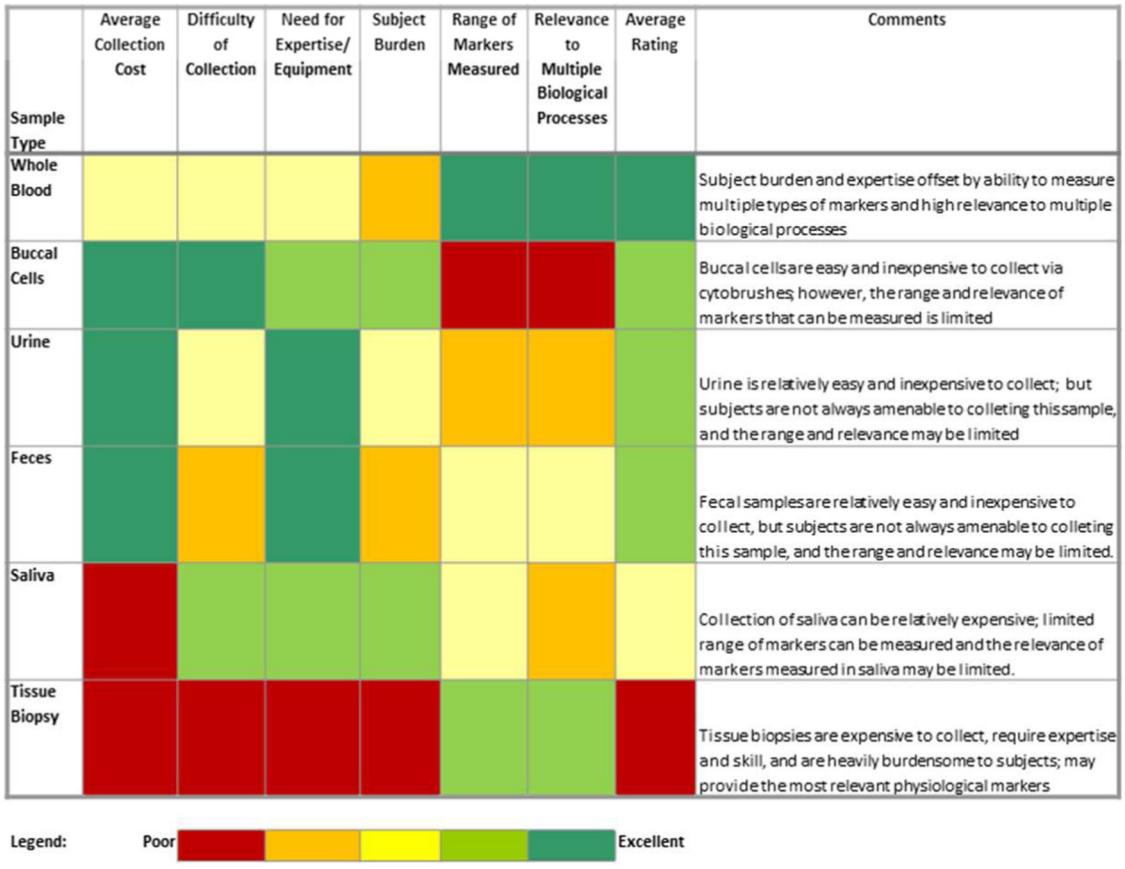

Figure 1.

Review of selection criteria for different tissues that could be biobanked. Whole blood is clearly the best fit for these criteria, though other tissues should not be eliminated if available depending upon their relevance to specific study. *Collection costs include creation of sample aliquots; measured markers include metabolites (M), nucleotides (N), and proteins (P).

Table 1:

Selected characteristics of recommended core measures for the ADOPT biological domain.

			Logistics					
Construct	**Measure**	**Measure type**	**Number of Items**	**Administration time (minutes)**	**Measurement Schedule**	**Resource Needs**	**Main Evidence Sources[1]**	**Suggested Additional Measures**
Whole body assessments								
Anthropometry	*Height, Weight, and BMI*	Technician	NA	~5	B, MA	Equipment, Trained technician	C, L, RCT	
Body Composition and Visceral Fat	*Bioelectrical Impedance Spectroscopy (BIS)*	Technician	NA			Equipment, Trained technician	C, L, RCT	*DXA, MRI, QMRS*
Body Fat Distribution	*Waist to Hip Ratio, Waist Circumference*	Technician	NA	5–10	B, MA	Equipment, Trained technician	C, L, RCT	
Expended Energy	*REE- Mifflin St.-Jeor equation, Total EE*	Calculated	NA	0			C, L	*DLW; VCO2, VO2 (calorimetry)*
Expended Energy	Physical Activity Level (PAL)	Questionnaire	2	<5			C, L	*VCO2, VO2 (calorimetry)*
Energy Intake	*Energy intake - steady state & change*	Calculated	NA	0	B, MA	Equations	C, L	*DLW*
Cardiorespiratory Fitness	*Resting heart rate*	Interviewer	NA	1		Equipment, Trained technician	C, L, RCT	*3-minute step test*
Brain Structure and Function		Technician	NA		B	Equipment, Trained technician	C, L	*Resting State fMRI; Fed and fasted fMRI*
Blood biomarkers								
Energy Homeostasis	*Leptin, Amylin, Adiponectin (panel)*	Blood	NA	Single blood draw		Phlebotomist	C, L, RCT	
Thyroid Hormones	TSH, T4, fT4I (panel)	Blood	NA			Phlebotomist	C, L, RCT	*T3, rT3*
Hunger/Satiety	*Total Ghrelin, GLP1, GIP, $PYY_{3–36}$ (panel)*	Blood	NA			Phlebotomist	C, L, RCT	*CCK, GIP, AgRP, postprandial responses of ghrelin, GLP-1, and PYY*
Nutrient Status	*Metabolite Panel (Glucose, NEFA, TG)*	Blood	NA			Phlebotomist	C, L, RCT	
Metabolic Function	Insulin, Glucagon	Blood	NA			Phlebotomist	C, L, RCT	
Metabolic Function	*Insulin Sensitivity - HOMA*	Blood	NA			Phlebotomist	C, L, RCT	

				Logistics				
Construct	**Measure**	**Measure type**	**Number of Items**	**Administration time (minutes)**	**Measurement Schedule**	**Resource Needs**	**Main Evidence Sources[1]**	**Suggested Additional Measures**
Metabolic Function	*Glucose Control - HBA1c*	Blood	NA			Phlebotomist	C, L, RCT	*OGTT*
Inflammation	*IL-6, TNF-alpha, CRP*	Blood	NA			Phlebotomist	C, L, RCT	
Biobanking Tissues								
Biobanking	*Whole Blood*	Blood	NA	NA		Phlebotomist	C, L, RCT	*Buccal, Saliva, Urine, Stool*
Genetic Screening		Blood	NA	NA	B	Phlebotomist	C, L, RCT	*BDNF, DRB3, FTO, GNPDA2, LYPLA, MC4R, MTCH2, MTIF3, NEGR1, PLIN, RANK, LEP, LEPR*

[1] SA=self-administered.

[2] B=baseline; MA=multiple assessments across the trial; F=follow-up.

[3] C=cross-sectional; L=longitudinal; RCT=randomized controlled trial. Evidence included both weight-related outcomes (e.g., weight loss) and weight-related behaviors (e.g., physical activity).

Italics= indicates an objective measure

BMI - Body Mass Index, BIS - Bioelectrical Impedance Spectroscopy, DXA - Dual Energy X-ray Absoprtiometry, MRI - Magnetic Resonance Imaging , QMR - Quantitiative Magnetic Resonance, PAL - Physical Activity Level, DLW - Doubly Labeled Water, GLP-1 - Glucagon-like Peptide I, $PYY_{3–36}$ - Peptide YY, TSH - Thyroid Stimulating Hormone, T4 - Thyroxine, fT4I - Free T4 Index, T3 - Triidothyronine, rT3 - reverse T3, CRP - C-Reactive Protein, IL-6 - Interleukin-6, TNF-? - Tumor Necrosis Factor alpha,

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