Obesity Science, Research Gaps and Opportunities in the New Era of Obesity Medicines - an Endocrine Society Scientific Statement

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Abstract

The medical management of obesity has been transformed by the introduction of Obesity Medicines (OMs), based on the actions of glucagon-like peptide-1 and other nutrient-stimulated hormones, enabling the achievement of unprecedented weight reduction through pharmacotherapy. Here we review our current understanding of key issues surrounding obesity treatment, weight reduction and improving health for people living with obesity. Key gaps in our knowledge of fundamental aspects of energy homeostasis are identified with a focus on their translational importance for improving outcomes. We discuss the utility of weight and health metrics, heterogeneity in achievement of clinical outcomes, individualization of treatment targets and goals, strengths and limitations of clinical trial, observational and real world data, opportunities for improving the joint use of lifestyle management and OMs, and gaps in our understanding of the long-term safety and side effects of current and emerging medicines, and potential negative effects of losing weight. Collectively, while not intended as guidance for treatment, this document highlights the considerable progress and new research opportunities for interrogating basic and clinical science with the goal of translating advances in endocrine science into optimized outcomes for a broad range of individuals along the continuum of weight journey.

INTRODUCTION

Obesity is the most prevalent chronic disease of our time (1) significantly impacting the health of most of the world. In 2017, the Endocrine Society brought together experts charged with assessing current knowledge regarding mechanisms underlying obesity (2). At that time, pharmacologic interventions were at a tipping point, emerging from efficacious (3) to highly efficacious mono-therapies, with the Food and Drug Administration's (FDA) approval of semaglutide and tirzepatide for a "chronic weight management" indication in 2021 and 2023, respectively (4,5) With the introduction of these and other novel nutrient-stimulated hormone receptor modulators (NuSH-RMs) (6,7) , the understanding of obesity pathophysiology, treatment, and disease state/lifecycle is rapidly expanding. These powerful agents can be used as probes to help elucidate the complexities of this disease as well as impact on overall health. Notably over a brief period of just three years, numerous studies have emerged underscoring the clear impact of treating obesity on improving health (8,9). These studies have led to a series of expanded indications for semaglutide and tirzepatide in the treatment of various obesity-related complications. In 2024, the FDA approved semaglutide for reduction of major adverse cardiovascular events in adults with cardiovascular disease and overweight and obesity and approved tirzepatide for moderate to severe obstructive sleep apnea. In 2025, semaglutide was FDA approved for metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver scarring (fibrosis) (10) without an overweight or obesity requirement (though 80-90% of people with MASH have overweight or obesity, by BMI). Clearly there is now a focus on utilizing these agents not only for treatment of overweight and obesity but also for obesity-related disease modification and potentially for other diseases (11,12).

As much as we have learned over the last five decades about obesity, our understanding of obesity is relatively nascent. Indeed, the environmental and physiological drivers of increasing obesity prevalence are still being debated (13). Furthermore, the recent ability to produce reduction of body weight by 25% or more in many individuals demands a better understanding of the physiology of weight loss and how best to achieve optimal body composition and body health in the weight-reduced state. Similarly, understanding the mechanisms of action of these agents beyond weight reduction is equally important (14). Here we highlight key gaps in our understanding of obesity with a focus on pharmacological interventions and propose studies which may help clarify fundamental aspects of our understanding of obesity.

There are transformational discoveries in medicine – the discovery of penicillin and insulin and vaccines – these discoveries not only saved lives but also reshaped how we understand the diseases they prevent and treat. Current and emerging pharmacotherapeutics for the treatment of obesity enable us to do just that, but we must seize the moment with intentionality, thoughtfully designing a research roadmap to better understand the disease, enabling optimal treatment and improving health outcomes for people living with obesity.

The six essential points of focus include:

1) The pathophysiology of obesity with a focus on body fat regulation/defended fat mass
2) The heterogeneity of obesity with a focus on treatment response

3) Redefining treatment targets beyond percent total body weight loss
4) The physiology of phases of treatment response to pharmacotherapy
5) Health outcomes with pharmacotherapy
6) Safety of pharmacotherapy

1) THE PATHOPHYSIOLOGY OF OBESITY

a. How does the brain regulate energy storage across the lifecycle, including both the quantity and location of body fat?
    i. What are the cellular and molecular mechanisms by which the body determines appropriate fat mass for each phase of the lifecycle?
    ii. Are there distinct mechanisms to determine the size of different fat depots
    iii. What are the cellular and molecular mechanisms by which the body defends total (and/or regional) fat mass?
    iv. What circuits in the brain are responsible for these regulatory mechanisms and how do they interact?
b. What are the pathophysiological mechanisms by which "normal" fat mass and regional distribution are disrupted in obesity?
    i. What are cellular and molecular mechanisms whose disturbance or disruption can lead to obesity?
    ii. Which of the mechanisms are common to most forms of obesity? Which are variable and likely to lead to clinically relevant obesity subtypes?
    iii. What are the cellular and molecular mechanisms by which effective obesity medications improve fat mass physiology?
    iv. To what degree are they distinct from or overlap with the mechanisms underlying the pathophysiology of obesity?
    v. To what degree are the mechanisms in common to different classes of obesity medications? To what degree do they vary based on the molecular mechanism(s) of the medication?
    vi. How can genetic evaluation shed light on these various mechanisms?
    vii. To what degree do genetic contributors to obesity vary among types of obesity that express different phenotypes
c. What are the primary environmental contributors to obesity?
    i. Are there environmental contributors common to all people with obesity?
    ii. Are there phenotypic differences among patients who exhibit different responses to specific environmental contributors
    iii. What are the similarities and differences in the phenotypes, cellular and molecular mechanisms, and genetic contributions to obesity induced by different classes of environmental obesogens?

a. How does the brain regulate energy storage across the lifecycle, including both the quantity and location of body fat?

Nearly all of the energy stored by animals is in the form of fat, most commonly triglycerides, and there is strong clinical and observational evidence that body fat mass and distribution is tightly but variably regulated across the life course. Decreases in baby fat, changes in fat mass associated with puberty, and the increase and decrease in body fat during and after pregnancy occur without purposeful management in both humans and animals, strongly suggesting that they are physiologically regulated. The anatomic distributions of baby fat, pregnancy-associated fat and aging-associated fat (including increased fat and changes in fat distribution associated with menopause) are distinct. There are also wide inter-individual variations in body fat distribution and the magnitude of inflammation-associated visceral adipose tissue that appear to reflect both familial and population-based differences (15). Despite these observations, the cellular and molecular mechanisms underlying these regulatory processes remain unclear.

Opinions vary as to the primary target of the regulation of adipose tissue mass and body weight, with possibilities including fat mass and body weight itself, energy balance, appetitive drives (e.g., food-driven reward, hunger, satiation and satiety), energy intake, taste attraction and aversion, energy expenditure, and a combination of all of these mechanisms. Underfeeding and overfeeding studies in animals and people have demonstrated that these manipulations often lead to compensatory changes (counter regulator forces) in both food intake and energy expenditure, promoting restoration of the pre-perturbation state (16-18). Most of the well-controlled studies have been in rodent models, which have demonstrated that this compensatory response is mediated primarily by changes in energy expenditure, leading to its description as "metabolic adaptation." While similar effects are seen in humans, the compensatory responses appear to be mediated more by changes in appetite than energy expenditure (17,19). Thus, we recommend the use of the more inclusive, expanded definition of the term "metabolic adaptation" allowing inclusivity of both of these counter-regulatory response/forces (energy expenditure and appetite). There is accumulating evidence that effective pharmacological and surgical therapies for obesity mitigate these compensatory responses (20,21). The suppression is most evident during acute treatment-induced weight loss and is mitigated as body weight and fat mass settle into a new plateau. Ongoing human studies are interrogating the importance of molecular, cellular, behavioral, physiological environmental as well as psychosocial factors that are associated with the ability to maintain a reduced body weight after successful weight loss (22).

These observations are all consistent with body fat mass (total or depot-specific) being the primary target of physiological regulation with appetitive drives and autonomically-regulated energy expenditure serving as the mechanisms by which the target fat mass is attained (**Figure 1**). Studies in hypothalamus-lesioned dogs by Keesey and colleagues provided early evidence for fat mass-targeted regulation (23), and more recent studies of the weight loss effects of bariatric surgery and obesity pharmacotherapy provide additional support for this model, which has often been described variously as physiological regulation to homeostatic energy balance resulting in a "defended" fat mass, or a fat mass "set-point" or "settling point" (20,24,25). This terminology can be misleading, however, as the changes in fat mass and location across the life course indicate that the target fat mass is not fixed, but varies in response to normal developmental and energy needs.

Multiple lines of evidence strongly suggest that regulation of body fat mass is directed primarily from the brain (26). Pathological or surgical damage to the medial hypothalamus is associated with obesity in both animals and humans, while similar damage to the lateral hypothalamus leads to a profound loss of body fat (23). Genome-wide association studies have revealed that more than 75% of genes whose allelic variations are associated with obesity are expressed exclusively or predominantly in the central nervous system (CNS) (27). Moreover, the therapeutic effects of bariatric surgery and highly effective OMs appear to result primarily from changes in CNS signaling.

Despite these observations, relatively little is known about either the cellular or molecular basis for normal body fat regulation. These are high priority areas of investigation (22), since their elucidation has the potential to uncover novel targets for effective treatment, biomarkers of early response to treatment, and more sensitive indicators of effective obesity prevention strategies. The regulation of body fat appears to be highly complex, suggesting the involvement of multiple regions of the brain. The medial hypothalamus, including the arcuate and adjacent nuclei are key to leptin-mediated regulation (28). Despite the requirement for effective leptin signaling to maintain normal fat mass regulation, leptin receptor agonist treatment provides minimal benefit for the common forms of obesity (29,30). In contrast, glucagon-like peptide-1 receptor (GLP-1R) signaling does *not* appear to be necessary for normal fat mass regulation, as evidenced by the lack of GLP-1R expression in major adipose tissue cell types, the absence of obesity in mice with genetic deficiency of the GLP-1 receptor (31,32) and lack of compelling genetic data linking variation in the human GLP1R to control of adipose tissue mass or body weight (33,34). Nonetheless, GLP-1 receptor agonists (GLP-1 RA), and other NuSH-RMs such as GIP/GLP-1 RA, have emerged as the most effective pharmacological means of treating obesity thus far identified. This apparent contradiction between the necessity and sufficiency of different signaling systems to regulate body fat mass underscores the complexity of the underlying physiology. It may also provide an explanation for the observation that the genetic variations that predispose to variation in body weight and obesity (determined by individual locus association or genome-wide polygenic scores) do not predict the weight loss response to bariatric surgery or obesity pharmacotherapy (35,36). Perhaps the mechanisms by which these therapies work *override* the pathophysiological changes causing obesity rather than simply undoing them.

After the initial discovery of the insulinotropic actions of native GLP-1 in the mid 1980s, observations that GLP-1 reduced food intake enabling weight reduction followed a decade later. As native GLP-1 is rapidly degraded by dipeptidyl peptidase-4 and cleared by the kidney, degradation-resistant molecules such as exendin-4 (exenatide) were pursued for T2D, resulting in the first clinical approval of twice daily exenatide in 2005. Nearly a decade later, once daily liraglutide was approved for chronic weight management in 2014, followed by semaglutide in 2021 and tirzepatide in 2023. These two medicines are small acylated peptides, suitable for once weekly administration, and have ushered in the modern era of the medical treatment of obesity. More recently, a daily oral formulation of semaglutide has also been approved for the therapy of obesity. Many other molecules are in development including small molecules suitable for oral administration, multi-hormone receptor modulators targeting new mechanisms, and monthly antibodies and peptides allowing for less frequent dosing (7).

Despite their powerful clinical benefit, we have limited knowledge of the regions, neural circuits and cells within the human brain where GLP-1 receptor activation promotes improvement in body fat mass regulation. We have even less knowledge of how that activation is translated into changes in defended fat mass. A striking example of the limitations of our understanding can be found in the comparison of liraglutide and semaglutide. Liraglutide, developed first, is a long-acting GLP-1 analog ($t_{½}$ of approximately 13 hours)(37) that induces significant weight loss. Semaglutide is a similar compound, with nearly identical receptor binding and activation properties in cell culture but designed to have an even longer half-life (approximately 160 hours). That semaglutide has twice the weight loss efficacy of liraglutide *in vivo* in animals and people was unexpected. Brain distribution studies in rodents have suggested that peripherally-administered semaglutide may penetrate the brain more effectively, perhaps generating a more effective stimulation of the medial hypothalamus, but careful assessment of the data suggest that higher concentrations of semaglutide are observed only in selected regions of the brain (20). Liraglutide concentrations are equal or higher than semaglutide in relevant regions of the hypothalamus, suggesting that other regions of the brain may be the most relevant sites of action of GLP-1 receptor

agonists (20). A recent study provides strong support for the role of hindbrain nuclei, particularly neurons in the area postrema and nucleus of the solitary tract, and particularly those neurons that express the gene encoding pituitary adenylate cyclase-activating peptide (PACAP) (38). Studies to generate more complete understanding of the cellular and molecular mechanisms by which regulators of the GLP-1, glucose-dependent insulinotropic polypeptide (GIP), glucagon, amylin and activin receptors influence body fat mass homeostasis could generate a variety of physiological and therapeutic benefits. For example, one of the challenges of current and emerging obesity pharmacotherapy is the high incidence of gastrointestinal adverse effects, requiring time-consuming dose escalation algorithms to allow tolerance of therapeutic drug levels. Although nausea and vomiting centers of the brain somewhat overlap with weight regulatory targets of these medications, several clinical studies have found little or no correlation between the presence or severity of adverse effects and the degree of weight loss induced by these medications (39,40). If these beneficial and adverse effects of the medications are independent, perhaps they are mediated by different mechanisms and therefore different groups of cells within the same region (41,42). If human GLP-1R+ neurons have characteristics different enough to allow for selective activation of the cells that regulate fat mass without activation of the cells that generate the aversive side effects (42), there would be an increased potential for developing a drug that avoids the need for dose escalation.

In general, greater mechanistic understanding can lead to greater treatment specificity. Advances in neuroimaging linked to clinically relevant changes in appetite, body weight and biomarkers gleaned from systems biology may provide greater insight into inter-individual heterogeneity and responses to OM. As we learn more about the differences among different clinical subtypes of obesity, greater mechanistic understanding may also be one of the most direct means of identifying novel biomarkers that could serve as effective predictors of treatment response and thereby facilitate more individualized and precise treatment strategies.

b. What are the pathophysiological mechanisms by which "normal" fat mass and distribution are disrupted in obesity?

As described earlier, genetic evidence suggests that effective surgical and pharmacological treatment of obesity may be mediated through mechanisms distinct from the those that cause the obesity in the first place. If so, these therapies have the capacity for re-regulating the fat mass control system (**Figure 1**) without directly "fixing" the dysregulation that causes the obesity. This approach to therapy has been obviously effective but is fundamentally different from directly addressing the underlying problem. For obesity, the best examples of addressing the underlying problem are seen with metreleptin treatment for people with genetic leptin deficiency and setmelanotide treatment for those with proopiomelanocortin (POMC) deficiency (43). As effective as the current and emerging therapies are for the most common types of obesity, we may be missing opportunities for directly ameliorating the pathophysiological causes of obesity, which may differ across individuals. Doing so will likely require more detailed understanding of the regulatory circuitry that is disrupted in obesity generally, or is dysfunctional in specific, identifiable subtypes of obesity.

Obesity appears to reflect a disturbance in the body's ability to *determine* or *establish* a physiologically appropriate amount, and balanced anatomic distribution, of energy stores (body fat). Fully understanding the mechanisms underlying obesity is therefore likely to require more complete understanding of the normal internal and external signals influencing the determination of body defended fat mass regulation and how the CNS regulatory circuits drive attainment of those dynamically regulated targets over time. There is far less evidence that obesity results from a disturbance in the physiological *defense* of the target fat mass against acute insults such as acute or chronic illness, injury or episodic overeating. Nonetheless, better understanding of these two components of body fat mass regulation could provide

new avenues of obesity prevention and treatment. The degree to which the cellular and molecular mechanisms of these two regulatory functions are distinct, overlapping or fully integrated could have important implications for development of more effective, targeted prevention and treatment strategies.

A more immediate benefit of greater understanding of the underlying pathophysiology of obesity and how it varies among different subtypes of obesity is likely to be seen in the development of personalized strategies for obesity management. As more OMs are developed with potentially different mechanisms of action, there will be a rapidly growing opportunity to assess patient response to different treatments or combinations of treatments. At present we can make educated guesses about the independence and complementarity of different classes of OMs. Better understanding of the mechanisms by which these medications influence the physiology of body fat mass regulation will provide important information about the most effective strategies for substituting or combining them.

Response to obesity therapy (or discontinuance of therapy) often occurs over long periods of time, and the underlying neurobiology and environmental food, and drug-related cues that shape interindividual heterogeneity in energy homeostasis and ultimately, control of body weight are being explored in preclinical studies (44) but are not well understood in humans. It remains impractical to rely exclusively on trial-and-error testing of different approaches in individual patients with weight loss as the primary outcome. Clinical trials to test the effectiveness of different strategies for selecting and combining medications (or lifestyle-based treatments or surgery) will benefit from rescue and crossover studies that will be made less cumbersome by the availability of early markers of response. Development of clinical (e.g., symptom-based), chemical, imaging-based and genetic predictors or early indicators of clinical response will be essential, and increased pathophysiological understanding will facilitate the identification and optimization of those early measures of therapeutic benefit and safety.

Early indicators of response could also be helpful in the individualization of appropriate doses of available medications. Currently, prescribing information accurately describes dose characteristics and regulatory guidance for forced dose escalation to maximally or near-maximally tolerated doses, reflecting the trial design, sometimes resulting in intolerance to the medications and excessive weight loss (45). This recommended dosing strategy is relatively unique to obesity among chronic metabolic and inflammatory diseases, perhaps a holdover from a time when anything less than maximal dosing was ineffective. Clinical trials and real-world evidence have demonstrated a wide inter-individual variation in the effectiveness of every type of obesity treatment, and clinical experience suggests that there is a similar wide variation in the dose response relationship of individual drugs (46). With the emergence of medications that can mimic bariatric surgery in their effectiveness, some individuals may experience very rapid and excessive weight loss, necessitating individualized dosing to optimize both benefit and safety.

c. What are the primary environmental contributors to obesity?

Most of our current understanding of the environmental contributors to the development of obesity are based on epidemiological studies. As genetics cannot fully explain the epidemiological trends and population-wide upward shifts in BMI over the last several decades (47), it is important to identify the multiple environmental factors that can promote obesity. For example, experimental changes in food environments can result in substantial changes in ad libitum energy intake and an apparent shift in the regulated fat mass(48,49) through biological mechanisms that remain unclear but appear to involve interactions between brain regions classically thought to mediate reward, motivation, and homeostatic appetite control(44,50) . The specific environmental factors influencing body fat regulation include several classes of therapeutic drugs, certain foods (e.g., highly processed, high-fat, high-carbohydrate or high glycemic index), food additives (e.g., emulsifiers), stress, sleep deprivation, circadian rhythm disruption, pollutants (45-48). Clinical experience suggests that relatively few patients experience major

obesogenic effects from each individual environmental influences and that there is a wide inter-individual variability in their contribution. Studies to determine the prevalence, exposure, and intensity of susceptibility to each of these influences would be helpful to our understanding of the degree to which they share similar pathophysiological mechanisms or are complementary and additive. As with similar studies of the effectiveness and optimization of pharmacotherapies described earlier, understanding the role of different environmental obesogens would strongly benefit from identification of genetic and other predictors of susceptibility to each of them, determination of early markers of obesogenicity to help identify disease subtypes and guide individualized obesity prevention and treatment strategies. Greater understanding of the pathophysiology of obesity would allow more sensitive and specific assessment of how these obesogens disrupt the normal physiology.

2) HETEROGENEITY

a. How do we/can we determine a priori who is susceptible to developing obesity?
b. (How) can we determine who will/will not respond to treatment and to what type of treatment?
c. (How) can we predict weight regain – degree, rate, composition?
d. (How) can we know who will develop obesity-related disease and which ones?

Heterogeneity in Obesity and Its Treatment

The development of obesity and the response to therapy reveals marked heterogeneity in biology that is poorly understood. It is fundamentally important to understand the how the underlying biology in different individuals interacts with the environment and contributes to weight gain, and how and why these interactions differ across individuals. Similarly, there exists tremendous heterogeneity in i) the response to treatment (**Figure 2**) ii) the durability of response and ii) the rapidity and extent of weight regain on or after discontinuation of treatment.

a. How do we determine a priori who is susceptible to developing obesity?

Much of the inter-individual variation in BMI within a given environment appears to be genetically determined (51,52). Skewing of the population BMI distribution over time indicates a genetic interaction with environmental changes that promote obesity (53). Genome-wide association studies (GWAS) have identified more than 1000 genetic loci associated with common obesity (54) and clinically meaningful polygenic risk scores for obesity have been developed (35,52,55). However, the majority of BMI heritability remains unexplained. Various physiological characteristics have been hypothesized to be determinants of individual weight changes, including aspects of gut function (56-58), energy metabolism (59-61), fuel selection (62,63) and neural responses to food stimuli (64,65). Given the wide variety of genes and physiological variables potentially contributing to propensity for weight gain, obesity is increasingly conceptualized as a heterogeneous condition with different etiologies, pathophysiological consequences, and clinical trajectories, thus underscoring the potential for different treatment strategies. Several approaches have been used to characterize obesity heterogeneity and partition individuals into more homogeneous subgroups (33,66-68).

b. Can we determine who will/will not respond to treatment and to what type of treatment?

The hope is that identification of more homogeneous obesity subgroups based on biological differences will result in more predictable clinical trajectories and responses to interventions (69,70). If we could prospectively identify patients who are more likely to successfully respond to one intervention over another, it would be possible to personalize obesity prescriptions. The ability to target the best drug to the right patient would be especially advantageous given that the number of approved obesity pharmacotherapies is growing substantially and will continue to expand in the coming years. However, precision medicine for obesity remains largely aspirational, as most studies identifying distinct obesity clusters have not yet conclusively demonstrated that these subgroups predict meaningfully different treatment responses in prospective trials. Indeed, we are still unable to explain much of the substantial variability of interindividual weight loss to lifestyle modification, pharmacotherapy, or bariatric surgery interventions (**Figure 2**) (36). For example, obesity polygenic risk scores do not predict clinically meaningful differences in weight loss to intensive lifestyle interventions (52,71). Similarly, a combination of GWAS and targeted analysis of genetic variation in genes important for GLP-1R signaling did not yield identification of inter-individual genetic variation that would explain important differences in weight loss responses after bariatric surgery, or following treatment with GLP-1 RA or GIP/GLP-1 RA medicines (36). Responsiveness to GLP-1 RA treatment appears to partly depend on average circulating concentrations of the GLP-1 medicine which can vary substantially between individuals even given the same dose and route of administration (72) .

Even under highly controlled experimental conditions, the measurement imprecision of energy balance variables at the individual level introduces a substantial expected variation in weight change trajectories entirely due to the uncertainty in the magnitude of the intervention (73). This suggests that identifying physiological mechanisms of individual weight loss variability will be technically difficult. There are also major challenges in prospectively validating intervention responders versus nonresponders. Retrospective subgroup analyses are prone to error and may not translate into predictable prospective responses (74). This may be because much of the treatment response variability is not repeatable or truly driven by biological differences (75). These limitations challenge an implicit presumption of the precision obesity medicine paradigm because variable intervention responses could also be explained by environmental variables interacting with the biological system regulating adiposity. For example, does the patient have a supportive social environment? Do they have stable employment? Do they have the resources and support to access and maintain successful lifestyle change and pharmacotherapy? More research is needed to assess individual reproducibility of treatment responses that could form the basis for identifying more robust obesity subgroups for precision medicine. For example, N-of-1 trials expose the same individual successively to various interventions that sometimes repeat to evaluate the reproducibility of their response (76). Unlike surrogate outcomes such as blood pressure or lipid profiles where interventions often exert their effects within weeks and washout quickly, N-of-1 trials for obesity treatment are challenged by the long time course to achieve maximal weight loss which also results in a different physiological state. However, early weight loss may be predictive of long-term weight loss in many individuals (77) and future research could examine how changes in individual weight loss trajectories or short-term assays of eating behavior or energy expenditure might be predictive of longer term weight loss responses as various treatments are applied. Such N-of-1 trials have the potential to more reliably identify responder groups to specific interventions. Subsequent identification of biological

differences between responder groups to different treatments might thereby provide a more reliable path towards precision obesity medicine.

c. (How) can we predict weight regain – degree, rate, composition?

Obesity is a chronic disease, hence weight regain is expected once its treatment ends unless the environment or underlying biology has changed in a way that no longer promotes excess adiposity. This has been demonstrated in several trials in participants who stopped semaglutide or tirzepatide treatment (78-80). However, there is wide interindividual variation in weight regained after cessation of obesity treatment and it is presently unclear what factors predict this variability. In the context of lifestyle interventions for weight loss, greater self-monitoring behaviors, physical activity, and dietary protein have been associated with improved maintenance of lost weight (81,82). Contrary to expectations, an increased rate of weight loss does not appear to increase the propensity for weight regain in clinical trials (83). A recently completed study was designed to elucidate the determinants of weight regain after a lifestyle intervention (22). However, it is unclear whether the same factors will be at play during weight regain after pharmacological obesity treatment.

Just as there has been much discussion about the composition of body weight loss during obesity interventions (84-86), the composition of regained weight is important to consider, especially since weight regain is so common in lifestyle interventions and obesity pharmacotherapies are often curtailed for a variety of reasons. The prospect of disproportionate body fat regain, reduced strength, and the potential for development of sarcopenic obesity with repeated weight loss and regain cycles has been suggested by cross-sectional analyses examining patients with varying histories of weight cycling (87). Longitudinal body composition and strength assessments are needed to help determine the direction of causality in these relationships.

d. Can we determine who will develop obesity-related disease and which ones?

Recent definitions of obesity as a disease have attempted to dissociate pathophysiology from overall adiposity per se (88,89) . In support of this concept, recent genetic studies have shown that BMI can be dissociated to some extent from risk of T2D and cardiometabolic disease (67,68). For example, individuals with a genetic predisposition to accumulate body fat preferentially in the gluteofemoral region are relatively protected from the pathophysiological consequences of excess adiposity as compared to those who are predisposed to gain fat in the abdomen (90). A potentially related concept involves the identification of a subset of individuals with high levels of adiposity who are deemed to have “metabolically healthy obesity” based on a collection of cardiometabolic biomarkers in the normal range and often associated with low amounts of visceral and ectopic fat (89,91,92). The degree to which weight loss interventions help resolve T2D may depend on reducing fat that has accumulated in metabolically sensitive ectopic regions such as the liver and the pancreas (93). To accomplish this, individuals likely require differing amounts of weight loss to reduce overall adiposity below their own personal threshold. Overall reductions in body fat mass result in reduced visceral adipose tissue in an allometric relationship whereby visceral adiposity preferentially decreases as compared to subcutaneous adipose tissue (94).More research is needed to determine whether interventions can preferentially target visceral and

ectopic fat depots and thereby have cardiometabolic benefits beyond overall weight loss, especially in individuals with greater visceral adiposity.

2) **TREATMENT TARGETS**
    a. How do we determine what treatment targets should be? What is clinically meaningful?
    b. What should we consistently be measuring/assessing in studies/trials?
    c. How should these targets be different for varied populations (older individuals, pediatric)
    d. What is needed to develop a composite score? Is there a potential for a biomarker?

Treatment Targets

a. How do we determine what treatment targets should be? What is clinically meaningful?

In the 19th century, Adolphe Quetelet introduced what has become known as the body mass index (BMI) which was the mathematical relationship between body weight and height that exhibited *minimal* inter-individual variation and had the expected normal distribution for the population (95). This index was forgotten until 1972 when experiments by Keys and colleagues showed it to be the best of the indices to correlate with body fat determination by densitometry and two skinfolds (96). Today, BMI is the most widely used anthropometric measure for estimating overall adiposity and its population mean and variation have both markedly increased in recent decades thereby indicating a substantial increase in overall adiposity and its inter-individual variability (47). Moreover, BMI is not a direct measure of body fat or the distribution of body fat.

These limitations of BMI have prompted ongoing discussion and revision of the definition and diagnostic criteria for obesity and any modifications will influence treatment targets. A group of international experts proposed a disease-oriented redefinition of obesity, and using terms clinical and preclinical to distinguish whether excess adiposity was causing organ dysfunction or functional impairment (89). This shift has important implications for diagnosis, epidemiology, and health policy but also has limitations, accounting for functional and some metabolic implications (T2D excluded) but does not account for psychological/mental health impacts and still relies largely on BMI. Therefore, their findings highlight the limitations of universal BMI thresholds, particularly in Asian populations with a predisposition to visceral adiposity at lower BMI levels (89). The findings also highlight important gaps in lack of validated anthropometric measures and their relationship to health complications across the lifespan, especially across childhood and adolescence, and for different races (97). Thus, at the same time that there is intense debate and discussion about a research agenda to better diagnose obesity, research to identify targets for weight reduction efforts must incorporate heterogeneity across populations and along the lifespan. For a better clinical obesity definition, more research is needed to identify 1) readily available clinical criteria to identify unhealthy body function and disease, and 2) population-based studies identifying and validating anthropometric indices across the lifespan in all races reflecting healthy body composition.

What we already know about the search for anthropometric targets of weight reduction as a reflection of obesity complication risk. Percentage weight reduction from baseline is the current primary endpoint by which effectiveness is measured for regulatory approval. Medications currently on the market for obesity treatment were approved under a guidance from 2007, the first modern standard utilized in determining regulatory approval for medications for treatment of overweight and obesity (98). Based on that guidance, the current clinical trial standard measure of weight reduction efficacy in adults is mean percentage body weight loss from baseline, usually in response to 52 weeks on a given dose or treatment or a point at which weight is maintained at a steady state while on treatment.

A new document circulated January 7, 2025 by the US Food and Drug Administration (FDA) *Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction Guidance for Industry(99)* is out for comment. It indicates that "The efficacy of a weight-reduction drug in adults should be assessed by analyses of mean percentage change from baseline body weight in the investigational drug group versus the control group. Note that in subjects with stable height (i.e., adults who have achieved terminal height) percentage change in body weight equals percentage change in BMI." In pediatrics, it prescribes that efficacy should be defined as "a function of change in BMI." This is essentially unchanged from the earlier Guidance and thus, percentage weight loss (or change in BMI) is the primary endpoint for phase 3 studies. These measures are not targets, *per se*, nor are they an overall satisfactory measure of success in all individuals.

Why is percentage weight loss not ideal as a measure of efficacy?
With lifestyle intervention and earlier medications that produced only modest weight loss, percentage weight reduction served well as a surrogate associated with measures of health improvement. However, since robust weight reduction became a reality with newer medications, a shift from emphasizing percentage weight loss as an efficacy marker to an anthropometric target is in order.

Mean percentage weight reduction from baseline ignores the huge variation in weight loss response, commonly observed in a population. Second, it also ignores that compared with individuals with BMI categorized as more severe in the obesity range, those with lower BMI will reach BMI categorized as "healthy" with a smaller percentage weight loss - magnifying the physiological impact of weight loss for those starting at lower BMI levels. For those with BMI <30 kg/m^2, exceeding 20% weight loss can result in undesirable and unhealthy BMI levels, and for many, health goals may be met with less weight reduction.

A somewhat different measure of efficacy has been used in metabolic and bariatric surgery, % excess weight loss (EWL). This is usually defined as the proportion of weight loss beyond that needed to achieve BMI 25 kg/m^2 or to achieve an ideal weight (from life insurance charts) (100). However, using BMI as an anthropometric target is problematic in that BMI does not directly measure body fat or changes in body composition or adipose tissue distribution .

Change in waist circumference (WC) or waist to height ratio (WHtR): these measures are frequently recommended as a surrogate for change in visceral adiposity, but waist circumference measurement has not been adopted widely in clinical practice. Waist circumference change is a surrogate for visceral adiposity change, which is in turn a surrogate for ectopic adiposity change. While targeting a waist

circumference cutoff point has some appeal, the waist circumference cutoff points must be adjusted by sex, race and BMI (101,102). The WHtR is not typically adjusted for sex, age or race.

Robust statistical evidence involving more than 300,000 adults in several ethnic groups has shown the superiority of WHtR over WC and BMI for detecting cardiometabolic risk factors in both sexes (103). According to the British data, healthy central adiposity is a waist-to-height ratio 0.4 to 0.49, indicating no increased health risks from abnormal fat distribution. When the value is increased to a waist-to-height ratio between 0.5 to 0.5, this indicates increased health risks from high central adiposity. An even higher value indicated by a waist-to-height ratio >0.6 indicated the highest risk from centrally located fat (103). However, drawbacks to using this index as a treatment target are lack of evidence supporting its validity in populations outside the UK, and widespread implementation is challenged in that waist circumference measurement is difficult to do accurately, has few trained measurers in clinical practice and thus has not been embraced in primary care.

Body composition assessments are needed to better define health impacts of obesity treatment. Measuring overall weight loss does not reveal the key organs contributing to loss of tissue mass or location of fat mass loss. The goal of obesity intervention is reduction in excess, abnormal body fat (not body mass or body size) to improve organ function and symptoms of disease. Reduction of excess abnormal or ectopic fat mass is a surrogate for health improvement with obesity treatment, that is, reduction of excess, abnormal body fat to levels that support optimal organ function and optimal body composition. However, there is no agreed-upon standard technique for measuring body composition effects of weight loss, such as fat mass, fat free mass, lean mass or muscle mass, much less consensus for the optimal methodology for the generalized assessment of these parameters.

Body composition is further complicated as an outcome as it is a moving target across the lifespan and characterization of these changes is limited for some of the measurement techniques. Body composition changes dramatically with sexual maturation and among adults, body composition differs by sex, age, race, and menopausal status. While there are multiple strategies to measure body composition (104,105), there is no consensus on how best to measure body composition changes with weight loss in clinical practice. *Impedance* can measure percentage body fat and is used in obesity clinics but is criticized for inaccuracy (106). *Digital anthropometry (3D optical systems)* is validated against DEXA for measuring percentage body fat and can also give an accurate measure of waist circumference but has not penetrated clinical use (107). *DEXA* assessment of body composition measures fat mass, fat free mass (removing bone mass) and lean mass (108) but does not give an accurate assessment of muscle mass. Magnetic Resonance Imaging (*MRI*) gives the best measurement of bone, muscle and fat and distribution of fat, but it is expensive, limiting its use in the clinic (109). Muscle mass is accurately measured by *MRI* and *D^3Cr dilution* [(110)] but these are not commonly available in the clinical setting. DEXA is the gold standard for precision measurement of bone; however, body fat changes can introduce artifact into accurate measurement of skeletal changes with weight loss (111). Thus, there is no current consensus on which body composition measures to use and no universal agreement on how changes to body composition should be assessed.

Bone changes with weight loss deserve special attention, since for older women, osteopenia is common. With more accurate measures of body composition, changes in the skeleton may be better understood

and managed. While individuals with obesity tend to have higher bone density and healthier microarchitecture, meta-analyses have identified a higher risk of humeral and distal lower extremity fractures, likely due to multiple factors(112,113) . Weight reduction by any method reduces the mechanical load on the skeleton – resulting in myriad physiologic changes to resorb bone and lower bone density(114).

This has been studied to a greater and longer extent in bariatric surgery, finding differing fracture risk by type of surgery(114), and leading to specific ASMBS recommendations for bone health monitoring, physical activity goals, and targets for calcium and vitamin D intake(115). With medical weight reduction, based on data from SELECT in older individuals with atherosclerotic cardiovascular disease followed for a mean of >3 years, more hip and pelvic fractures were seen in the subset of women >75 years who received active treatment(116). Systematic studies are needed to identify the best scalable measurement techniques, describe changes in bone health and fracture risk in the setting of obesity medication, and identify interventions to limit skeletal effects of mechanical offloading. Carefully designed trials can help to understand why some individuals develop bone fragility and others do not and whether there is a threshold or quantity by which bone density decreases with varied degrees of medical weight loss.

Some guidance may emerge in the near future regarding better measures of body composition which are affordable and scalable, thus useful in the clinic. REAL Body is planned as an 18-month collaborative effort designed to advance the development of a diagnostic body composition biomarker to support the following: Aim 1: To determine if body composition measurements of total fat mass and total fat-free mass from BIA and 3D optical systems are valid and reliable alternates for DXA as the reference method; and Aim 2: To determine if body composition measurements of visceral fat from BIA and 3D optical systems are valid and reliable alternates for MRI as the reference method; and Aim 3: To determine if body composition predictions of total fat, fat-free mass, and visceral fat from a blood-based multiomics are a valid alternate for DXA and MRI as reference methods. If the results of this work are promising, similar studies can be expanded across the lifespan and in different populations.

Anthropometric targets needed to be validated to serve as surrogates for obesity-related cardio-renal-metabolic risk/improvements and for obesity-related mechanical complications, to define weight loss efficacy linked to these health outcomes. Moreover, depending on what complication one is seeking to address, the anthropometric targets may vary since tissues respond differently by degree of weight loss. For example, complications of obesity may be due to the mechanical burden of excess adiposity or to the cardio-renal-metabolic lipotoxic complications of excess abnormal body fat (117). For cardiometabolic complications of obesity, the extent of weight reduction required to improve individual cardiometabolic risk factors will reflect differences in the sensitivity of these complications to degrees of weight loss (118). Weight reduction of only 2 to 5% of body weight can improve glycemia and lower triglycerides, with greater degrees of weight loss producing even more improvement. For some comorbid conditions, more weight loss is needed – 10% to 15% - to translate into clinically meaningful improvement. This is true when considering the importance of weight reduction for improvement in obstructive sleep apnea, knee osteoarthritis and non-alcoholic steatotic hepatitis. There is a graded improvement in measures of quality of life, depression, mobility, sexual dysfunction, and urinary stress incontinence, whereby benefits are demonstrable with modest weight loss (5–10%) and further weight reduction leads to even greater improvements. For polycystic ovarian syndrome and infertility, modest weight loss (beginning at 2–5%)

can bring restoration of menstrual cycles, ovulation and fertility. Moderate weight reduction(5–10%) has been shown to be associated with reduced health care costs (118). Effects of weight loss on inflammatory markers such as hsCRP are generally larger with greater degrees of weight loss, but there may be a threshold effect where >11% weight loss is required for hsCRP reduction (118). Nevertheless, GLP-1 medicines such as semaglutide reduce circulating levels of hsCRP in clinical trials through mechanisms partially dissociated from the extent of weight loss (119). For conditions like knee arthritis, obstructive sleep apnea, and Gastroesophageal Reflux Disease (GERD) which are associated with the mechanical burden of excess fat mass, substantial weight loss may be required to improve symptoms. Hence, attaining specific BMI thresholds may be a good target for reducing mechanical complications of obesity rather than striving for a percentage weight or body fat reduction.

Relationship of anthropometric targets to 10-year risk of obesity complications in electronic health record data sets. A promising approach to identifying anthropometric targets was reported at the European Obesity Congress in 2024 by Busetto et al (120). Using a UK primary care electronic health records database, the relationship of BMI and waist to height ratio (WHtR) to 10-year risk of developing four obesity related complications (type 2 diabetes, hypertension, hip or knee osteoarthritis and ASCVD) was interrogated to identify anthropometric cut off points. BMI of 27 kg/m^2 and/or WHtR of $\leq$0.53 after weight loss were good indicators of low absolute risk of incident T2D, hypertension, hip/knee OA, and ASCVD (120). Subsequently, this group evaluated the magnitude of BMI and WHtR changes needed to reach a low reference risk of the obesity-related complications and to identify biomarkers that might be used to identify risk. In a population of >280,000 primary care patients, the risk for T2D and ASCVD was inferred to be modulated by different combinations of BMI, WHtR and biomarker (SBP, DBP, lipid) levels , thus suggesting that personalizing targets using both anthropometric and biomarker input could be valuable.

What are the gaps and studies needed?

A more accurate characterization of what is 'healthy' in terms of BMI, WHtR and even other anthropometric targets such as quantity and percentage body fat and visceral fat, is needed in both sexes, all races, according to menopausal status, across the lifespan. We need clear definition of what we mean by "health" with which to correlate anthropometric and/or biometric targets. While there is a good understanding of correlates of cardiometabolic health with anthropometric measures such as BMI and WC, how mechanical and functional signs and symptoms relate to anthropometrics and biomarkers is less refined. Moreover, mental health is more challenging to ascertain and remains poorly defined as a target. The imi SOPHIA – Stratification of Obesity Phenotypes to Optimize Future Therapy – Trial explored this relationship in a qualitative study but does not provide guidance for tracking (121). Ideally, we need to determine if anthropomorphic targets are sufficient by themselves or whether they should be combined with biomarkers and patient reported outcomes to develop a more comprehensive and clinically useful risk assessment and target goal index. Better (accurate, validated and correlated with outcomes) characterization of healthy body composition measures (FM, FFM, Bone mass, Muscle mass) in both sexes, all races, according to pubertal and menopausal status, across the lifespan. An expanded scientific understanding of what healthy body composition looks like is required.

Additional studies on the changes in physiology associated with varied degrees of weight reduction (5%, 10%, 15%, 20% and 25%) with medications that affect appetite to determine the corresponding

physiologic responses to weight loss in different tissues in populations of persons with obesity and type 2 diabetes (T2D) and weight-associated co-morbidities. Implementation of new targets and measurements requires easier, less expensive and more accurate assessment tools and more data generated from large studies to better understand the effects of weight loss and validate clinically useful measurements. For example, the clinical and predictive utility of *digital anthropometry (3D optical systems)*, a potentially easy, accurate, safe and affordable solution vs. tape-derived measurements could be compared in large clinical trials. Technological advances to replace DEXA as a component of weight loss evaluation in older individuals, ideally deploying less expensive, simpler machines to determine fat mass, lean mass, bone mass, bone density, require evaluation. Similarly, assessing the utility of D3Cr dilution-based measurements in research settings is required, as is the evaluation of changes in muscle mass and function during weight loss, particularly in women aged >60 and men >70 years.

What should we be measuring/assessing in studies/trials of obesity medications?

In addition to the usual primary endpoint required by regulator guidance for medication approval (percent weight reduction from baseline), we should add secondary and exploratory endpoints such as percent excess weight loss (percent of weight loss ≥BMI 25 kg/m^2) (for pediatrics - measures of BMI change). And, other secondary endpoints in all medication studies should explore anthropometric cut off points associated with health; these would be based on the usual taping measures t(Height, WC, WHtR) and based on digital anthropometry (3D optical systems) for WC and % fat and fat mass and on bioimpedance measured % fat and fat mass. Beyond the usual %WL category targets (≥5%, ≥10%, ≥15%, ≥20%), we should expand to ≥25%, ≥30%, ≥35% to characterize more powerful medications. For all of these we should evaluate BMI subgroup response rates. In addition to the usual BMI targets of % achieving <40, <30, <25, we should add <35, <27, <22, <18.5 (adapted for Asian race). For pediatrics, we should assess the proportion of individuals achieving BMI <140th % and <120th % of the 95th percentile and achieving BMI <95% and 85%. Other measures would be the proportion of individuals achieving BMI <27 and WHtR <0.53 (or other predetermined composite score associated with reduced complication risk. % change in 10-year complication risk score (to be determined)

c. How should these targets be different for varied populations (older individuals, pediatrics)?

For children who have likely not reached their terminal height the Z-score can reflect degree of adiposity. However, at very high BMI, change in the z-score may not recognize clinically relevant shifts in BMI (122). Therefore, in clinical practice, severe obesity in youth is measured using the BMI percentage above the 95% (123). Consideration of the utility of change in Z score in the adult population, given the likelihood of robust weight loss and the broad range of starting BMI. For older individuals (above age 60), bone density and muscle mass and function are important outcomes to consider.

d. What is needed to develop a composite score?

Large data sets with relevant and detailed electronic health records with >10 years of observation are needed to explore composite scores. These composites could consist of intermediate outcome measurements (risk factors), anthropometric measures and relevant disease-related outcomes (OA knee & hip, ASCVD, T2D, HTN, OSA, MASH, others)

Is there a potential for a biomarker or biomarkers or separately or in combination as composite scores?

This is an important area for research as there are existing and emerging biomarkers that have potential when used in combination for usefulness in assessing targeted health improvement.

Core Body Composition biomarkers are typically derived through anthropometry, bioelectrical impedance analysis (BIA), or medical imaging like DXA and MRI. Visceral Adipose Tissue (VAT) describes fat around internal organs. Subcutaneous Adipose Tissue (SAT) describes fat stored directly under the skin. Intramuscular Adipose Tissue (IMAT) describes fat within muscle tissue (myosteatosis). Waist Circumference, Waist-to-Hip Ratio (WHR) and Waist to Height Ratio (WHtR) are all proxies for central adiposity and stronger predictor of cardiovascular risk than BMI. Skeletal Muscle Index (SMI) describes muscle mass normalized for height and is used to diagnose sarcopenia. Bone Mineral Density (BMD) indicates bone strength and risk of osteoporosis. Fat-Free Mass (FFM is the combined weight of muscle, bone, and organs (124).

Circulating & Metabolic Correlates. While not direct "measures" of composition, these blood-based biomarkers often reflect an individual's body composition status and reflect health status as well. Adipokines such as leptin and adiponectin correlate with total and visceral fat mass. Inflammatory markers such as hsCRP, IL-6, and ferritin are often elevated in cases of high visceral adiposity. Myokines like Myostatin or Myoglobin can reflect muscle health and turnover. Other measures or a combination with existing biomarkers may be beneficial in understanding disease severity as well as response to treatment.

Omics Markers of Obesity. Obesity's metabolic heterogeneity is not fully captured by body mass index (BMI). Deep multi-omics phenotyping is showing promise in identifying biomarkers that might be used to identify obesity more accurately and thus serve as targets for response. This includes adipose tissue-microbiome interactions (125), lipidomic based models for BMI (126), and other multi-omics based strategies (127).

Emerging Radiomic Biomarkers. New automated tools extract advanced "radiomic" features from routine CT or MRI scans, such as Sarcopenia Marker (SM) which is calculated as muscle volume relative to bone and fat; Cardiac Marker (CM) which normalizes epicardial fat to muscle volume to predict heart health. Muscle density which reflects fatty infiltration into muscle may also be useful. There could be efforts to explore the utility of developing a risk score based on a combination of anthropometrics, biochemical intermediates, omics and even patient reported outcomes.

Research Priority Areas (Box):

-Large scale population-based representative samples for validation of anthropometric indices across the lifespan in all races reflecting healthy body composition.

-Scalable assessments to define excess adiposity impacting health and organ function

-Validated, accessible measures of bone health with accuracy across weight reduction

-Defined domains of health impacted by obesity treatment and standardized indices to evaluate change in these domains, including mental health

3) **UNDERSTANDING FAT MASS DYNAMICS THROUGH TREATMENT (WHAT CAN WE LEARN FROM PHASES OF TREATMENT WITH OBESITY MEDICATIONS)**
    a. What do we know about the physiology of weight loss (down slope), plateau, durability (new steady state) with medicines? Metabolic/global adaptation
    b. How do we optimize health with lifestyle during the weight loss (and maintenance) phase?
    c. What is the optimal rate of weight reduction? (to improve function, nutrition)
    d. How do we determine if there is a role for dose de-escalation, changing medications/therapies, etc. during maintenance phase?

a. What do we know about the physiology of fat mass dynamics with pharmacotherapy and what can it teach us about the physiology of obesity?

The emergence of highly efficacious obesity pharmacotherapeutics enables the investigations of fat mass dynamics in the setting of weight loss (described in Section 1). Prior to these therapies, we were limited to studying non-physiologic weight loss (weight loss induced by diet/exercise, a consequence of which is metabolic adaptation). The evidence to date suggests that weight loss achieved with GLP-1 medicines such as tirzepatide does not mitigate metabolic adaptation and reduction of energy expenditure(128). To break fat mass dynamics into "phases" is a somewhat artificial construct, but it is brought out in part due to the inherent prolonged initial weight loss phase (i.e., fat loss and other associated changes take time versus, for example, blood pressure control which can be near immediate) which can be continuously monitored by the individual experiencing the weight loss [**Figure 3**]. Nevertheless, a clearer understanding of what occurs during various times/stages of treatment may provide critical insights into disease physiology as well as help communicate expectations of treatment response to patients.

In this section, we will describe how we may approach describing fat mass dynamics and what pharmacologic treatment can teach us about obesity physiology, treatment, what people with obesity may experience as a result of changes associated with weight loss, and how a better understanding of what occurs physiologically during treatment may help us better understand the disease itself.

We can consider these "phases" as fat mass dynamics insomuch as the phase when weight loss is actively occurring is a negative energy balance state (chasing the reduced defended fat mass) and when weight is stable is a homeostatic energy balance state (existing at the defended fat mass). We know very little about the distinct physiology of these states or phases in the setting of pharmacotherapy, with information being extrapolated from lifestyle intervention studies. Yet, treatment with pharmacotherapeutic interventions is distinct from that of lifestyle interventions. As described in Section 1, fat mass changes with pharmacotherapy can be describes as being "physiologic" versus fat loss from diet/exercise can be described as "non-physiologic". Meaning that when pharmacotherapy is used, the regulated level of fat mass/defended fat mass is reduced and the weight (fat mass) follows. But when diet/exercise are used, the regulated level of fat mass/defended fat mass is not reduced, hence the body's constant pull ("global" metabolic adaptation) back up to regain the weight to the higher regulated level of fat mass. Stated yet another way, non-physiological weight loss can be defined as inducing a counter regulatory response (as described in Section 1), whereas physiologic weight loss does not.

We can consider the approach in other diseases where treatment is considered in phases. In cancer, phases of treatment can be broken down into “induction” (with goal of achieving remission), “consolidation/intensification” (adjusting treatment based on response), and “maintenance” (maintaining so that the body is cancer-free). For diabetes or hypertension, phases of treatment are not broken down explicitly, rather the disease is described as “uncontrolled” versus “controlled” (once goal glycemic or blood pressure parameters are reached) and this often occurs much more quickly than in these other diseases. These changes are not often observed by the patient, but with some opportunities (for example, a continuous glucose monitor allows for moment-to-moment monitoring of interstitial glucose levels). In some settings “remission” has been used to connote a patient who has reverted to normoglycemia, at least temporarily. In obesity the goal is improving health in part through achieving a level and distribution of fat which optimizes body functions. Perhaps describing treatment response falls somewhere in between the prior examples, given that the goal is to reach a certain target (though not yet defined as described in Section 3) of healthier measured/actual fat mass which is in equilibrium with the regulated level of fat mass/defended fat mass. Of course, the goal is not to rid the body of fat (as is the case with cancer).

To break it down simply, fat mass dynamics with treatment with obesity pharmacotherapy can be described as follows: the weight/fat mass reduction phase (induction, when the regulated level of body fat/defended fat mass is lower than the body’s current fat mass, thus not at homeostasis), weight plateau (reaching nadir weight with no further weight reduction on a given treatment regimen/dose – the body reaches homeostasis), and weight maintenance/durability (long-term maintenance, disease control in the setting of potential disease progression, maintaining homeostasis). During plateau and maintenance the body is at homeostasis, with the caveat that during maintenance disease progression may occur over time. For the purposes of this discussion, we separate out plateau and maintenance with the consideration that if obesity progresses, dose adjustment or additional therapies would be implemented in order to maintain disease control. It is also important to understand what is occurring at baseline prior to initiation of pharmacotherapy. The assumption may be that most are living below their defended fat mass, though for some patients this may not be the case. They may be in equilibrium at the elevated defended fat mass. In sum, a deeper understanding of the physiology of the following is needed: 1) untreated/pretreatment – body not at homeostasis where the regulated level of fat mass (defended fat mass) is higher than current measured/actual fat mass, 2) initiation of therapy/induction/weight reduced state – body not at homeostasis where the regulated level of fat mass (defended fat mass) is lower than current measured/actual fat mass, “chasing” the new fat mass, 3) plateau – body at homeostasis – the regulated level of fat mass and current measured/actual fat mass are aligned, 4) maintenance/durability – pharmacotherapy keeps state in homeostasis with the defended level of body fat increasing and actual body fat is again below the defended fat mass. Defining the threshold weight loss required to improve key health outcomes will continue to underlie the definition of treatment goals and the individualization of weight loss and health goals in the clinic (129).

Prior to the OMs, the phases of treatment were investigated in studies of weight-reduction with non-pharmacological interventions leading to non-physiologic weight loss (Section 1). Caloric restriction, leading to 10% body weight reduction, results in a decrease in energy expenditure, with the body compensating by becoming more efficient (17) with the decrease in energy expenditure appearing to persist over time (130). Acute caloric restriction (10 weeks) also results in NuSH hormone changes and

increase in hunger (18). The hormonal changes persist beyond the acute weight reduction phase over the course of the subsequent year even after the onset of weight regain (18). These changes are collectively referred to as "metabolic adaptation." Longer term studies of intensive lifestyle interventions, assessing the maintenance phase, demonstrated the challenge of maintaining a clinically meaningful amount of weight loss over time (131,132). We are in the early stages of understanding the long-term physiology of weight change in the setting of non-pharmacological interventions, yet even less is known in the setting of the OMs (physiologic weight loss).

The weight reduction/weight loss phase

Most of the studies of obesity treatment with the novel obesity medications (OMs) examine the initial weight reduction (weight loss) phase. Given the FDAs regulatory requirement (99) of 52 weeks on treatment for a given agent at a specific dose, the average duration of the trials is one year to one and a half years allowing for a period of dose-escalation, followed by time on target dose, resulting in limited longer-term data. As a result, most of what we know thus far is what occurs as individuals lose weight but not thereafter. The latter two stages are largely unstudied leaving a significant gap in our understanding of the physiology of plateau phase and maintenance of weight reduction. Additionally, most human studies of the weight loss phase in general have not assessed physiologic changes (EE, EI, etc.) though there are a few which have begun to tackle these questions (128,133,134). These studies have provided insight into the acute changes in appetite which occur during the weight reduction phase (namely decrease in hunger, craving, food intake with NuSH receptor modulators) (134). Studies of EE in humans treated with OM have (thus far) not demonstrated a key role for changes in EE as contributing to weight loss (128) though there may be a dampening of the decrease in EE observed with non-physiologic weight loss (with diet/exercise) that may be more subtle and thus more challenging to detect.

During the weight reduction phase of treatment as an OM is initiated, the hypothesis is that the regulated fat mass (the defended fat mass) level is recalibrated and decreased by the pharmacotherapeutic. This acute decrease in the regulated level of body fat mutes hunger, craving, and food noise (defined as persistent, intrusive, disruptive thought of food), while potentially also blunting the expected decrease in energy expenditure all in an effort to allow the body's fat stores to equilibrate with the recalibrated body fat level commensurate with biological regulation. In a sense, the body chases its new (lower) defended fat mass which is why during this phase individuals report lower appetite.

Evidence for this can be found in several pivotal studies. Treatment with semaglutide (12 weeks) or tirzepatide (3 weeks) both demonstrate decrease in observed food intake, hunger, and craving, and impact food preference, but the impact on energy expenditure is less clear (128,133,135,136). Notably, it is challenging to match weight-loss in the OM treatment group versus the lifestyle intervention group owing to the efficacy of the OMs making studies of energy expenditure particularly challenging. Using a lower effective dose of a OM may allow for weight-loss matching with the caveat that the overall treatment effect will be dampened and thus potentially more difficult to detect. To better understand the physiology of the acute weight reduction phase, studies are needed which match weight-loss with OMs alone vs. OMs paired with lifestyle vs. lifestyle alone during which energy intake and expenditure are assessed. Additional critical measures include changes in hormonal response, body composition, patient reported outcomes (PROs) and adverse events.

b. What is the optimal rate of weight reduction in the weight reduction phase?

Until recently, there was little consideration of the rate of weight reduction given a paucity of tools which would enable a significant amount of weight loss. In the setting of bariatric surgery, we do not have the means of slowing down weight loss. In the setting of medications, the rate of weight reduction can be finely tuned by thoughtful dose titration. A majority of current trials have implemented rapid, timed dose titration, to minimize the dose escalation period while ensuring 52-weeks on a specific target dose, per the FDA regulatory requirement. This has provided information on more rapid weight loss but has not informed or directly compared whether different rates of weight reduction impact health outcomes, including impact on muscle function, bone mass, energy levels, adverse events, and other health outcomes.

It is well known that rapid dose escalation increases the potential and severity of gastrointestinal side effects and that slowing dose titration can prevent or mitigate these side effects. It is also known that rapid weight reduction with bariatric surgery, medications, or caloric restriction can increase incidence/prevenance of cholelithiasis . Rapid weight loss, albeit in the setting of bariatric surgery (which also has a restrictive component) and very low-calorie diet (VLCD), has also been associated with nutrient deficiencies (micronutrient), electrolyte imbalance, fatigue in the setting of markedly reduced food intake (137,138). Given OMs are now near or approaching the efficacy of bariatric surgery, it is critical to monitor for markedly decreased food intake and closely monitor rate of weight reduction to prevent potential negative outcomes. Studies implementing the lowest effective dose (LED) with dose titration targeting a set goal, rather than maximum treatment dose (MTD) which is what has been done to date, are critical. With few exceptions, most therapies treat to target (see section 3 treatment targets) rather than use a specific dose (exceptions include statin therapy). The critical questions which need to be answered are at which point the rate of weight reduction has detrimental impacts on health, and beyond mitigating potential side effects, what are the potential benefits of targeting a specific, more gradual rate of weight reduction. For example, studies examining weight reduction of up to 1% body weight reduction per week versus >1% per week, should examine changes in body composition, physical function, metabolic measures, mental health and wellbeing (energy level, mood, and quality of life).

The weight plateau phase and maintenance of lower weight

What is known about reaching and maintaining a weight plateau with OMs is from a handful of longer trials of at least 3 years which were designed with measured outcomes disparate from studying physiology. The SELECT semaglutide CVOT trial(8) (5 years), the SURMOUNT-1 tirzepatide 3-year trial (3 years)(139), the SCALE liraglutide obesity and diabetes trial (3 years)(140) are some of the longest trials to date. These trials were not designed to examine details of energy intake or expenditure or any other accompanying physiological changes. Nevertheless, they have each demonstrated that if the therapeutic agent is continued, the weight loss is maintained. A limitation of these studies is that there is no data on participants who drop out of the trials.

There is considerable interest in maintenance/durability of maintaining lower weight given that obesity is a chronic disease, necessitating long-term treatment. In the real-world, people stop medications owing to many factors, with a main one being lack of access (141) or potentially due to misunderstanding that losing weight does not result in disease remission, but rather disease control (as is the case with T2D and

normalization of blood glucose levels) (142). In trials stopping the therapy, weight regain, albeit to achieve stabilized body weights less than baseline(143), has been demonstrated with semaglutide in the STEP-4 trial (144) and the STEP-1 extension (78) and tirzepatide in the SURMOUNT-4 trial (79). Weight regain after cessation of OMs has also been demonstrated in real-world outcomes (145). Furthermore, not only is the weight regained with cessation of the OMs, but there is also reversion of various cardiometabolic measures of health including increase in blood pressure, lipids, and glycemia (78,79). Thus, a multitude of health gains (reached during the weight reduction phase) are lost with cessation of therapy, as would be the case if treatment was discontinued for any other chronic disease. Perhaps not surprisingly, inter-individual variability in the rate of weight regain occurs (79) with lack of long-term studies to assess whether weight returns to baseline or close to baseline over time. Real-world data may be able to best answer this question, given that discontinuation of therapy in a trial, without providing active comparator control raises ethical concerns.

There are several additional considerations for maintenance which need to be addressed in studies. If the assumption is that obesity is a progressive disease, then maintaining a weight plateau may be different from reaching a weight nadir and initial weight plateau. Given lack of highly effective, durable treatments for obesity until recently, with the exception of bariatric surgery, it is also important to consider that a given weight plateau may optimize health for an individual at a certain stage in life whereas various factors may impact the treatment goal (as discussed in Section 3 of this Statement). A parallel can be drawn from goals of treating (T2D), where the glycated hemoglobin (hemoglobin A1c) goal may change depending on factors such as age, overall health, risks of side effects such as hypoglycemia. In the same way, the goals of obesity treatment may change over an individual's lifetime. Finally, longevity has been studied in the setting of non-physiologic weight loss (146) with reduced temperature, blood pressure and pulse, reduced insulin and T3 are all associated with longevity. Nevertheless, whether any long term health risks, potentially related to alteration in immune function, are associated with sustained caloric restriction in individuals with weight loss has not been carefully studied (147). Furthermore, it is not known whether it is the energy state or these physiologic changes which contribute to the extended lifespan, and this has yet to be studied in the setting of the OMs as we have not yet characterized the physiologic status of the NuSH weight/fat mass-reduced state.

c. How do we determine if there is a role for dose de-escalation or changing medications/therapies, during the maintenance phase?

Perhaps in large part due to initial lack of consistent access to treatment with OMs, the question has been raised whether medications need to or should be changed, switched, or doses lowered during the maintenance phase. As an example, if a specific treatment works for a patient with (T2D) to lower a patient's glycated hemoglobin, for the most part that treatment is continued and not lowered or switched (unless due to side effects, other health issues, or access). An inherent assumption within the question of maintenance is whether there is something distinctly different about the weight loss phase and maintenance phase of obesity that is distinct from other chronic diseasesv(148). If clinically, we do not think/find there is a meaningful difference, then the question returns to access, cost and ease of chronic medical treatment to maximize adherence. If we do think/find there is something inherently different, then the focus should be on understanding the differences of maintenance physiology and designing treatments that best target.

Studies are ongoing investigating various maintenance strategies including maintaining dose versus lowering dose [NCT06780449; IRAS ID 1009583] or spacing out the frequency of the dosing interval (149), or switching from an injectable agent to an oral medication [NCT06584916]. Retrospective, real world-data has provided initial information on switching from a OM to older medications, assessing whether weight reduction can be maintained with promising results (150). Retrospective real-world studies as well as small prospective studies have begun to examine the role of switching therapies to older medications (150). These studies will begin to inform about outcomes with additional studies needed to specifically understand the physiology.

d. How do we optimize health with lifestyle during the weight loss (and maintenance) phase?

The role of lifestyle intervention in the setting of OMs offers an opportunity to focus on the goal of obesity treatment, namely improving health. The role of lifestyle interventions in improving health is clear despite the fact that these interventions do not lead to a high degree of maintained long-term weight reduction (131) .

The FDA has revised the obesity/overweight indication language to "in combination with a reduced calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term…" appropriately shifting the onus away from relying strictly on lifestyle to treat this complex disease, but rather to parallel treatments for other chronic diseases, such as diabetes, which pair pharmacologic interventions with healthful diet and physical activity all with the goal to improve overall health.

A key question is how pairing pharmacologic interventions with physical activity, nutrition diet, quality sleep, and stress management can work together to optimize health outcomes in people with obesity. Pairing liraglutide with physical activity resulted in a greater decrease in percent body fat loss as well as improvements in glycated hemoglobin and insulin resistance (81). The STEP-3 trial (151) which combined semaglutide with intensive lifestyle interventions demonstrated weight reduction within about 1% of STEP-1 (semaglutide without intensive lifestyle intervention, with standard of care lifestyle intervention). Though the data cannot be compared directly given that these were two distinct trials, it does provide insight that the rate of weight reduction was initially potentially slightly faster but that the outcome was nearly the same. The SURMOUNT-3 trial (152) demonstrated that individuals who had lost 5-10% with intensive lifestyle intervention experienced additional weight reduction with the addition of tirzepatide. Studies are needed which directly examine medication with and without intensive lifestyle intervention and impact on body composition, muscle function, quality of life and other health measures.

What studies are needed?

Understanding the physiology of fat mass dynamics in the setting of physiologic weight loss via treatment with pharmacotherapy will enable deeper understanding of the disease and discovery of increasingly targeted therapies. Studies are needed which examine energy expenditure, energy intake, hormonal changes, neural responses/changes, and resulting impact on eating behavior during the weight reduction (negative energy) "phase" and weight plateau (energy homeostasis) "phase". As each "phase" of treatment designed studies that will support a deeper understanding of physiologic changes centrally (neurobiological changes), peripherally (adipose tissue specific) and systemically (other organs, CKM,

systemic and localized inflammatory disorders) which will not only lead to the development of targeted, better tolerated, highly efficacious obesity treatment, but also potentially obesity prevention.

Research priorities (Box)

Human physiology studies investigating physiological weight loss (in the setting of pharmacotherapy) versus nonphysiological weight loss – assessing metabolic adaptation (counter-regulatory response).

Studies which enable a better understanding of the weight reduction "phase" verses weight plateau "phase" in the setting of pharmacotherapy, including assessment of energy expenditure, energy intake, hormonal changes, neural responses/changes, and resulting impact on eating behavior.

Rate of weight reduction – studies to compare whether rate of weight reduction has an impact on body composition (including function), bone health, nutritional status, adverse events (including gallbladder events), and hair loss.

Pairing pharmacotherapy with type/quality of diet, macronutrient composition, type and amount of physical activity – impact on health outcomes.

Assessment of minimal effective dose versus maximum tolerated dose on weight, health outcomes and incidence/prevenance or adverse events.

4) **HEALTH OUTCOMES**
    a. What is the risk of not treating vs. treating obesity?
    b. What are the potential impacts on obesity-related disease (heart, kidney, obstructive sleep apnea, etc)?
    c. What are the weight dependent vs. weight-independent effects of the novel medications?
    d. When should we be treating in the trajectory of obesity? (early/late) - initiate treatment to improve health outcomes

Health Outcomes

As noted in earlier sections of this statement, obesity is a chronic, progressive disease that leads to the maintenance of a new energy balance state with excess energy stored in various fat depots (i.e., excess adiposity). The consequences of the excess adiposity are cumulative and likely a function of the duration of exposure (i.e., chronicity), locations of excess fat deposits (i.e., visceral versus subcutaneous), and amounts of excess adiposity (i.e., total mass). This means that individuals may have varying burden of disease and health consequences resulting from development of obesity.

This section of the statement will focus on those health outcomes associated with obesity in the context of new and emerging obesity medications. The key topics for consideration include the comparative risks of treating obesity versus not treating it, the impact on organ systems, weight-dependent versus drug-specific effects of treatment, and the ideal timing for intervention. Within these topic areas, the

statement will assess what do we already know, what are key gaps in our current understanding, and what research is needed to address these gaps and improve clinical outcomes.

a. What is the risk of not treating vs. treating obesity?

What do we already know? *Risks of untreated versus treated obesity*

Untreated obesity: The risks of obesity are often described in terms of impact on metabolic health. The phenotype of metabolically health obesity (MHO) has been used to identify individuals who have obesity but do not exhibit a complex of abnormalities in related biomarkers of metabolic health (92). Putting aside the challenges with how MHO is defined in the literature (e.g., dichotomous cut points, differing cut points, threshold for cluster), there is clear evidence that this state is transient, and longer exposure to excess adiposity appears to be associated with eventual development of metabolic abnormalities in most individuals (153,154). Therefore, left untreated, obesity is frequently associated with poor health outcomes over time, even when there may be little evidence of poor metabolic health early in life (153). Accordingly, most children with obesity continue to have obesity as adults (155,156).

The more recently developed Cardiovascular-Kidney-Metabolic (CKM) framework provides an alternative perspective for understanding how obesity perpetuates a cycle of metabolic and organ dysfunction in a progressive fashion that is compounded over time (157). The CKM model emphasizes the interconnectedness of cardiovascular, kidney, and metabolic health, highlighting how excess and dysfunctional adipose tissue, particularly visceral fat, drives inflammation, insulin resistance, and metabolic risk factors, including hypertension, hypertriglyceridemia, and type 2 diabetes. These metabolic disturbances contribute to chronic kidney disease and cardiovascular disease, including heart failure, coronary artery disease, and stroke. The CKM framework stages the progression from excess adiposity (Stage 1) to metabolic risk factors and moderate-to-high risk CKD (Stage 2), subclinical CVD (Stage 3), and clinical CVD (Stage 4), underscoring the importance of early intervention to prevent the escalation of CKM-related health outcomes (157,158).

Beyond metabolic health, it is equally important to consider the mental health and biomechanical impacts in individuals with obesity. Limitations in physical functioning due to joint disease, poor sleep quality due to obstructive sleep apnea, and exposure to societal bias and stigma are all important impacts on health outcomes (159,160). These health outcomes are costly, debilitating, and have implications for metabolic and overall health. Ultimately, the evidence suggests that the impact of untreated obesity over time is largely negative, as it drives abnormalities in health, and has broad effects on individuals from metabolic health to physical function to mental health.

Treated obesity - Risks of treatment: The risks of treating obesity with GLP-1 RA or GIP/GLP-1 RA medicines have been fairly consistent based on evidence from large clinical trials and real-world evidence. The primary risk is experiencing an adverse event, predominantly gastrointestinal (GI) side effects that frequently occur early during the course of treatment (39,40,161).

The most frequently reported GI side effects include nausea, diarrhea, constipation and vomiting; they tend to appear early in the treatment course during initiation of medications and are often associated

with dose up titration especially when (inappropriately) rapid. GI side effects are generally mild-moderate in severity and diminish over time with ongoing use. While many patients may experience a GI-related side effect, only a small percentage of people discontinue therapy due to side effects in the clinical trials. For example, in the SURMOUNT 5 trial that compared tirzepatide with semaglutide, only 2.7% and 5.6% respectively discontinued treatment due to GI side effects (162). Gallbladder disease is associated with weight loss with various forms of treatment including bariatric surgery and very low-calorie diet (VLCD) (163) noted in up to 1% of people treated with GLP-1 RA or GLP-1/GIP RA medicines(163), whereas pancreatitis, listed as an adverse event in prescribing event, has not been consistently detected in RVTS where all suspected pancreatitis events are adjudicated(161).

Loss of lean mass will also occur as a result of weight loss, as seen with lifestyle modification, bariatric surgery, and use of GLP-1 RA or GLP-1/GIP RA medicines (84). The greater extent of weight loss achieved with newer GLP-1 RA or GLP-1/GIP RA medicines will increase the amount of all fat-free mass lost, and the proportion of weight loss from skeletal muscle in particular may be disproportionately high. Current evidence suggests that the majority of lost weight is indeed from fat mass. A pooled analysis of nine controlled trials showed that GLP-1 receptor agonists reduce lean mass by about 2 kg—roughly 30% of the total 7 kg decrease—mirroring the composition of weight loss seen with lifestyle regimens and bariatric surgery (164). In STEP-1, 45% of the weight loss with semaglutide 2.4 mg qw was lean mass (-6.9 kg), whereas in SURMOUNT-1, tirzepatide 15 mg qw had a smaller proportional lean-mass decline of 26% (–5.7 kg)(4,5). Further research is needed to better understand the functional implications of lean mass loss with established and investigational GLP-1 RA or GLP-1/GIP RA medicines. Current evidence suggests that despite the loss of lean mass, the quality and function of muscle mass preserved after substantial weight loss is sufficient to support improvements in patient reported physical function and quality of life assessments (165).

The psychiatric safety of GLP-1 RA or GLP-1/GIP RA medicines has been scrutinized, including analysis of whether use of these medicines increases risk of suicide. A large real-world study using TriNetX including 11,683,623 individuals with obesity identified 162,253 propensity-matched patients and noted roughly 2-fold higher rates of depression, anxiety, and suicidal ideation in users of GLP-1 RA or GLP-1/GIP RA medicines compared to non-users (166). In contrast, a 2025 meta-analysis of RCTs (~108,000 patients) found no increase in psychiatric adverse events with GLP-1 RA or GLP-1/GIP RA medicines, instead observing improvements in quality of life and reductions in emotional eating behaviors(167). Likewise, pooled trial data for semaglutide 2.4 mg qw showed no elevation in rates of depression or suicidality relative to placebo and a slight improvement in mood scores(168). After analysis of mental health outcomes from a large number of clinical trials, the FDA has requested removal of the suicidality warning from labeling for GLP-1RA medications.

b. What are the potential impacts on obesity-related disease (heart, kidney, obstructive sleep apnea, etc)?

Treated obesity- Health impacts:
Health improvements, including blood pressure and glycemia, have been documented with weight reduction, beginning with losses of 3-5% of body weight (169). However, greater weight loss often leads to larger magnitudes of health improvements and several complications of obesity can be resolved or

remitted with sufficient weight reduction. Additionally, greater weight loss may be necessary for health improvements that are associated with the mechanical effects of excess adiposity such as obstructive sleep apnea and osteoarthritis (169). GLP-1 RA or GLP-1/GIP RA medicines frequently generate weight loss exceeding the 5% threshold associated with clinical effectiveness, and as a result of >10% weight reduction achieved in most trials, there has been a greater number of health improvements observed with treatment.

Type 2 diabetes (T2D) and glycemia outcomes: Clinical trial data from phase 3 obesity programs demonstrated that semaglutide 2.4 mg qw and tirzepatide 10-15 mg qw produce clinically meaningful and durable improvements in glycemic control for adults with obesity and T2D. In the STEP 2 trial, semaglutide 2.4 mg qw lowered mean HbA1c from 8.1% to about 6.5% over 68 weeks, and more than two-thirds of participants achieved an HbA1c of <7% (170). In patients treated with tirzepatide in the SURMOUNT-2 trial, HbA1c fell from 8.0% to ~6% at 72 weeks, and more than three-quarters of participants reached ≤6.5%; nearly half attained HbA1c <5.7%, a level consistent with diabetes remission (171). Similarly, mean HbA1c reduction was 2.23% in tirzepatide-treated youth with T2D (172). Both semaglutide and tirzepatide also produce large reductions in fasting plasma glucose, lowering the need for background glucose-lowering medications, while maintaining glycemic improvements through >1 year of follow-up. These results demonstrate that modern GLP-1 RA or GLP-1/GIP RA medicines used for obesity management enable a high proportion of patients with T2D to meet or even surpass current glycemic targets while concurrently achieving significant weight loss.

Pre-diabetes and prevention of T2D: Both semaglutide and tirzepatide significantly attenuate the proportion of patients progressing from impaired glucose tolerance to T2D. In the STEP-10 trial program for obesity, semaglutide 2.4 mg qw led to 81% of participants with prediabetes achieving normoglycemia at 1 year, versus only 14% on placebo (173). Adolescents in the STEP TEENS trial treated with semaglutide 2.4mg qw had a 0.3% placebo-subtracted reduction in HbA1c after 68 weeks (174). Similarly, analysis of extended follow-up in the SURMOUNT-1 trial confirms sustained effects of tirzepatide evident over ~3 years in patients with obesity and prediabetes, with tirzepatide reduced progression to T2D by ~94%(139). Notably, 17 weeks after discontinuation of study medication, T2D was diagnosed in 2.4% vs.13.7% of tirzepatide-vs. placebo-treated subjects.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): Bariatric surgery consistently reduces liver fat and improves liver architecture, while reducing rates of progression to Metabolic dysfunction-associated steatohepatitis (MASH) (158,175). In the Phase 3 ESSENCE trial studying patients with biopsy-proven MASH (fibrosis stage 2–3), weekly semaglutide 2.4 mg led to 62.9% of patients achieving MASH resolution (without fibrosis worsening) after 72 weeks, compared to 34.3% on placebo(10). Fibrosis progression was also attenuated: 36.8% of semaglutide-treated patients had fibrosis stage improvement (no worsening of steatohepatitis) versus 22.4% with placebo. Mean weight loss was ~10%. There is emerging evidence from phase 2 trials that GLP1 medicines that include glucagon receptor agonism may have even greater effectiveness for improving MASH (176,177).

Cardiovascular risk factors and events: Weight loss ensuing from modern GLP-1 RA or GLP-1/GIP RA medicines produces multifaceted cardiovascular benefits. In trials, semaglutide (~15% weight loss) and tirzepatide (~20% weight loss) is associated with reduced systolic blood pressure (BP) by ~5–10 mmHg on

average and decreased diastolic (BP) by ~3–5 mmHg, compared to placebo(4,5). Both treatments also provide significant improvements in lipid profiles, including reductions in total and LDL-cholesterol and triglycerides, along with increased HDL-cholesterol.

The SELECT cardiovascular safety trial showed that treating people with overweight or obesity and known cardiovascular disease (CVD) without T2D with semaglutide 2.4 mg qw led to a 20% reduction in major adverse cardiovascular events and a 19% reduction in all-cause mortality (8). Notably, these benefits emerged even though the average weight loss in SELECT (~9–10%) was lower than in shorter trials such as STEP 1. These findings are consistent with weight loss-independent benefits of GLP-1 medicines in the reduction of rates of atherosclerotic heart disease, beyond simply reduction of excess adiposity (178). The dedicated cardiovascular outcome trial for tirzepatide in people with overweight or obesity, SURMOUNT-MMO is ongoing (NCT05556512). However, tirzepatide demonstrated cardiovascular safety, reduced all-cause mortality and was non-inferior to dulaglutide in patients with T2D and a history of atherosclerotic CVD, mean baseline BMI of 32.6 kg/m^2, in the SURPASS-CVOT(179).

Heart failure with preserved ejection fraction (HFpEF): The STEP-HFpEF trial demonstrated that semaglutide 2.4 mg qw is associated with improved cardiac function and quality of life in this patient population. Over 52 weeks, semaglutide-treated patients (who lost ~13% body weight) had a +16.6 point increase in the Kansas City Cardiomyopathy Questionnaire score (indicating better symptoms and fewer physical limitations), versus only +8.7 point change with placebo (180). Exercise capacity rose as well, with 6-minute walk distance improving by ~21 meters with semaglutide, compared to essentially no change (+1 m) on placebo (180).

Obstructive sleep apnea(OSA): Weight loss is one of the most effective therapies for OSA, as reducing pharyngeal fat and abdominal pressure improves airway patency (9). However, substantial weight loss is usually required – on the order of 10–15% – to meaningfully reduce apnea-hypopnea index (AHI) severity. The first dedicated pharmacotherapy trial for OSA studying the efficacy of tirzepatide 10–15 mg qw demonstrated a ~60 % reduction in apnea–hypopnea index and allowed many participants to achieve mild or no clinical OSA after 52 weeks, underpinning its 2024 FDA approval for adults with obesity and OSA(9).

Renal outcomes: GLP-1 medicines slow diabetic kidney disease progression; semaglutide recently received an FDA label to reduce risk of kidney-function decline, end-stage kidney disease, and renal death in at risk individuals with T2D based on the results of the FLOW trial studying 1mg semaglutide qw over a mean follow-up period of 3.4 years (181). Mechanistically, contributions from lowering of BP and anti-inflammatory effects together with direct effects of GLP-1 medicines on the kidney contribute to conferring renoprotection in patients with obesity without diabetes, as revealed by a reduction of renal outcomes in people with overweight or obesity treated with semaglutide in the SELECT trial(182). The potential for tirzepatide to confer renoprotective benefits in people with obesity with or without T2D is being studied in the TREASURE-CKD trial (NCT05536804).

Quality of life and patient-reported outcomes

Across the STEP and SURMOUNT trials, >50 % of treated participants attained clinically meaningful improvements in weight-specific quality of life, versus ~25 % on placebo (183,184). Improved weight-

related quality of life was also seen in treated STEP TEEN trial participants(174). In a dedicated knee-osteoarthritis study, semaglutide reduced the WOMAC pain score by 42 points (58% from baseline) and improved physical function, delaying joint-replacement consideration (185). Notably, self-esteem and emotional well-being improve in patients achieving weight loss with semaglutide or tirzepatide: both drugs reduced feelings of public distress and weight-related stigma (183,184). GLP-1 RA or GLP-1/GIP RA medicines also impact eating behavior and associated emotional health. A meta-analysis of over 100 trials found significantly decreased maladaptive eating behaviors, with a moderate effect size for reducing emotional eating. Patients reported feeling more control over food and less compelled to eat when stressed or upset (167).

What are the gaps in our knowledge?

As noted, for many health improvements, there appears to be a threshold effect such that achieving a particular percent weight loss is associated with an increase in the probability of detecting improvements in specific health conditions and related outcomes (169). However, some of the health improvements observed in clinical trials, including SELECT and ESSENCE, have been achieved without achieving the same extent of weight loss effect seen in the primary registration trials. For example, the mean weight loss achieved in SELECT trial was <10% compared to the mean weight loss reported in STEP 1 of ~15% (4,8), yet the SELECT trial showed clear benefit for secondary prevention of cardiovascular events. These observations, along with the early separation of the event curves prior to significant reductions in body weight, add to the clinical evidence linking GLP-1 RA or GLP-1/GIP RA medicines to weight loss-independent benefits on multiple health outcomes (14). This raises several important points. One is, that of targets (discussed in Section 3) and that percent weight loss should be replaced with a more clinically meaningful target. The second is that these medicines likely have disease modifying effects which are separate from the weight reduction itself. And lastly, it raises that question of whether maintenance of the health benefits requires long-term exposure to the treatment and not just maintenance of a lower weight.

c. What are the weight dependent vs. weight-independent effects of the novel medications?

It is difficult to isolate the health benefits ensuing from weight reduction from the weight loss-independent benefits of GLP-1 RA or GLP-1/GIP RA medicines based on observations in clinical trials. The dose-response relationships for clinical benefit are different for multiple outcomes. For example, effective glucose control is achieved without weight reduction, as there are significant improvements in glycemia based on mechanism of action (i.e., stimulation of insulin and inhibition of glucagon secretion and reduction of gastric emptying, actions that do not require weight loss (186). However, remission of T2D may depend on reduction in ectopic fat stores reflecting achievement of a weight reduction to enable simultaneous improvements in β-cell function and insulin sensitivity (171,187).

The value of understanding the weight loss-independent contributions and mechanisms linking improved health outcomes with use of GLP-1 RA or GLP-1/GIP RA medicines is that it helps to define treatment targets. If weight reduction is the primary driver of the health benefits, clinicians should inform patients about treatment targets based on health goals. If the weight reduction target is not likely to be achieved with a given therapy, the treatment strategy should be revised. On the other hand, if the exposure to the

drug is the primary driver of the health benefits, then the type of therapy and weight loss-independent goals may be critical to the treatment strategy.

Additional data is required to better understand the ideal time to initiate treatment with GLP-1 RA or GLP-1/GIP RA medicines to achieve the best health outcomes. Initiating treatment early in the development of complications related to obesity would be prudent but costly in the short term. If modest weight reduction is the primary treatment goal, lower cost, more accessible medications may be key to scaling cost-effective treatment of obesity, reserving newer and more costly agents for specific treatment targets or goals not feasibly achieved with older agents.

Personalization of treatment recommendations could be a function of the associated symptoms of obesity, contributing factors supporting excess weight gain, and health goals related to established complications of obesity. To achieve the intended target effects, specific molecules with targeted metabolic actions may be necessary. For example, achieving optimal resolution of steatohepatitis without worsening fibrosis may benefit from a GLP-1 RA medicine with glucagon receptor agonism as a part of the treatment strategy, although the superiority of this approach relative to GLP-1 medicine mono-agonists such as semaglutide has not yet been conclusively demonstrated.

Section 3: What research is needed to address these gaps and improve clinical outcomes?

The arrival of highly effective GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines has transformed therapeutic possibilities but also exposed critical evidence gaps. Clinicians still do not know whether the various health improvements reported are due principally to weight reduction or to weight-independent drug actions. It remains uncertain when in the obesity trajectory pharmacotherapy should begin, how long treatment must be continued to sustain health improvements, and how benefits and risks vary across diverse patient groups. Addressing these questions requires a coordinated research agenda that combines mechanistic experimentation, comparative-effectiveness trials, and pragmatic real-world investigations.

Weight-dependent and drug-specific treatment effects

A fundamental research question is how much of the benefits produced by GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines are a function of weight loss versus direct pharmacologic activity that may be slightly different with various agents. To answer this question, future trials could assign individuals with obesity and associated health complications to various treatment strategies (e.g., a combination of intensive behavioral intervention ±early generation OM ± metabolic and bariatric surgery vs. OM) with the goal of achieving a specific weight loss threshold (15-20%) that is matched across the treatment strategies. In this context where weight loss is matched, we can test whether remission of T2D, regression of MASH, resolution of obstructive sleep apnea, or prevention of major adverse cardiovascular events differs by treatment modality. Embedded mechanistic sub-studies that assess changes in fat depots, metabolomics, proteomics and changes in obesity-related signaling pathways may identify weight-independent mechanisms, while propensity-matched analyses within electronic health-record networks can corroborate trial findings at scale.

d. When should we be treating in the trajectory of obesity?

Timing and personalization for disease prevention

By the time an individual has accumulated sufficient excess fat stores to reach a BMI of 30 kg/m^2, that individual has been exposed to the adverse effects of positive energy balance for an extended period; this means that accumulation of excess body weight is a lagging indicator of metabolic dysregulation in response to the environment. Preventing early metabolic dysfunction raises the question of when in the course of disease pathophysiology should GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines be introduced as viable treatment options. Research is also needed to elucidate the impact of treating obesity at varying stages of childhood and adolescence.

Future clinical trials are needed that include individuals with early weight gain and limited or mild cardiometabolic disease risk that may be outside of the current indications for OM. These individuals would be randomized to early treatment versus standard initiation (i.e., watching and waiting). Endpoints such as incident diabetes, hypertension, and chronic kidney disease will quantify the yield of early therapy. Adaptive platform designs can simultaneously test personalized algorithms that assign drug class according to phenotype—visceral adiposity, liver fat content, appetite dysregulation, or atherosclerotic cardiovascular disease risk score—thereby establishing whether precision prescribing outperforms a one-size-fits-all approach.

Duration of treatment to sustain health outcomes

Phase III trials show substantial weight gain and metabolic relapse when GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines are withdrawn, suggesting long-term therapy is necessary for most patients. Randomized withdrawal and step-down designs should therefore compare continued full-dose treatment with alternative maintenance regimens that taper to intermittent dosing, combine a lower-dose injectable with supportive lifestyle interventions, use flexible dosing based on symptoms or metabolic parameters, or substitute inexpensive earlier generation agents once target weight loss is achieved. Key outcomes must include long-term weight trajectory, muscle and bone preservation, control of obesity-related conditions, cardiometabolic markers, health-related quality of life, and cost per quality-adjusted life year. Cost-utility and budget-impact analyses will inform payers about the affordability of continuous versus staged therapy.

Broadening the health outcomes evidence base

Important populations remain underrepresented. Older adults require trials that monitor sarcopenia, bone density and fracture outcomes, and impacts on physical function; we have much to learn about what is needed to safeguard functional status with these agents. Reproductive-aged women need robust pregnancy exposure registries capable of detecting rare teratogenic signals and clarifying safe wash-out intervals before conception. We should also include follow up of the infants conceived post-treatment to understand the implications for the metabolic health and trajectory for these offspring. Pediatric trials will continue to be needed to evaluate effects of GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines on physical health, mental health, development, and long-term health impacts. Purposeful enrollment of racially and socio-economically minoritized groups is critical for understanding the potential of these medications to address health outcome disparities that may be driven in part by social

determinants of health. If optimal health outcomes are only achievable in supportive environments, this reinforces the need for policy that addresses the drivers of disparities. If therapy with GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines is effective regardless of the surrounding context, this reinforces the need for building strategies that improve equitable access to treatment.

In summary, addressing research gaps related to GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines and health outcomes requires a collective research agenda that is agnostic of the specific medicine but addresses some broader therapeutic class effects. Addressing these fundamental questions will allow for greater personalization of treatment as the toolbox of available therapies continues to expand. Integrating real-world evidence with a broad array of comparative effectiveness trials that assess objective health outcomes, patient-reported outcomes, and remotely monitored outcomes (e.g., physical activity, function, adherence), will allow us to advance the application of current and emerging GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines to achieve optimal health outcomes for all while minimizing undue adverse effects.

5) SAFETY

a. What are the safety concerns as millions of people take these medications?
b. What are the negative impacts of losing a substantial amount of weight (bone, muscle, nutrient def?) (role for new meds such as myostatin/activin pathway inhibiters)
c. What are the hypothetical risks or safety concerns? (i.e., cancer)
d. What is the optimal approach to collecting and using real-world data with medications?

a. What are the safety concerns in broader populations taking the OMs? What are the hypothetical risks or safety concerns? (i.e., cancer)

GLP-1 RA medicines have been extensively studied in people with T2D and individuals with overweight and obesity with or without T2D, in multiple phase 3 trials. Nevertheless, the duration of many of these trials may be as short as 6 months for people with T2D, and range from 52-104 weeks in people with obesity. Although the safety and efficacy of GLP-1 RA, GLP-1/GIP RA medicines used for the treatment of obesity such as liraglutide, semaglutide, and tirzepatide, has been scrutinized in tens of thousands of individuals with overweight and/or obesity in phase 3 trials, these trials are neither long enough nor large enough to detect rare safety events, including many types of cancer, or rare infections, that might arise only in 1:10,000 people with more prolonged drug exposure. Furthermore, these trials specify precise eligibility criteria, generally excluding individuals with fluctuations in body weight, type 1 diabetes, NYHA Class 4 Heart Failure, varying degrees of renal impairment, a recent (within 5 years) history of cancer, active thyroid disorders, a history of major psychiatric disorders and a recent history of depression, including a history of suicidal ideation. Hence, there is limited understanding of whether these broad categories of individuals might be uniquely susceptible to a subset of adverse events.
Moreover, individuals with a history of acute or chronic pancreatitis, active or chronic hepatitis, substance abuse, ongoing pregnancy, or breastfeeding, are also excluded from most of these diabetes

and obesity trials (188). Some of the semaglutide or tirzepatide trials also exclude individuals with obesity secondary to endocrine causes, or a genetic disorder (4,5). Hence, clinicians looking for evidence and guidance supporting the safety and efficacy of these medications in people with the aforementioned conditions will not find relevant useful information in the majority of clinical trial publications. Additional scrutiny of safety in the real world would benefit from regular analyses of large registries, pharmacovigilance studies, and periodic scrutiny of health care claims linking use of obesity medicines with rare reports of adverse events in multiple populations.

The popularization of GLP-1 RA, GLP-1/GIP RA medicines for weight loss has led to their use among many individuals seeking weight loss who were not studied in or excluded from phase 3 clinical trials, including people with a BMI<27, individuals with type 1 diabetes (T1D), as well as individuals using the medicines for short periods of time, sometimes at doses above or below those recommended for clinical use in extensively studied populations. Collectively, the expanding use of these medicines in people not previously studied in clinical trials creates an evidence gap and uncertainty regarding their efficacy and safety beyond that defined for other populations in phase 3 trials. Larger outcome studies have been carried out in people with T2D and/or obesity, usually with risk factors for or known pre-existing cardiovascular disease, yet the long-term safety of these medicines in other populations is not yet supported by rigorous evidence (161).

Although the GLP-1RA class of medicines was introduced clinically for the treatment of T2D in 2005, the first GLP-1RA medicine (liraglutide) was approved for weight management in 2014, and the use of semaglutide at a maximum dose of 2.4mg qw and tirzepatide at does up to 15mg qw for obesity commenced in 2021 and 2023, respectively. Although many individuals with T2D are also living with overweight or obesity, information on the long-term safety of GLP-1 medicines in people without T2D is more limited, and only a single outcome trial, the SELECT trial, has reported on the safety of a GLP-1 medicine, semaglutide in people with overweight or obesity with a previous history of atherogenic cardiovascular disease (8). Although the results of the SELECT trial included a 19% reduction in all-cause mortality, and no new safety concerns, our understanding of the long-term safety of GLP-1 medicines in people with obesity, including individuals without cardiovascular disease, is still limited.

Detection of rare safety issues arising from more prolonged exposure to GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines in susceptible individuals is currently challenging due to insufficient durations of exposure in clinical trials, compounded by evidence suggesting that many individuals discontinue these medicines in the real world after 12-24 months, and may cycle on and off therapy. Rates of persistence vary widely in the real world, with some studies reporting up to 55-68% persistence (189), with others reporting much lower rates after 1 year of follow-up (190,191). Although ongoing use of the medications remains high, often exceeding 90% in phase 3 weight loss trials with semaglutide and tirzepatide, rates of discontinuation and re-initiation of liraglutide, semaglutide, and tirzepatide are higher and lower respectively, for people with obesity vs. individuals with T2D in real world observational studies, hampering studies of long term safety (191).

Compounded semaglutide and tirzepatide. The use of GLP-1 RA, GLP-1/GIP RA medicines to achieve weight reduction and improved health is ideally achieved together with an experienced health care practitioner and often a team approach that involves counselling in lifestyle management, optimization of

mental health and recommendations for activity, appropriate exercise, nutrition, and diet counselling. Due to drug shortages and FDA regulation governing supply shortages, considerable quantities of semaglutide and tirzepatide were dispensed that were not made by the manufacturers Novo Nordisk and Eli Lilly. Rather, they were synthesized by a large number of suppliers providing synthetic peptides, often of uncertain quantity and purity. In late 2024, one estimate suggested that at least 80 million prescriptions for compounded semaglutide had been filled in the previous 12 months (192). Multiple reports of harm, and several dozen deaths have been reported to date associated with use of compounded medicines, and the potential for long-term safety issues to arise secondary to the use of compounded semaglutide or semaglutide is not yet known, and requires evaluation (192). Moreover the quality of information and guidance surrounding the dispensing and use of compounded GLP-1 RA medicines that is provided by the suppliers appears to be highly variable (192). Whether the extensive use of dozens of different versions of semaglutide and tirzepatide is associated with safety and efficacy profiles resembling those described for FDA-approved semaglutide and tirzepatide produced by Novo Nordisk and Eli Lilly Inc is not known and requires ongoing scrutiny. It is not currently known whether the effectiveness of the medicines and attainable weight loss is similar to that achieved in clinical trials with authentic semaglutide or tirzepatide. However, evidence suggests that the ultimate dose level and weight loss achieved may be less in the real world relative to that reported in RCTs (189). Although supply constraints are easing, compounded GLP-1 RA medicines are still sold in many jurisdictions, hence lingering safety concerns surrounding the supply chain endure. The FDA as well as various societies including The Obesity Action Coalition (OAC), Obesity Society (TOS), and Obesity Medicine Association (OMA) also issued a statement advising against the use of compounded alternatives (15).

Pregnancy

Obesity may be associated with impaired fertility and delayed time to successful pregnancy in both men and women (193), however, there is insufficient data to determine whether treatment with GLP-1 RA, GLP-1/GIP RA medicines improves fertility in people living with obesity. Furthermore, whether the putative improvement in fertility is related to specific weight loss thresholds or reflects contributions from weight loss-independent mechanisms is uncertain. Current guidance does not recommend the use of GLP-1 RA, GLP-1/GIP RA medicines during pregnancy, largely due to pre-clinical studies demonstrating small for gestational date babies and some congenital abnormalities, where non-obese pregnant animals were exposed to high doses of GLP-1 RA medicines, resulting in fetal energy restriction and suboptimal weight gain or weight loss during pregnancy (194).

Current standards of practice include counselling women to consider birth control to avoid pregnancy and/or cessation of GLP-1 RA medicines several months prior to attempts at conception. Nevertheless, after 20 years of GLP-1 medicines in the clinic, it seems likely that thousands of pregnancies have been carried to term in women with T2D and/or obesity who were exposed at some point during pregnancy to GLP-1 medicines, and little information has been reported on the outcomes for mother and baby. The available evidence from registry and real-world databases does not reveal an increased risk of major malformations for women with T2D or obesity exposed to GLP-1 RA medicines in the first trimester (195,196). Hanif and colleagues identified 1,826 pregnant women with T2D exposed to GLP-1 medicines in the first trimester of pregnancy in the TriNetX database. Compared to data from propensity-matched non-exposed control pregnancies, there was no difference in a wide range of maternal outcomes, nor any imbalance in rates of fetal cardiac or kidney abnormalities in the GLP-1 RA medicine-exposed cohort

(197). However, longer follow-up and careful scrutiny of maternal and infant outcomes in the context of women with obesity previously treated with GLP-1 RA medicines is needed.

Given the increased risk of hypertension and preeclampsia in pregnant women with obesity, as well as anovulation frequently associated with polycystic ovary syndrome, there is considerable interest in understanding whether prior use of GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines in women planning pregnancy might be advantageous to improve chances of conception and outcomes. A retrospective study of female patients in the TriNetX database, age >18, who had used GLP-1 RA medicines at some point in the 2 years prior to conception (4,267 individuals in exposed vs. control cohorts), demonstrated reduced rates of gestational diabetes, hypertensive disorders, preterm delivery, and cesarian deliveries, in the GLP-1 RA-exposed cohort (198).

Nevertheless, there is currently little evidence to guide timing, and optimal use of GLP-1 medicines prior to conception in at risk women and some real-world studies report an increase in adverse outcomes such as greater gestational weight gain, birth weight, gestational diabetes, hypertensive disorders and pre-term deliveries. in women who stopped GLP-1 RA medicines prior to or at the start of pregnancy (199) .As evidence accumulates supporting the safety of GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines during pregnancy, it would seem reasonable to initiate randomized control trials to examine the safety and possible benefits of continuing use of GLP-1 medicines during pregnancy for women with obesity at high risk for pregnancy-associated complications.

The timing of re-initiation of GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines following delivery in breastfeeding women has not been established. Semaglutide was not detected in the breast milk of 8 women, assessed at 12 and 24 h after semaglutide administration, suggesting a low likelihood of harm to breastfed infants, especially since semaglutide is unlikely to be absorbed across the infant gut at meaningful levels in the absence of co-formulated absorption enhancers (200). Nevertheless, a more extensive data set, associated with clinical outcomes, and data informing guidance for re-initiation of GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines postpartum, would be useful. Moreover, the forthcoming introduction of small molecule GLP-1 medicines RA, GLP-1/GIP RA, NuSH receptor modulator, each with different potential for excretion into breast milk will require careful scrutiny of the unique safety of these medicines for use, prior to, during and after pregnancy.

b. What are the negative impacts of losing a substantial amount of weight (bone, muscle, nutrient deficiencies) and what is the role for new medicines such as myostatin/activin pathway inhibiters)

Fractures and loss of lean mass

GLP-1 RA, GLP-1/GIP RA medicines do not exert direct effects on bone formation or resorption in humans. Although people with T2D may exhibit defects in bone structure and quality, there is little evidence linking use of GLP-1 medicines to non-traumatic fractures (201). Rapid and extensive weight loss will increase the loss of adipose tissue, bone and lean mass, predisposing some susceptible individuals to clinical sarcopenia, falls and fractures (202,203). A supervised exercise regimen together with daily liraglutide therapy improved the maintenance of weight loss even 1 year after discontinuation of the exercise/liraglutide regimen (204). There is limited data examining whether the extent of loss of lean

mass in people with obesity treated with GLP-1 RA, GLP-1/GIP RA medicines can be mitigated with high protein diet, resistance exercise, strategies to reduce the rates of weight loss, or with one of several pharmacological agents now being tested either with semaglutide or tirzepatide in the clinic (85). Furthermore, special populations including the frail elderly, individuals with chronic kidney disease, and metabolic liver disease, may be at higher risk for fractures and there is insufficient data examining the impact of GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines on musculoskeletal health across a wide range of individuals living with overweight or obesity. As clinical trials assessing investigational anabolic agents that spare or augment lean mass in combination with semaglutide or tirzepatide are underway, how should we assess changes in muscle quantity, quality and function, and judge the success of these agents; what are the key outcomes? How do we select patient populations most likely to benefit from preservation of functional muscle mass, and what should the duration of therapy be? There are currently no guidelines that address the type and frequency of monitoring for bone and functional muscle health that should be considered in individuals using GLP-1 medicines. More trials are needed to assess whether different types and frequency of exercise, with or without high protein diets, can effectively mitigate loss of functional lean mass and improve clinically meaningful outcomes in people with obesity treated with GLP-1 RA, GLP-1/GIP RA, NuSH receptor modulator medicines.

Eye disease

The safety of semaglutide in people with T2D is being studied in the FOCUS trial. The use of semaglutide in people with T2D has been linked to an increased risk of non-arteritic anterior ischemic optic neuropathy (NAION) in case-series and real-world observational data in some but not all analyses (205-208). Less information is available about the relative risk of NAION with use of GLP-1 RA medicines for weight loss in people with obesity, and most of the data reflects use of semaglutide, not tirzepatide (208-210). Given the low rates of NAION, additional scrutiny of this entity in registries and real-world databases will be required to understand the validity of the possible association and relative risk.

Persistence and adherence in the real world-what is known about why people stop? Rates of persistence vary widely in the real world, with some studies reporting up to 55-68% persistence (189). Whether rates of discontinuation predominantly reflect challenges with tolerability, supply chain constraints, affordability and reimbursement, attainment of weight loss goals and individual decisions to interrupt or stop medications, is not well understood and requires clarification for development of effective strategies to optimize persistence (211). Moreover, rates of discontinuation of GLP-1 RA, GLP-1/GIP RA medicines in the real world are higher for individuals with obesity using these agents for weight loss, relative to lower rates of discontinuation in people with T2D (190,212). The reasons why people discontinue GLP-1 RA, GLP-1/GIP RA medicines, ranging from cost or challenges with access, to adverse events, to lack of efficacy, to achievement of short-term goals, are poorly understood. Whether education, coaching, incentives or additional approaches will increase the long-term persistence and clinical benefits associated with these medicines requires additional scrutiny.

Safety research priorities (Box)

Are there any unique long term safety issues for using new obesity medicines in a) children and adolescents b) pregnancy and c) the elderly?

What are the most effective adjunctive measures to offset deleterious loss of bone or muscle in at risk individuals?

Will nation-wide registries be useful for understanding whether new obesity medicines increase the risk of rare eye conditions in specific at risk populations?
Should all new obesity medicines be studied in large randomized trials in people with or at risk for cardiorenal complications of obesity?
Are new obesity medicines similar or unique in regard to their potential safety in people with cancer?

CONCLUSIONS

Our collective overarching goal is prioritizing research to improve health outcomes in individuals with obesity. A focus on the six key areas described brings us closer to achieving this goal. A better understanding of obesity physiology and defended fat mass regulation enables the development of therapies targeted to obesity pathophysiology. Beginning to unravel the heterogeneity of obesity may enable pairing of pharmacotherapeutic treatments more specifically to disease (sub)type allowing for less trial and error and thus earlier and better disease control. As with any chronic disease, targets supported by evidence of improvement in health outcomes, shape standard of care guidance directly impacting clinical practice. Clarifying the physiology of treatment response and fat dynamics may provide critical insights into disease physiology. Improving and optimizing health outcomes are the goal of obesity treatment beyond weight reduction alone and when paired with safety outcomes, enable ascertainment of risk-to-benefit ratio of these therapeutics. A better understanding of these areas as well as others will begin to fill gaps in knowledge about treatment with novel obesity medications and impact on improving the health of millions around the world.

FIGURE LEGENDS

Figure 1. Fat mass-targeted model of energy storage regulation. According to this model, the regulated parameter is body fat mass, either as a single entity, or more likely, as a group of targets for different adipose depots. According to this model, energy intake and utilization is regulated to achieve and maintain energy stores and fat distribution appropriate to developmental stage and energy needs. Energy balance, itself determined by appetitive drives and non-volitional energy expenditure, is not the target of regulation. Rather, these parameters are mechanisms used by the body to regulate fat mass and distribution. In this model, durable changes in fat mass, whether normal or disrupted in obesity, are determined by changes in central regulation and then mediated by secondary alterations in appetite and energy expenditure. **A. Non-physiological weight loss.** Non-physiological weight loss is characterized by illness- or injury-induced, or purposeful decrease in food intake or increase in energy expenditure (physical activity), without changing the underlying fat mass regulatory apparatus. While the initial effect is loss of fat and, consequently, body weight, it is followed by physiological compensation (a combination of increased appetite and decreased energy expenditure) to return the body to the original target fat mass. This is commonly seen after acute illness and can account for the regain of lost weight as the body seeks to restore physiologically mandated energy stores. After non-physiological weight loss, the only way to maintain weight loss is to continually resist the physiological drive for restoration of energy stores. **B. Physiological weight loss.** Physiological weight loss is weight loss determined by normal developmental processes such as loss of baby fat, loss of body fat in males undergoing puberty, and loss of maternal fat after pregnancy and cessation of post-partum milk production. According to this model, it is also the mechanism that drives durably effective treatment of obesity, whether caused by changes in dietary composition (not calories), discontinuation of obesogenic medications, removal of environmental obesogens, obesity management medications or bariatric/metabolic surgery. With physiological weight loss, the intervention rapidly alters physiological regulation to decrease the target fat mass. Normal physiological mechanisms then recognize the need to decrease fat mass, which is accomplished by a combination of decreased appetitive drives (decreased hunger, craving, and "food noise," and enhanced satiation and satiety) and increased or preserved energy expenditure. Once fat mass falls to the new target, these physiological forces normalize to maintain homeostasis at the new target by partially reversing the decreased appetite and increased energy expenditure. Under this model, maintenance of physiologically-induced weight loss does not require purposeful resistance to enhanced appetitive drives.

Figure 2. Heterogeneity of response to obesity treatment. There is a wide variation in the weight loss response to all categories of obesity treatment. This figure shows the distribution for a low-carbohydrate diet, tirzepatide 15 mg/week in people without type 2 diabetes, treatment with the Endobarrier® duodenojejunal liner device and Roux-en-Y gastric bypass. Despite the large differences in average weight loss among these treatment modalities, the interindividual variation is similar in each with a standard deviation of 10-12% total body weight loss. The distributions are unimodal, approaching a normal distribution, which suggests that biological factors are more likely responsible for the variation than differences in behavioral compliance, which would be predicted to produce evidence of a bimodal distribution. Adapted from (5,213,214),

Figure 3. Dynamic changes in markers of health after treatment of metabolic disease. Effective, physiological treatment of metabolic disease leads to a change in measurable physiological markers. Changes in those markers, including blood pressure for hypertension, fasting glucose for type 2 diabetes, LDL-cholesterol for hypercholesterolemia and body weight for obesity, follow an initial pattern of improvement followed by a longer period of homeostasis marked by "maintenance" of the improved physiological state. For most metabolic diseases, the distinction between the initial correction and maintenance is generally inapparent to the patient because the biological marker is generally tested after the new steady state is reached. Several characteristics of obesity and its treatment highlight the differences between the initial correction and steady state. Unlike other metabolic diseases, whose improvement can be completed in days or weeks, improvement in obesity typically occurs over a much longer period. During this period, patients perceive the improvement continuously through changes in body shape and the fit of clothing, as well as dynamic changes in appetitive drives. Weight loss is sensed over an extended period, and it is easy to discern when a new steady state has been reached. Appetitive drives that are often diminished during the period of fat mobilization and weight loss commonly increase as the body reaches a new plateau. These features of obesity provide a perception of two distinct phases in the response to treatment. As described in Figure 1, those two phases (weight loss and then weight restoration in response to metabolic adaptation) are more distinguishable with non-physiological weight loss, but with physiological weight loss, as with effective treatment of other metabolic disorders, clinical observation suggests a single phase, with a steady progress toward a new, healthier steady state.

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Non-physiological weight loss

Examples: fat excision, caloric restriction, intensive exercise)

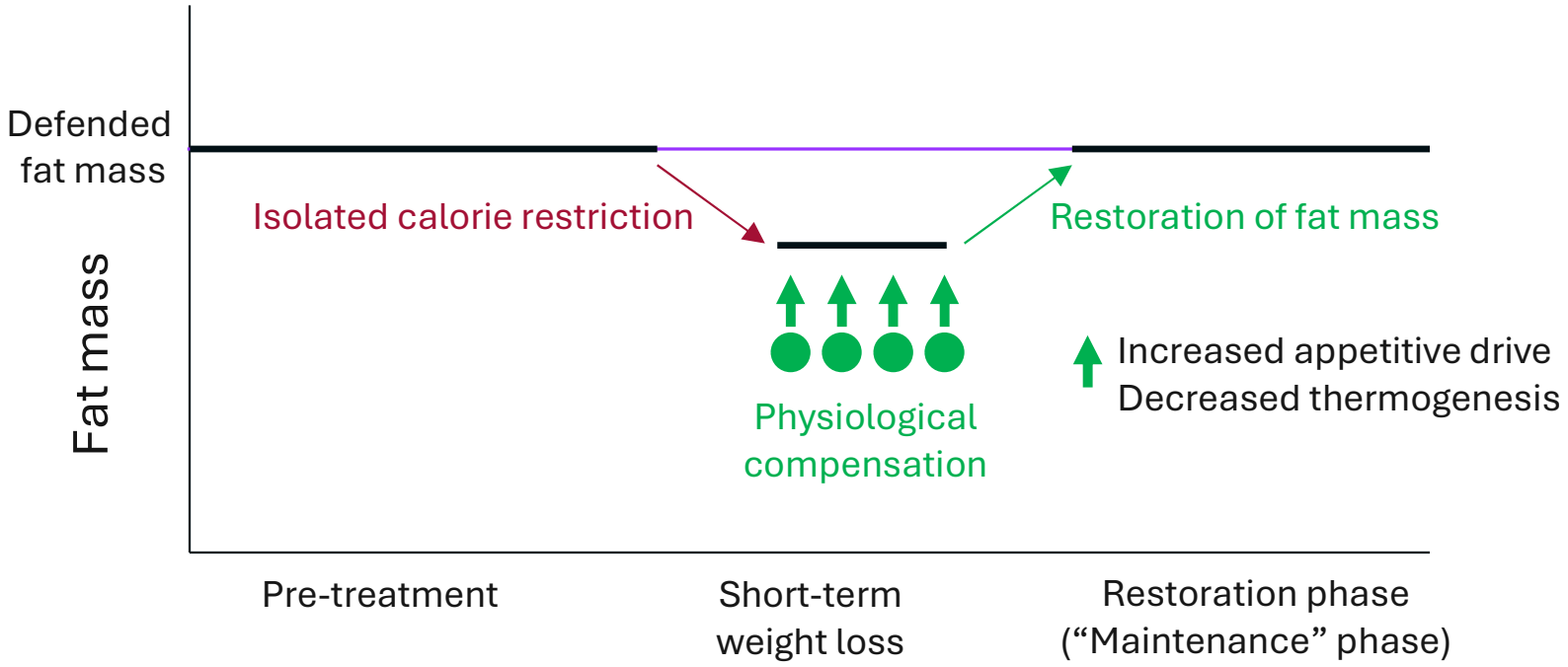

Figure 1A

Physiological weight loss

Examples: targeted lifestyle change, effective medications, bariatric surgery)

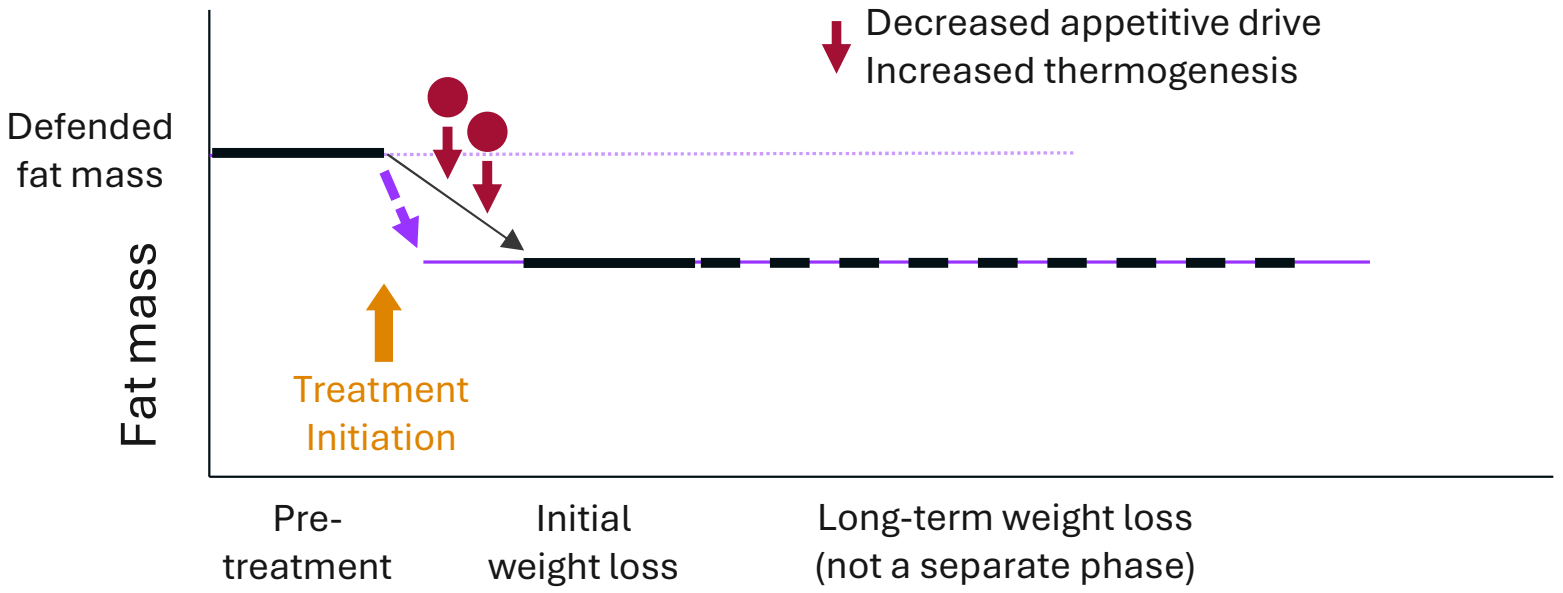

Figure 1B

Weight loss varies widely among individual patients – regardless of treatment

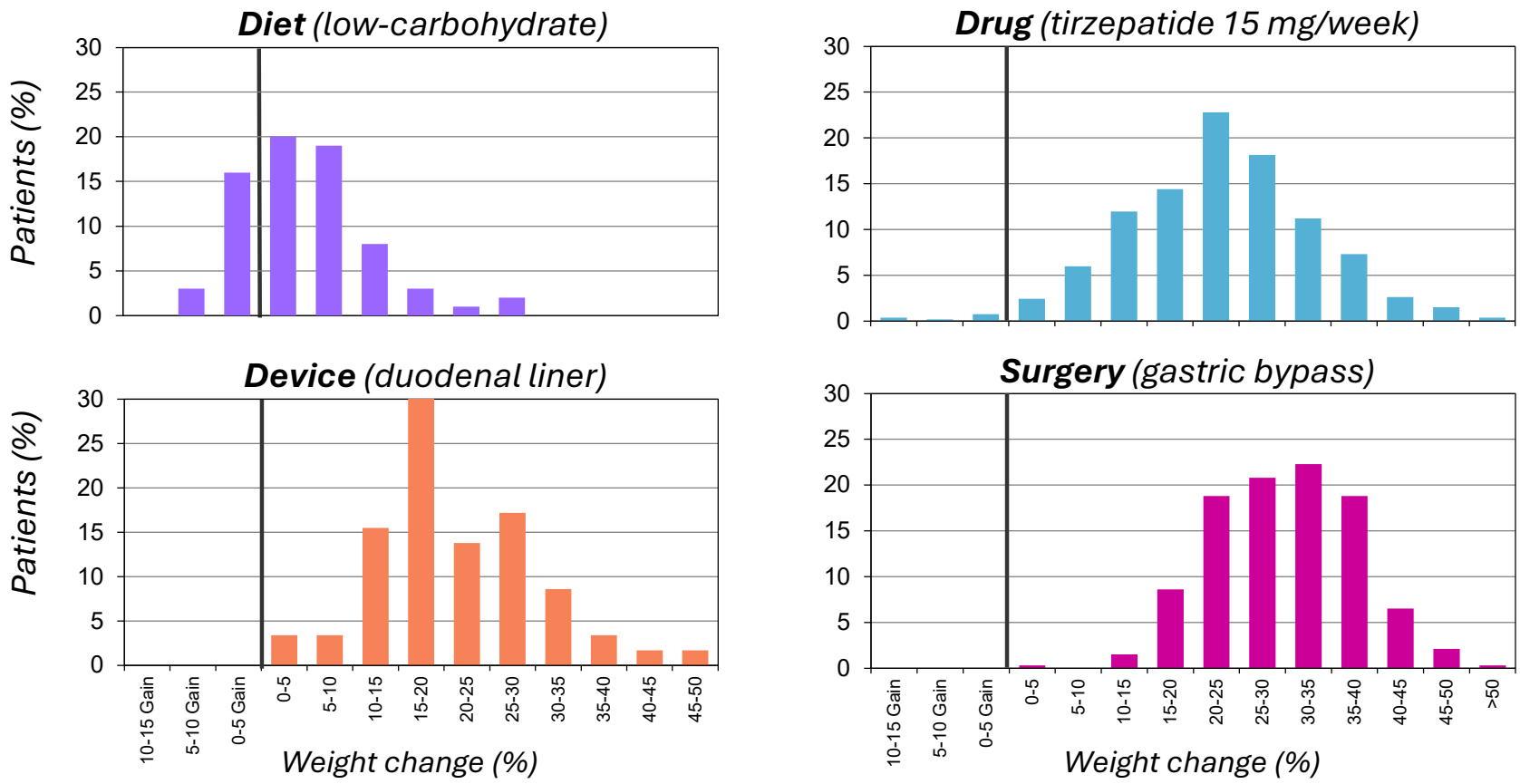

Figure 2

Typical response to metabolic therapies

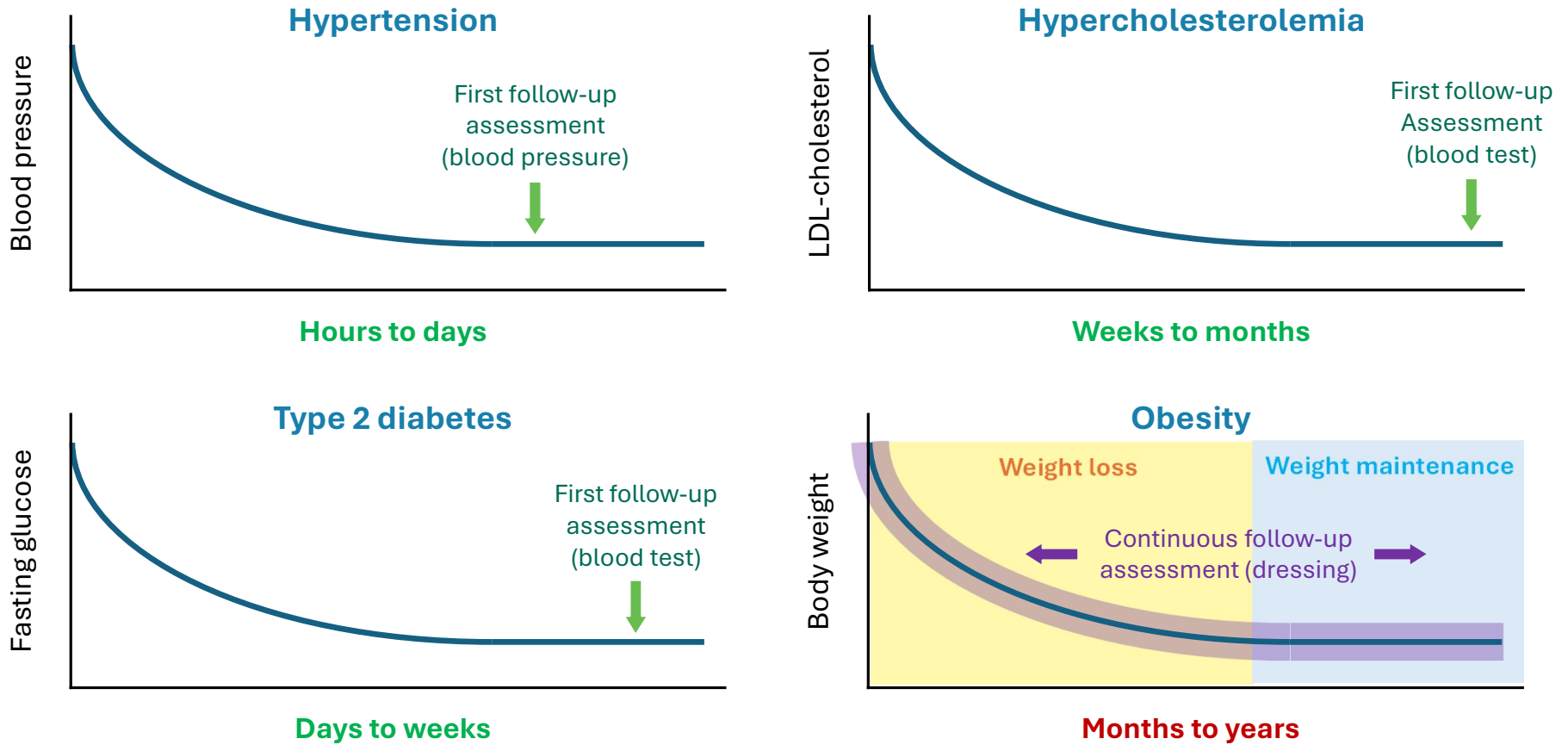

Figure 3