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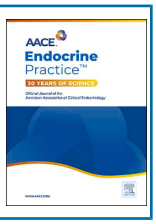

AACE Clinical Guidance

American Association of Clinical Endocrinology Consensus Statement: Algorithm for the Evaluation and Treatment of Adults with Obesity/Adiposity-Based Chronic Disease — 2025 Update

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Objective: This 2025 consensus statement provides evidence-based visual guidance in graphic algorithms and a summary of evidence to assist health care professionals and adults with obesity and adiposity-based chronic disease (ABCD) in shared decision making to improve care and achieve health goals.
Methods: AACE selected a task force of medical experts to update the 2016 AACE algorithm for the medical care of patients with obesity and align this algorithm update with related AACE clinical guidance. Details on surgical and procedural therapies for obesity treatment as well as the care of pediatric-aged patients are beyond the scope of this algorithm.
Results: The algorithm includes 11 sections: (1) principles of person-centered and complication-centric management of obesity/ABCD, (2) care model for people with obesity/ABCD: screening and diagnosis, (3) diagnosis: anthropometric component, (4) diagnosis: clinical component, (5) individualized treatment plan, therapeutic goals, and follow-up, (6) response to therapy and weight-loss targets for people with ABCD, (7) behavioral/lifestyle therapy for people with obesity/ABCD, (8) hierarchies of preferred medications for complication-centric care of people with ABCD, (9) lower-

Abbreviations: AACE, American Association of Clinical Endocrinology; ABCD, adiposity-based chronic disease; A1C, hemoglobin A1c; BBS, Bardet-Biedl Syndrome; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DXA, dual-energy x-ray absorptiometry; ER, extended release; FDA, U.S. Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; GIP/GLP-1 RA, glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist; HFpEF, heart failure with preserved ejection fracture; HTN, hypertension; IWB, internalized weight bias; MACE, major adverse cardiovascular events; MC4R, melanocortin 4 receptor; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, magnetic resonance imaging; ORCD, obesity-related complications and diseases; PCOS, polycystic ovary syndrome; POMC, proopiomelanocortin; OA, osteoarthritis; OSA, obstructive sleep apnea; SC, subcutaneous; T2D, type 2 diabetes; WC, waist circumference.

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Disclaimer: This document represents the official position of the American Association of Clinical Endocrinology on the subject matter at the time of publication. Subject matter experts who participated on the task force used their judgment and experience supported by relevant scientific evidence as available. Every effort was made to achieve consensus among the task force members. Consensus statements are meant to provide guidance, but they are not to be considered prescriptive for any individual patient and cannot replace the judgment of a clinician. We encourage health care professionals to use this information in conjunction with their best clinical judgement. The presented guidance may not be appropriate in all situations. Any decision(s) by health care professionals to apply this guidance provided in this consensus statement must be made in consideration of local resources and individual patient circumstances.

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obesity algorithm
obesity management
obesity medications

cost pharmacologic step therapy for ABCD, (10) medications for obesity: individualization of therapy, and (11) medications for obesity approved by the U.S. Food and Drug Administration.
Conclusions: This 2025 algorithm for the medical care of adults with obesity underscores that ABCD is a complex, chronic disease that necessitates long-term treatment and care. Emphasis is placed on optimizing health rather than just weight reduction and achieving clinical goals other than a singular focus on body mass index (ie, complication-centric care). Choice of interventions and intensity of treatment should be individualized, taking disease severity or stage into account. Equality of care and reducing weight bias and stigma through a biopsychosocial chronic care model are critical and included throughout this clinical guidance statement.

Introduction

The first AACE consensus statement on the management of obesity was published in 1997,[1] followed by position statements in 1998,[2] 2012,[3] and 2014[4] (for a new diagnosis of obesity as a chronic disease). In 2016, AACE published a guideline and algorithm for the comprehensive care of patients with obesity which were designed within the context of a chronic care model and diagnostic framework to align with the definition and pathophysiology of obesity as a chronic disease.[5] This was the first evidence-based obesity guideline to explicitly advocate a complication-centric approach to care. The 2016 clinical guidance supported mode and intensity of therapy to match disease severity based on complications and not on body mass index (BMI), emphasizing that BMI conveys no direct information regarding the impact of excess adiposity on an individual's health.[5,4] The 2016 guideline and algorithm added staging of obesity based on the risk, presence, and clinical severity of complications as the clinical component of the diagnosis. Anthropometric and clinical evaluations are then used to stage the severity of the disease which can guide goals and intensity of the complication-centric treatment plan.[6-8] In 2017, AACE published a position statement that proposed a diagnostic term to explicitly identify obesity as a chronic disease: adiposity-based chronic disease (ABCD).[9] The European Association for the Study of Obesity followed suit in 2019 with a position statement endorsing ABCD as a diagnostic term in line with their previous proposal to improve the *International Classification of Diseases* diagnostic criteria beyond BMI.[10]

ABCD refers to what is being treated (neurohormonal-driven dysregulation of energy balance leading to abnormalities in the mass, distribution, and function of adipose) and why the disease is treated (a chronic disease with complications that impair quality of life and confer morbidity and mortality). This diagnosis goes beyond that of obesity based on BMI. The international Lancet Commission on Obesity recently developed definitions of "preclinical" obesity to indicate a state of excess adiposity without obesity-related diseases or complications and "clinical" obesity to convey the presence of complications, defined as alterations in organ structure and/or function usually producing symptoms that arise because of the presence of excess adiposity per se.[11] The Lancet Commission regards obesity-related diseases as entities that are more common in obesity and share pathophysiology processes but require an additional pathophysiological contribution unrelated to the presence of excess adiposity. AACE views ABCD as an umbrella term that encompasses all aspects of the disease, from risk factors requiring primary prevention of obesity, to preclinical and clinical obesity, and all obesity-related complications and diseases (ORCD). Figure 1 shows the interrelationships between terms used by the Lancet Commission and the AACE obesity algorithm and the comprehensive nature of ABCD as a diagnostic term that comprises all aspects of the disease. Evidence-based interventions should be considered and available over the spectrum of ABCD—including obesity prevention, treatment of stage 1 obesity, and in people with stage 2 or 3 disease and ORCD—when needed to improve health. Operational definitions for the AACE algorithm update are contained in Box A.

Obesity is a neurohormonal metabolic disease that is chronic and heterogenous.[11] The unifying phenotypic feature of obesity is excess or abnormally distributed adipose tissue with the potential to impair health.[12-15] The physiology of energy homeostasis involves the coordinated interaction of multiple neuroendocrine satiety factors arising peripherally and acting on feeding centers in the brain.[15] Obesity results from an interplay between complex genetic and environmental factors that produce dysregulated energy homeostasis involving these satiety factors and central neuroregulation, resulting in excess accumulation of adipose tissue.[16-19] Dysregulated secretion of satiety factors and their actions in the hypothalamus, brain stem, mesolimbic system, and other centers generate and sustain a state of excess adiposity. Observations are consistent with the model that the body defends its fat mass (fuel stores) around an equilibrium based on interactions involving genetics, behavior, biological factors, and our current obesogenic environment.[19] Thus, body fat is biologically defended, which explains why weight regain frequently occurs after achieving weight reduction by behavioral efforts alone.[20-22] With the exception of orlistat and cellulose hydrogels, all other obesity medications target these central mechanisms that generate excess adiposity and the maladaptive responses driving weight regain after weight loss.[23]

With the addition of newer second-generation obesity medications and their enhanced ability to optimize the health of people with ABCD by preventing and treating complications, this 2025 AACE algorithm for the evaluation and treatment of adults with obesity/ABCD builds on the 2016 AACE obesity algorithm.[5] This algorithm update expands on the Lancet Commission staging framework for obesity[11] and aligns with the international joint consensus statement on obesity stigma,[24] the European Association for the Study of Obesity new framework for the diagnosis, staging, and management of obesity,[25] and the AACE consensus statement on internalized weight bias, stigma, and mental health[26] as key components of obesity care. Furthermore, the algorithm for the first time establishes hierarchies of preferred medications for the complication-centric care of people with specific ORCD based on clinical trial evidence for the amelioration of specified cardiometabolic and biomechanical outcomes.[27] As in the 2023 AACE type 2 diabetes algorithm and 2023 AACE consensus statement on obesity stigma,[26,28] this consensus statement on treatment of those with ABCD centers on the principles of individualized and whole-person health while de-emphasizing weight reduction alone.[9,26]

The first algorithm (Algorithm 1) includes 9 principles developed by uniform consensus for person-centered care of adults with obesity/ABCD. These principles constitute optimal care for people with ABCD. Conversely, management plans that do not feature one or more of these principles are considered suboptimal in the care of these individuals.

The principles in Algorithm 1 direct a care model for people with ABCD consistent with the overall AACE obesity algorithm. Essential to person-centered care of those with ABCD is a thorough diagnostic evaluation followed by the development and implementation of a personalized treatment plan with individualized health goals that consider weight reduction in the context of prevention, mitigation, and treatment of ORCD. Care should be delivered in an empathetic and culturally sensitive manner, and social determinants of health should be considered in the development of an individualized care plan. Algorithms 2 through 5 show the complication-centric care model and include: (1) screening and diagnosis involving both anthropometric and clinical components, which necessitates clinical evaluation and basic laboratory testing (Algorithm 2); (2) criteria for the anthropometric component of the diagnosis using ethnic-specific cutoffs for BMI and adipose distribution (Algorithm 3); (3) the clinical component of the diagnosis and the staging of clinical severity based upon ABCD ORCD (Algorithm 4); and (4) the use of disease staging in developing and implementing an individualized holistic treatment plan, establishing the clinical goals of therapy through shared decision making, and following up with appropriate treatment modifications based upon both the clinical response to therapy and a longer-term strategy for health maintenance (Algorithm 5).

The diagnosis of ABCD involves both an anthropometric component to assess adiposity and a clinical component to determine disease severity and the impact of adiposity on health and quality of life.

Anthropometric Component

BMI is appropriate for screening; however, excess adiposity must be confirmed by inspection and physical examination. Assess the mass and distribution of body fat using BMI and waist-to-height ratio. The measurement of waist-to-height ratio involves the measurement of waist circumference (WC), and BMI and WC should be interpreted considering age, sex, and ethnicity. Additional modalities such as dual-energy x-ray absorptiometry (DXA) or impedance plethysmography may be used to assess body composition and/or distribution of adipose tissue when the anthropometric measurements and examination are discordant or do not match the clinical findings. BMI measurements should be interpreted clinically, taking into account muscle mass, edema, soft tissue masses, and any contributions to body weight other than adipose tissue. Special consideration should be given to the presence of sarcopenia and sarcopenic obesity in patients who are at risk.

Clinical Component

Stage the clinical severity of ABCD based on risk, presence, and severity of ORCD. Staging requires a thorough weight and medical history, review of systems, physical examination, key biochemical data, and possibly imaging or other diagnostic testing. Clinical evaluation should include an assessment for potential monogenic or syndromic causes, weight-gain promoting medications, endocrinopathies, psychosocial factors, and/or other potential contributors.

Highlights for *Endocrine Practice*

AACE Consensus Statement: Algorithm for the Evaluation and Treatment of Adults with Obesity/Adiposity-Based Chronic Disease – 2025 Update

Clinical Relevance

This updated algorithm provides evidence-based visual guidance in graphic algorithms and tables as well as a narrative summary of evidence to assist health care professionals and adults with obesity and adiposity-based chronic disease (ABCD) in shared decision making to improve care and achieve health goals.

Clinical Practice Points

- Underscores that ABCD is a complex, chronic disease that necessitates long-term treatment and care.
- Emphasizes the importance of treating an adult with obesity/ABCD to improve health and target clinical goals rather than just focusing on weight reduction or body mass index.
- Incorporates newer and more effective second-generation medications achieving 15% or more average weight loss with associated clinical benefits in clinical trials in addition to therapy for monogenic and syndromic obesity.
- Emphasizes stage and severity of ABCD to guide and individualize choice and intensity of interventions such as lifestyle, pharmacotherapy, and surgical interventions, including hierarchies of preferred medications for specific obesity-related complications and diseases.
- Deemphasizes "weight," per se, but includes weight-loss targets expected to achieve the prioritized clinical goals.
- Considers equality of care and reduction of weight bias and stigma through a biopsychosocial chronic care model critical and are included throughout this clinical guidance statement.

Screening and Assessment

As indicated in the care model (Algorithm 2), the anthropometric component of diagnosis begins with screening using BMI (Algorithm 3). A physical examination is needed, however, to confirm the presence of excess adiposity. As BMI does not inform about the distribution of adiposity, WC and waist-to-height ratio are assessed as indicators of central body adiposity which reflects cardiometabolic health. The assessment of adipose tissue mass and distribution and body composition may require additional methodologies beyond a physical examination. Assessment of body composition using DXA scanning, bioelectric impedance, 3-dimensional photoimaging, or magnetic resonance imaging (MRI) should be used to refine measurements of adipose tissue mass and distribution when needed. DXA or MRI can be used to assess lean body mass or muscle volume and bone mass/mineral density in people who are at high risk or who are experiencing symptoms or outcomes of sarcopenia and osteopenia.

BMI

After physical confirmation of excess adiposity, use BMI to classify individuals into categories of overweight (BMI 25.0-29.9 kg/m^2), class I obesity (BMI $\geq$30.0-34.9 kg/m^2), class II obesity

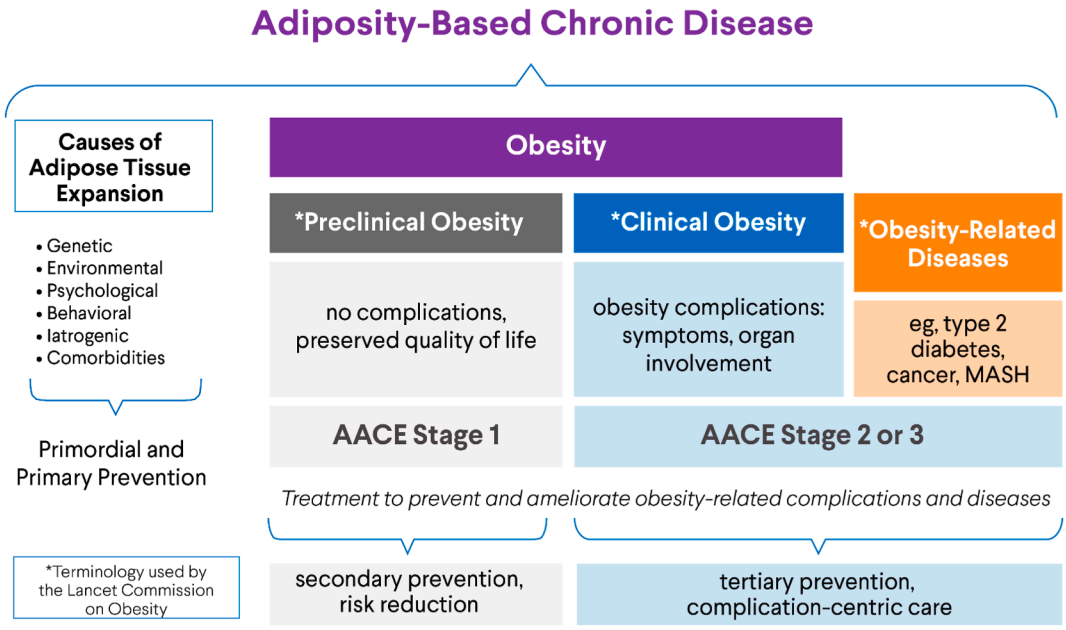


Fig. 1. Adiposity-based chronic disease and relationships involving the AACE obesity algorithm and terms used by the Lancet Commission on Obesity. *MASH* = metabolic dysfunction-associated steatohepatitis.

(BMI ≥35.0-39.9 kg/m^2), or class III obesity (BMI ≥40.0 kg/m^2). These cutoffs are generally recommended by the World Health Organizatoin[29] and are operative in North and South America, Europe, sub-Saharan Africa, the Middle East, and Australia. In the Asia-Pacific region, lower cutoff values for overweight and obesity are recognized because of the greater health risk at lower levels of BMI in these populations.[30-34] For example, in India,[30] South Korea,[35] and Japan,[36] a cutoff point of ≥25.0 kg/m^2 is indicative of obesity and 23.0 kg/m^2 to 24.9 kg/m^2 is the range for overweight. In China, BMI ≥28.0 kg/m^2 represents obesity and 24.0 kg/m^2 to 27.9 kg/m^2 overweight.[37] Other research suggests that these cut-off values may need to be modified for individuals from Asian-Pacific regions who have been living in Western societies.[31] In South and Central American adults, a cutoff for obesity of 27.2 kg/m^2 has been recommended in older adults.[38] In any case, clinical interpretation of BMI includes the need to confirm that elevated BMI values represent excess adiposity after considering an individual's age, sex, muscularity, fluid status (hydration, edema, third space fluid collection), and the presence of sarcopenia (sarcopenic obesity can refer to people with low BMI but presence of adiposity) and osteopenia in those who are at risk.[5,11,14,39,40] It is important to consider that BMI may underestimate adiposity and

Box A
Definitions of Terms

Obesity is a state of excessive adiposity with or without abnormal distribution or function of adipose tissue.

Adiposity-based chronic disease (ABCD) is a diagnostic term that signifies a heterogeneous, progressive, chronic disease that arises due to abnormal neuroendocrine control of energy balance and caloric intake leading to excess or abnormal adiposity, which can give rise to obesity-related complications and diseases that confer morbidity and mortality and/or impair quality of life. ABCD encompasses primary risk factors, disease pathophysiology together with prevention and treatment at the primordial, primary, secondary, and tertiary phases of progression, and includes all disease stages (1, 2, and 3) based on the presence and severity of obesity-related complications and diseases. Treatment is required at all stages to prevent, ameliorate, or reverse obesity-related complications and diseases.

Obesity-related complications and diseases (ORCD) is a term used in this algorithm to include both obesity complications and obesity-related diseases as defined below. The presence of ORCD warrants designation of ABCD as stage 2 (if mild to moderate) or stage 3 (if severe). AACE prefers this umbrella term because treatment can be warranted and effective irrespective of the pathophysiological differentiation between complications and related diseases.

Obesity complications* are the clinical consequences caused by progressive organ dysfunction or end-organ damage induced by excess adiposity. These complications arise due to structural and/or functional changes in tissues or organs, often producing symptoms, and are integrally related to effects of excess adiposity. The presence of complications warrants AACE staging as 2 or 3 ABCD based on severity.

Obesity-related diseases* meet 3 criteria: (1) they are commonly associated with obesity and/or more prevalent in people with obesity than in the general population, (2) they are pathophysiologic processes in obesity that contribute to overall pathogenesis, and (3) they involve the contribution of a pathophysiological process unrelated to obesity per se (eg, type 2 diabetes, which requires an insulin secretory defect, or certain forms of cancer that may require the expression of an oncogene). The presence of obesity-related diseases warrants AACE staging as 2 or 3 ABCD based on severity.

Comorbidities* represent diseases or conditions that incidentally coexist with obesity but are not caused or facilitated by obesity.

Preclinical obesity* is the state of obesity without any ORCD. These patients are at risk of complications and exist within the spectrum of ABCD as disease stage 1, which requires treatment to prevent ORCD.

Clinical obesity* applies to patients who have developed demonstrable or symptomatic complications as defined above. Note that while the distinction between ORCD is relevant to pathophysiology, AACE does not make this distinction in the clinical staging of ABCD (stage 2 or 3) because both can be treated effectively via weight-loss therapy.

* The authors view these definitions as consistent with those advanced by the 2025 Lancet Commission on Obesity.{Rubino, 2025 #4682}[11]

PRINCIPLES OF PERSON-CENTERED AND COMPLICATION-CENTRIC MANAGEMENT OF OBESITY/ABCD

1.	Emphasize whole-person health and de-emphasize BMI and weight-centric approaches in the treatment of individuals with obesity/ABCD.
2.	People with obesity/ABCD should be evaluated by an empathetic trained health care professional to include both the anthropometric and clinical components of the diagnosis and should be followed long-term by a health care professional who will manage weight loss and assure that treatment goals for optimizing health are achieved.
3.	For the anthropometric component of the diagnosis, obesity is evaluated using BMI with clinical confirmation of excess adiposity, waist circumference, waist-to-height ratio, and assessment of body composition when clinically needed.
4.	For the clinical component of the diagnosis and disease staging of ABCD, assess the risk, presence, and severity of ORCD. Include internalized weight bias and impact of stigmatization as part of clinical staging.
5.	Involve the individual in shared decision-making to determine personalized health goals while targeting sufficient weight loss to achieve clinical treatment goals for health.
6.	Develop treatment plans involving lifestyle, pharmacologic, and surgical options using an individualized approach that considers complications and their severity, patient preferences, social determinants of health, psychological disorders, and access to care.
7.	The goals of therapy are to improve health and the quality of life by preventing or treating ORCD, not solely defined by the loss of a specific amount of weight.
8.	Therapy, beyond behavioral/lifestyle alone, should be considered at all stages of ABCD (stages 1, 2, or 3) when needed to improve the health of patients.
9.	Implement a plan for long-term follow-up with each patient to monitor maintenance of healthy goals, clinical outcomes, and treatment modifications as needed.

Abbreviations: **ABCD**, adiposity-based chronic disease; **BMI**, body mass index; **ORCD**, obesity-related complications and diseases

Algorithm Figure 1 - Guiding Principles

Algorithm 1. Principles of person-centered and complication-centric management of obesity/adiposity-based chronic disease.

risk among frail or elderly individuals and overestimate adiposity in muscular athletes.

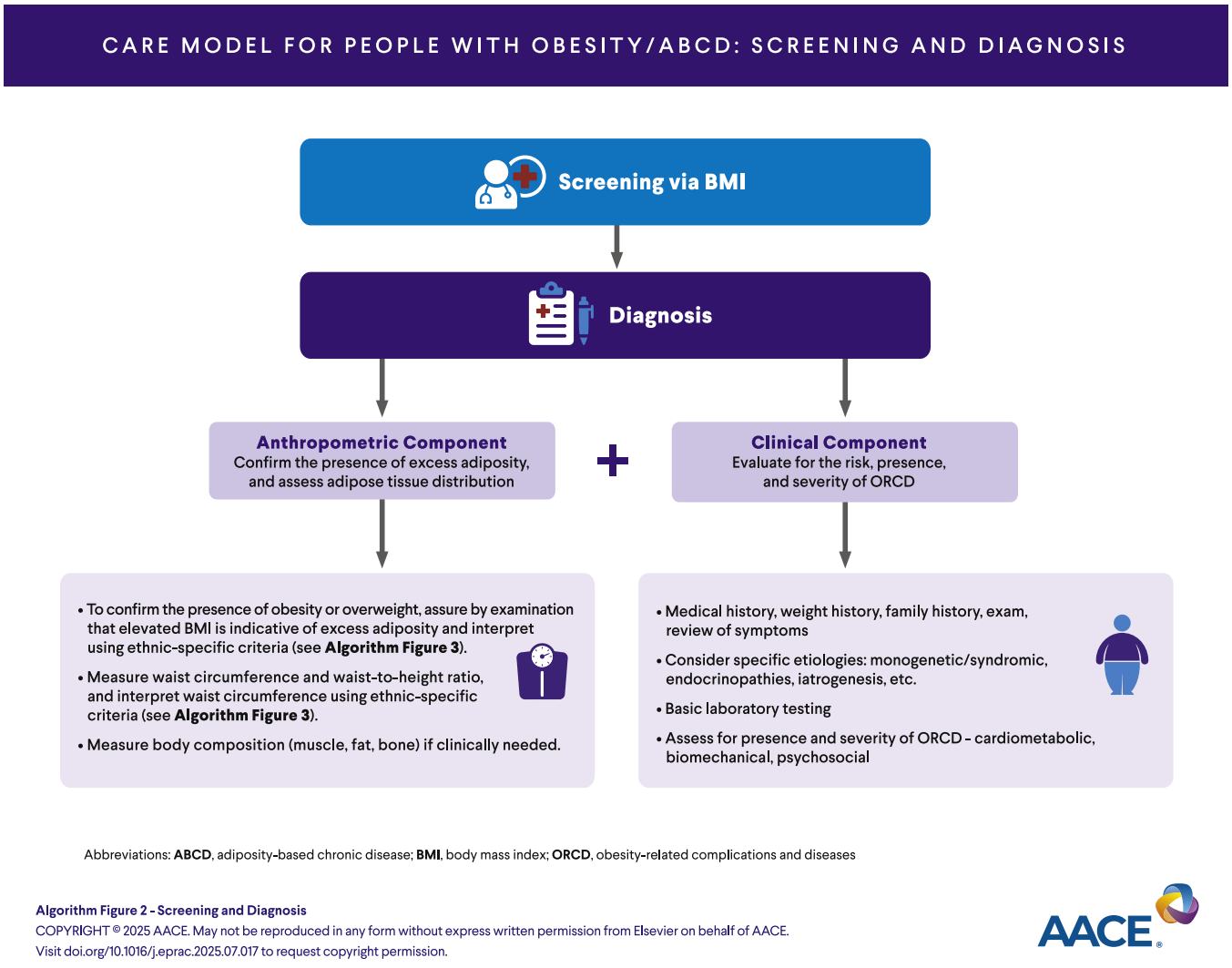
WC and Waist-to-Height Ratio

WC and waist-to-height ratio are valuable and practical measurements for evaluating the distribution of adipose tissue.[41,42] In the United States and Canada, WC cutoff values of ≥102 cm (≥40 in) in men and ≥88 cm (≥34.5 in) in women have been suggested to indicate increased cardiometabolic risk. In Europe, sub-Saharan African, and the Middle East, the recommended cutoffs are ≥94 cm (≥37 in) in men and ≥80 cm (≥31.5 in) in women, and in East and South Asian populations and in South and Central America, these cutoffs are generally considered to be ≥90 cm (≥35 in) in men and ≥80 cm (≥31.5 in) in women as indicative of abdominal obesity. Evidence indicates that waist-to-height ratio is a superior indicator of cardiovascular disease (CVD) risk compared with WC.[33] The waist-to-height threshold value of ≥0.5 is indicative of increased risk in both males and females and across ethnic populations, and has been advocated by professional societies and various organizations.[25,33,43] Additional measurements of adiposity, such as bioelectric impedance, air/water displacement plethysmography, 3-dimensional imaging, or DXA, may be useful if BMI and physical examination results are equivocal, inconclusive, or require further clarification. Although more research is needed to define precise cutoffs, body fat percentages above 25% in men and 32% in women may indicate obesity-related cardiometabolic risk.[44-46] These methods are particularly helpful for evaluating frail individuals with suspected sarcopenic obesity or patients with low BMI but signs of obesity-related disease.[47] They are also valuable for monitoring fat-free mass and skeletal muscle changes during weight loss induced by effective pharmacotherapy or bariatric surgery.[48] However, at this time, the clinical utility of these measures is limited by clinical interpretation, availability, and cost, and outcome data for validated reference ranges are critically needed.[49-55]

After screening and anthropometric assessment, people with obesity should receive a comprehensive evaluation for ORCD that includes an obesity-focused history, physical examination, and key laboratory tests.

Staging

Staging the clinical severity of ABCD is based upon the presence of ORCD, which guide therapy intensity. As outlined in Algorithm 4 and Table 1, AACE recommends a simple and clinically intuitive

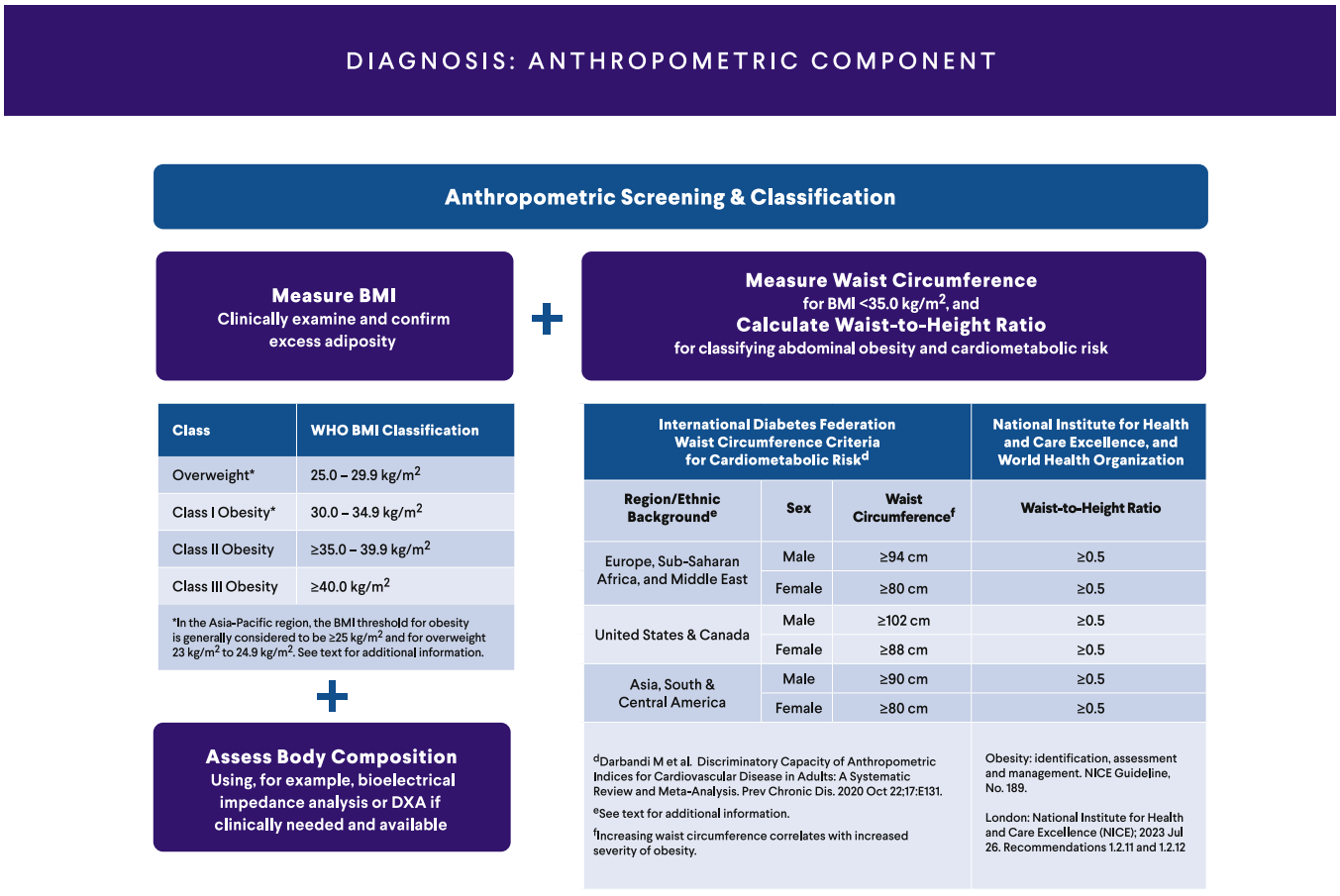


Algorithm 2. Care model for people with obesity/adiposity-based chronic disease: screening and diagnosis.

staging paradigm. In stage 1, a person has no ORCD. Individuals in stage 1, however, are at risk of developing ORCD and should be considered for therapeutic interventions. The intent of treatment in stage 1 is to prevent further weight gain and the emergence of ORCD. Stage 2 indicates the presence of ORCD that are mild to moderate in intensity. In stage 3, a person has 1 or more severe ORCD. The intent of treatment in stages 2 and 3 of disease is to restore health by ameliorating or reversing ORCD to a targeted level of improvement. The degree of weight loss needed to achieve these clinical goals will vary as a function of an individual's specific ORCD and their severity.

With reference to terminology recommended by the Lancet Commission on Obesity,[11] stage 1 is analogous to "preclinical" obesity from the perspective of no identifiable complications while "clinical" obesity comprises people with stage 2 or 3 disease who have obesity-related diseases or complications. Of note, stage 1 or preclinical obesity does not imply that treatment is not warranted. Importantly, stage 1 or preclinical obesity can place individuals at high risk of future ORCD, and they should be offered preventive treatment in the shared decision-making process. Notably, stage 1 carries the risk of progression to complications that define clinical obesity[56] as well as an increased risk of obesity-related diseases such as type 2 diabetes (T2D) and obesity-related cancers (eg, colon, esophageal, thyroid, myeloma, non-Hodgkin lymphoma, endometrial, and postmenopausal breast cancers).[57] AACE regards stage 1 or preclinical obesity as part of the spectrum of ABCD (Fig. 1).

Clinical staging systems have shown superiority in predicting health outcomes, including mortality, to a greater degree than anthropometric measures alone.[6,8,9,58-63] The AACE staging system for ABCD assesses the presence and severity of multiple key ORCD that can be prevented or treated via weight loss (Fig. 2) including hypertension (HTN), dyslipidemia, dysglycemia from prediabetes and risk of T2D, overt diabetes, obstructive sleep apnea (OSA),[64] metabolic dysfunction–associated steatotic liver disease (MASLD), polycystic ovary syndrome (PCOS), osteoarthritis (OA),[65] atherosclerotic cardiovascular disease, heart failure with preserved ejection fracture (HFpEF), chronic kidney disease (CKD), and many others.[5] The degree of severity for these complications is based on clinical judgment, incorporating findings from the physical examination, laboratory testing, and/or other diagnostic procedures, as well as a person's symptomatology, in ways that apply to each individual complication.



Abbreviations: **BMI**, body mass index; **DXA**, dual-energy X-ray absorptiometry; **WHO**, World Health Organization

Algorithm Figure 3 - Diagnosis: Anthropometric Component

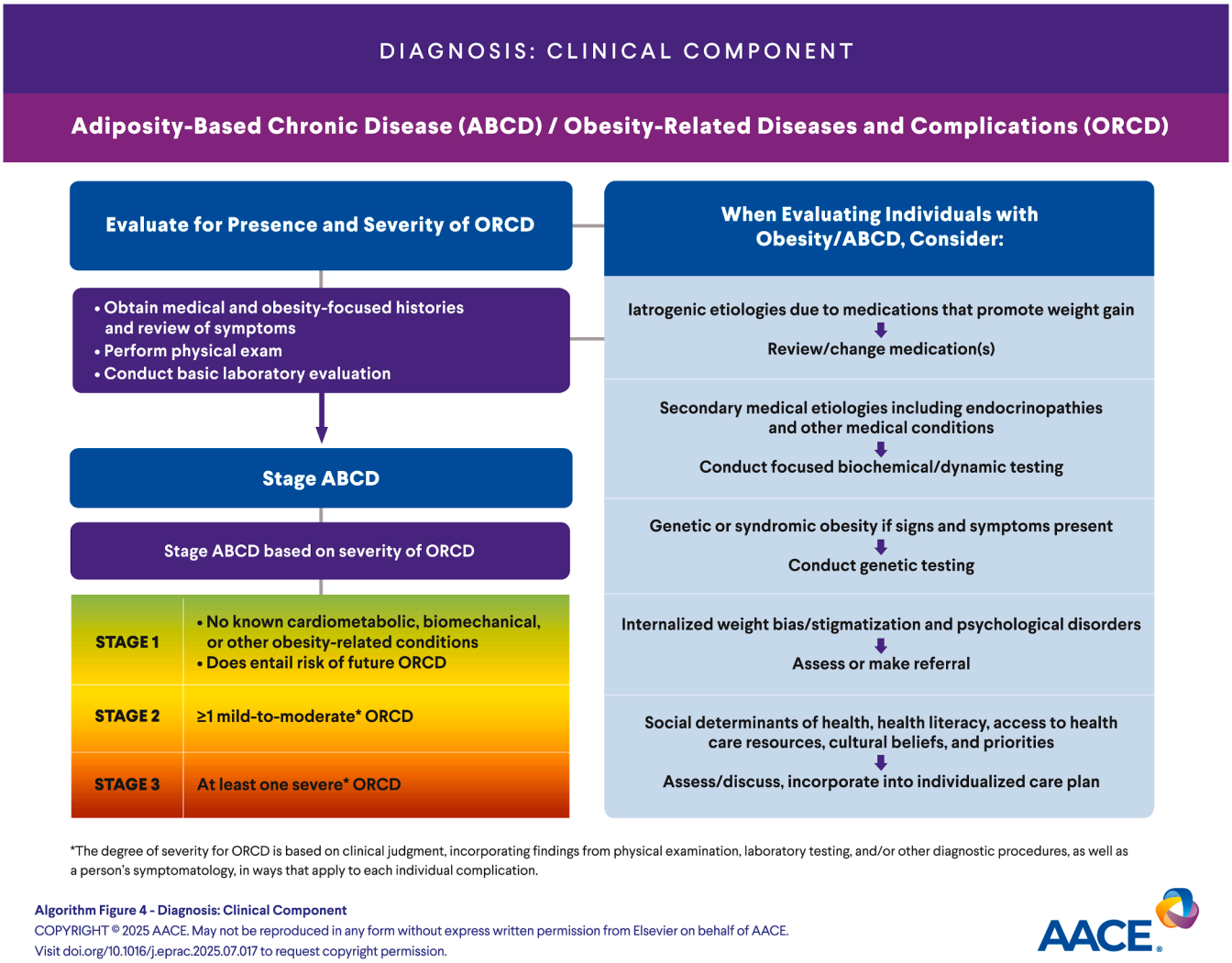
Algorithm 3. Diagnosis: anthropometric component.

Clinical Evaluation

People with ABCD should be seen by a trained health care professional who conducts a clinical evaluation with an orientation to complication-centric care, and with the capability to assure long-term care either personally or through referral. As shown in Algorithm 4 and Figure 3, the evaluation should include a medical and weight-related history that considers previous attempts to lose weight and involves a physical examination, an ABCD-focused review of systems, a family and social history, a review of medications, and laboratory testing as indicated to screen for ORCD. Laboratory tests specifically recommended for assessing cardiometabolic risk include serum creatinine (for estimated glomerular filtration rate), lipid panel, fasting blood glucose, hemoglobin A1c (A1C), and aspartate aminotransferase, alanine aminotransferase, and platelet count (for calculation of fibrosis-4).[66-69] Other laboratory tests can be obtained to assess general health, including complete blood cell count, electrolytes/comprehensive metabolic panel, electrocardiogram, and urine analysis. Further testing may be needed, only when clinically indicated, based upon history, examination, review of systems, and initial laboratory results to assess the presence and severity of specific ORCD (eg, oral glucose tolerance testing,[70] thyroid-stimulating hormone, apolipoprotein B-100, cortisol, knee radiographs, hepatic elastography, polysomnography, or genetic testing as well as psychology, sociology, or nutrition referrals).

Figure 2 lists examples of ORCD that may potentially be identified in the course of the clinical evaluation of people with ABCD. AACE stage 2 (mild-moderate) and stage 3 (severe) are equally applicable to both obesity-related diseases and obesity complications as defined by the Lancet Commission on Obesity (see definitions in Box A). While this differentiation is of conceptual and pathophysiological interest, operationally this does not have practical import in the AACE obesity algorithm, since both ORCD can warrant weight-loss therapy based on the stage of severity. People with stage 1 obesity also merit treatment based on clinical judgment and the risk of disease progression. Therapy, beyond behavioral/lifestyle alone, should be considered at all stages of ABCD when needed to improve patient health, including treatment of stage 1 obesity, and in people with stage 2 or 3 disease.

In Figure 2, ABCD stages 2 and 3 in the AACE obesity algorithm do not differentiate between ORCD, since both complications and diseases can be ameliorated by weight-loss therapy. Also note that the



Algorithm 4. Diagnosis: clinical component.

distinction between ORCD as defined by the Lancet Commission can become blurred, and complications may be considered to be more consistent with related diseases and vice versa in some individuals depending on the pathophysiological contributions of obesity.

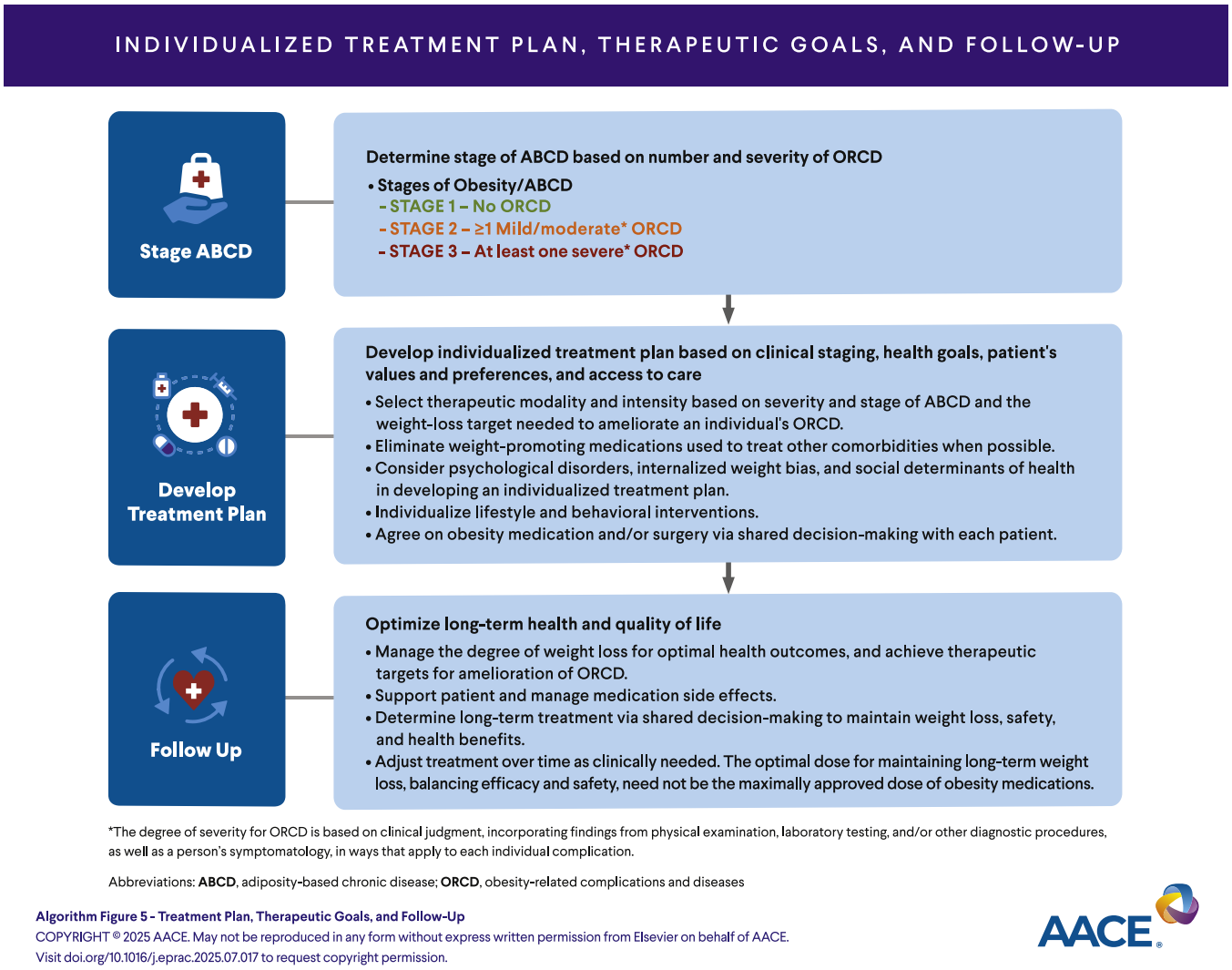
Personalized Therapeutic Care Plan

The development of an individualized care plan begins with the staging of ABCD. The modality and intensity of interventions should be proportional to the clinical stage of ABCD, reflecting the risk, presence, and severity of ORCD. Select the modality and intensity of treatment based on the degree of weight loss and/or other beneficial aspects of treatment needed to prevent or ameliorate specific ORCD. Interventions may be adjusted if there is insufficient weight loss to achieve targets for improvement in quality of life and adequate resolution of ORCD impairing health and conferring morbidity and mortality.

Each patient should be engaged in developing a personalized care plan. Each person's values, preferences, and access to care should be considered in establishing their treatment goals, weight-reduction targets, and selection of lifestyle intervention, obesity medications, and/or bariatric surgery. The goals of therapy for each person with ABCD are to achieve reduction, stabilization, and maintenance of weight loss while preventing, mitigating, and treating ORCD and emphasizing overall health outcomes and quality of life.

To support the development of individualized care plans, it is important to assess:

1. History of early childhood obesity (onset before the age of 5 years) and/or early hyperphagia because this should prompt genetic testing with potential counseling for specific monogenic or syndromic etiologies of obesity[71,72]
2. Secondary etiologies or iatrogenic contributors such as weight-gain promoting medications, endocrinopathies, disability/immobility, and other medical conditions
3. Use of weight-promoting medications used to treat comorbidities and complications to the extent possible (eg, insulin, sulfonylureas, certain antipsychotics and antidepressants, corticosteroids)[73]
4. The impact of internalized weight bias and stigmatization on quality of life and the extent to which this could compromise a person's engagement in their therapeutic plan[24,26]
5. The presence of psychological disorders, such as depression, anxiety, and disordered eating, which may require intervention
6. Social determinants of health, health literacy, and access to health care and resources



Algorithm 5. Individualized treatment plan, therapeutic goals, and follow-up.

7. A person's reasons for seeking care, treatment goals, and individual and cultural preferences for diet and physical activity

Long-Term Follow-Up

People with ABCD have a lifelong disease and require long-term follow-up. The maintenance of weight loss is critical for sustaining health benefits. This is difficult over the long term because of the pathophysiology of metabolic adaptation with central and peripheral mechanisms driving weight regain, which is predictably associated with exacerbation or recurrence of ORCD. Individual weight maintenance plans must be personalized to address the environmental, behavioral, and physiological mechanisms through continued monitoring, lifestyle support, medical therapy, and follow-up to mitigate adverse health consequences. Modifications in lifestyle interventions and adjustments in obesity medications may be warranted, and this includes patients who have had bariatric surgery who often experience weight regain over time. The therapeutic approach to early weight loss may be different than that used to maintain weight loss over an extended period. Different or lower doses of obesity medications that are well-tolerated, accessible, and safe, particularly with respect to muscle and bone loss, may be advantageous. Further research and medication development is needed to inform optimal strategies for long-term effective and safe therapy.

Individualization of Weight-Loss Targets

Algorithm 6 shows the range of therapeutic weight-reduction goals generally needed to achieve desired clinical health outcomes in complication-centric care. The weight-reduction target is based on the degree of weight loss that predictably ameliorates ORCD present in individual patients that are remediable in response to weight loss. As shown in Algorithm 6 and Table 2, treatment of different ORCD requires different degrees of weight loss. Percent weight reduction serves as a "biomarker" that can be targeted to assure sufficient weight loss required for predictable improvements in various ORCD as monitored by clinical findings, laboratory data (eg, blood pressure [BP], A1C, lipids, functional measures, etc.), and symptomatology reported by a patient.[27] Weight reduction and response to therapy are assessed both anthropometrically and clinically to inform the next steps in therapy. A person's health guides the shared clinical decision-making discussion, including intensification or de-escalation of therapeutic

Table 1
Staging of Adiposity-Based Chronic Disease and the Incorporation of Bias and Stigmatization, Psychological Health, and Social Determinants of Health in the Assessment of Disease Severity and Individualized Care Plans

Stage No.	Description	Across All Stages
1	No known obesity-related cardiometabolic, biomechanical, or other psychological disease. Associated with increased risk of developing obesity complications and related diseases which may be mitigated by weight reduction	Internalized weight bias and stigmatization, psychological conditions, and social determinants of health should be assessed in all stages for the degree to which they impact quality of life or treatment and incorporated into individualized care plans
2	1 or more mild to moderate obesity-related diseases	
3	At least 1 severe, or multiple, obesity-related disease and/or complications	

Adapted from Garvey et al[5] and Nadolsky et al.[26]

interventions. The task force proposes categories of weight reduction correlating with clinical benefits as the following: (1) ≤5% indicates an incomplete response, because this is often insufficient to treat complications; (2) >5% to <15% indicates a good response, which may or may not be optimal for certain complications; and (3) ≥15% indicates an excellent response, because this is sufficient to treat or prevent a broad array of ORCD. Importantly, however, for any given intervention, the individual clinical response regarding improvements in obesity complications and the degree of weight loss are variable.[74] The goal is always to achieve sufficient weight loss needed for clinical improvement in each person.[27,75]

The early response to obesity medications should be assessed after about 3 months on the treatment dose. If the treatment has not resulted in at least a 5% weight reduction, longer-term efficacy will likely be insufficient, and this calls for a change in therapeutic approach whether this involves an intensification of lifestyle therapy, a different obesity medication, or a combination of obesity medications.[140-145] People who achieve weight reduction of ≥5% should continue with the current treatment. With ongoing follow-up, the need to intensify therapy may become evident if targets for improvement in ORCD are not being achieved.[143-145] The intensity of therapy both at initiation of treatment and with ongoing follow-up should correspond with the severity or stage of ABCD (Algorithm 6). Patients who experience a weight reduction of ≥15% (the level produced on average by second-generation obesity medications) will have achieved a response to therapy that predictably prevents or improves a broad array of ORCD[25,27] (Table 2 and Algorithm 6).

When choosing an obesity medication that will achieve an individualized weight-reduction target, the relative efficacy for weight loss should be considered. This is made problematic by the lack of head-to-head comparison studies. However, in phase III trials, the average weight loss with first-generation medications approved for chronic therapy on or before 2014 is <10%, including orlistat, naltrexone/bupropion, liraglutide, and phentermine/topiramate. Of these medications, phentermine/topiramate appears to be the most effective with average weight loss approaching 10%. Second-generation medications such as semaglutide and tirzepatide achieve on average of ≥15% weight loss in phase III trials.

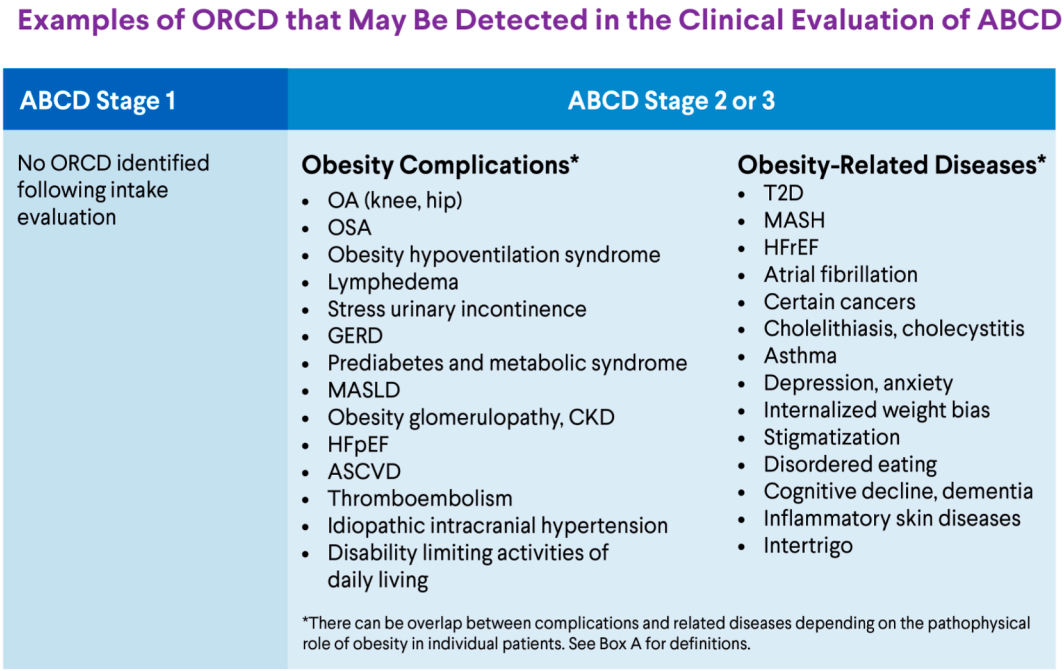


Fig. 2. Examples of ORCD that may be detected in the clinical evaluation of ABCD. Note that ABCD stages 2 and 3 in the AACE obesity algorithm do not differentiate between obesity complications and related diseases since both can be ameliorated by weight-loss therapy. *ABCD* = adiposity-based chronic disease; *ASCVD* = atherosclerotic cardiovascular disease; *CKD* = chronic kidney disease; *GERD* = gastroesophageal reflux disease; *HFpEF* = heart failure with preserved ejection fraction; *HFrEF* = heart failure with reduced ejection fraction; *MASH* = metabolic dysfunction-associated steatohepatitis; *MASLD* = metabolic dysfunction-associated steatotic liver disease; *OA* = osteoarthritis; *ORCD* = obesity-related complications and diseases; *OSA* = obstructive sleep apnea; *T2D* = type 2 diabetes.

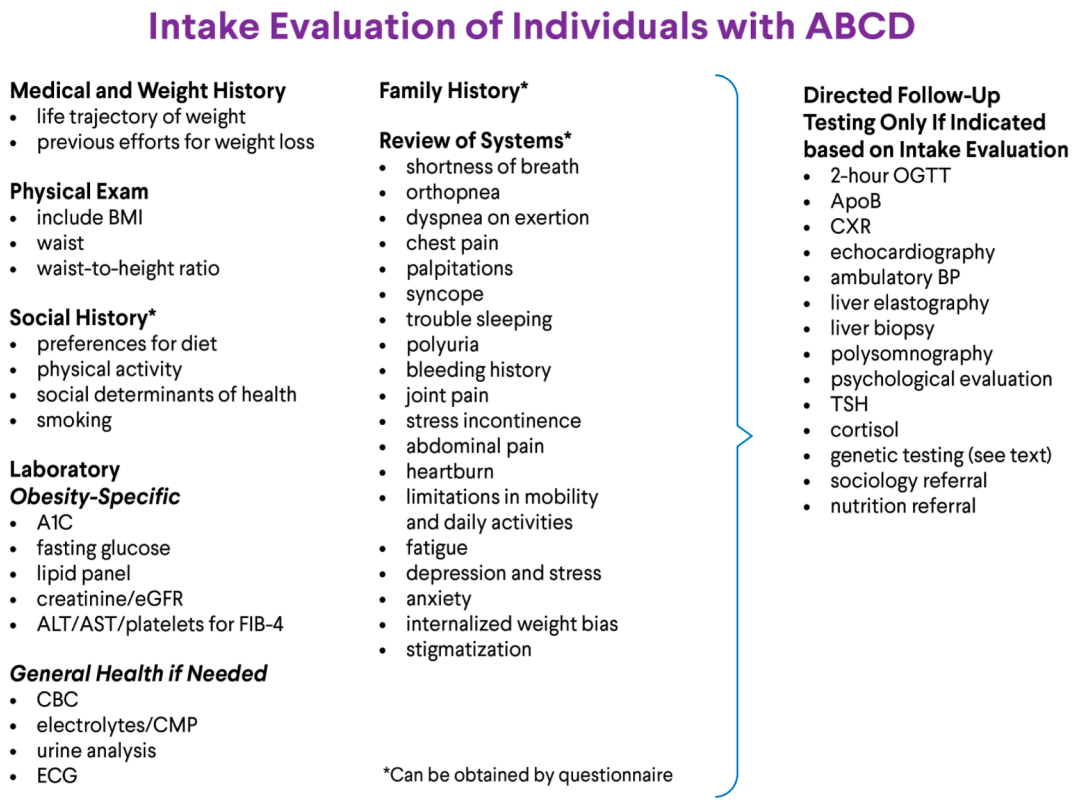


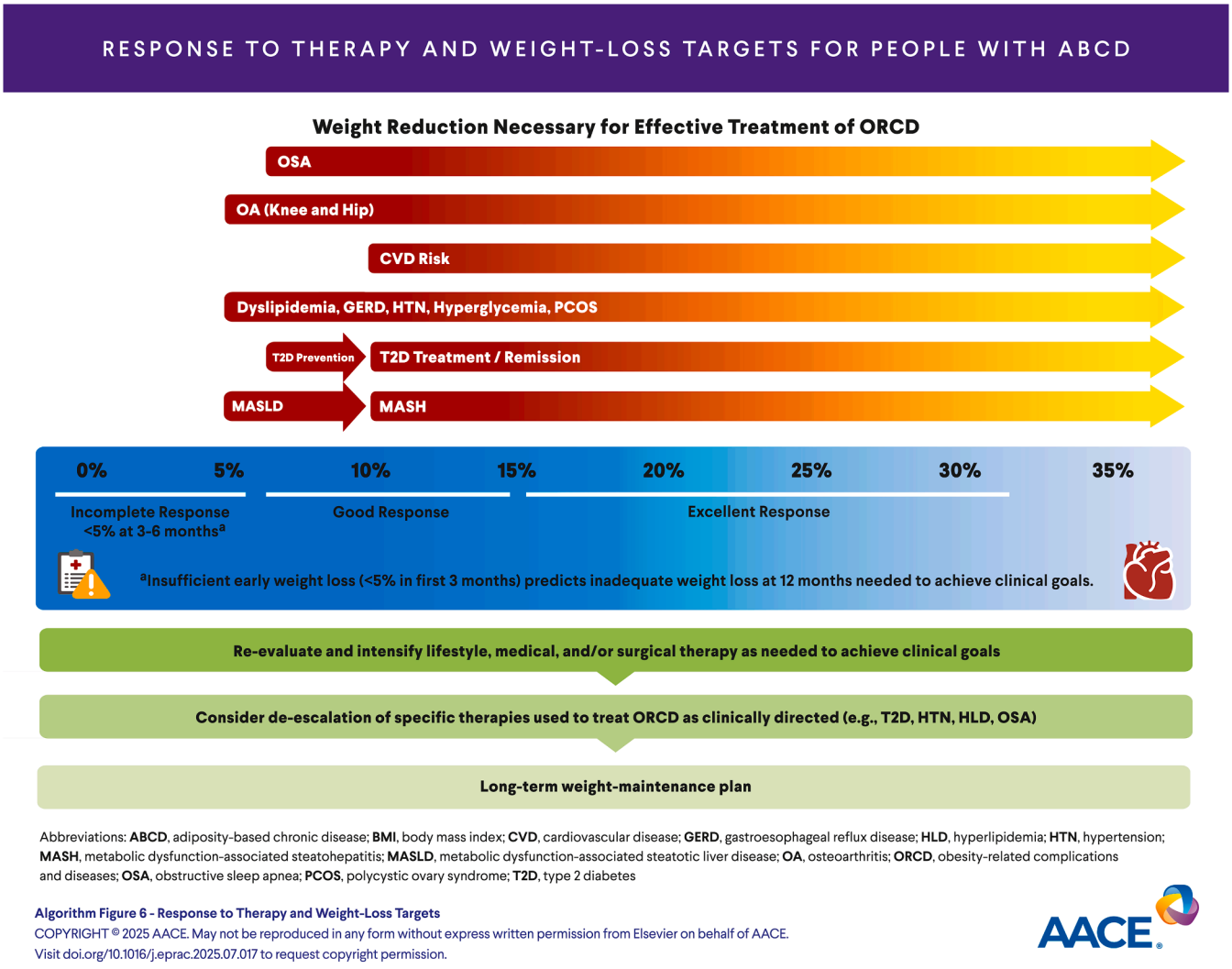
Fig. 3. Intake evaluation of individuals with ABCD. *A1C* = hemoglobin A1C; *ABCD* = adiposity-based chronic disease; *ALT* = alanine transaminase; *ApoB* = apolipoprotein B; *AST* = aspartate aminotransferase; *BMI* = body mass index; *BP* = blood pressure; *CBC* = complete blood cell count; *CMP* = comprehensive metabolic panel; *CXR* = chest radiography; *ECG* = electrocardiogram; *eGFR* = estimated glomerular filtration rate; *FIB-4* = fibrosis 4; *OGTT* = oral glucose tolerance test; *TSH* = thyroid-stimulating hormone.

Setmelanotide produces this degree of weight loss in individuals with certain forms of monogenic obesity. In addition, evidence can now support hierarchies of preferred medications for complication-centric care based on the presence of specific ORCD, as discussed in Algorithm 8. Maintaining weight reduction is crucial for preserving the health benefits of weight loss. Worsening ORCD accompany weight regain. De-escalation of specific therapies for ORCD (eg, medications for T2D, HTN, and hyperlipidemia) may begin after a modest reduction of initial weight and, thus, an individual's response must be monitored closely and medications adjusted as needed.[83,146-148]

Metabolic and Bariatric Surgeries

Metabolic and bariatric surgeries, such as surgical sleeve gastrectomy, Roux-en-Y gastric bypass, and one anastomosis gastric bypass have been well established as highly efficacious treatment modalities for reducing weight and achieving clinical benefits for individuals with ABCD, especially those with BMI $\geq$40.0 kg/m^2 class 3 obesity or class 2 obesity with ORCD. Currently, the foremost procedures are surgical sleeve gastrectomy and Roux-en-Y gastric bypass (around 90% of operations globally), with each having well-studied mid- and long-term safety data in addition to efficacy outcomes.[149] Other operations performed include biliopancreatic diversion with duodenal switch, one anastomosis gastric bypass, and adjustable gastric banding, though the suboptimal long-term efficacy of adjustable gastric banding has significantly diminished its use. Several bariatric procedures are now usually performed via minimally invasive surgical approaches (laparoscopic or robotic-assisted). Other endoscopic therapies that are short term, such as intragastric balloons, can be less efficacious and lacking in evidence for long-term benefits at the present time. Nevertheless, endoscopic devices may be considered and could represent effective adjunctive therapy in combination with obesity medications.

A BMI of $\geq$40.0 kg/m^2, and a BMI of $\geq$35.0 kg/m^2 with ORCD, have long been the proposed thresholds for surgical indications. In 2016, 45 international professional societies issued a joint statement that metabolic surgery should be considered for people with T2D and a BMI of 30.0 kg/m^2 to 34.9 kg/m^2 if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications.[150] The American Society for Metabolic and Bariatric Surgery and International Federation for the Surgery of Obesity and Metabolic Disorders now recommend bariatric surgery as a treatment option for adults with BMI $\geq$35.0 kg/m^2, regardless of the presence, absence, or severity of obesity-related conditions and also for adults with BMI of 30.0 kg/m^2 to 34.9 kg/m^2 who have severe cardiometabolic disease, such as T2D, and CVD.[151,152] These highly effective interventions should be combined with nutrition, physical activity, and behavioral therapy with the potential use of obesity medications before or after surgery if needed. A multidisciplinary team approach to perioperative and long-term care is mandatory for optimal clinical outcomes.[153] For further details beyond the scope of this consensus algorithm, see the 2020 Clinical Practice Guidelines for the Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures cosponsored by AACE, The Obesity Society, American Society for Metabolic and Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists.[154]



Algorithm 6. Response to therapy and weight-loss targets for people with adiposity-based chronic disease.

Table 2
Weight-Loss Targets Associated With Clinical Benefits for Different Adiposity-Based Chronic Disease Complications

Obesity Complication or Related Disease	Percent Weight Reduction Resulting in Clinically Meaningful Benefit	Percent Weight Reduction Resulting in Additional Benefit
T2D prevention[76-82]	7%-10% (may vary if medication has glycemic benefits independent of weight loss)	>10% (may vary if medication has glycemic benefits independent of weight loss)
T2D remission[83-87]	10%	>10%
Improved hyperglycemia[88-94]	5%-15%	>15%
Hypertension[88,95,96]	5%-15%	>15%
Dyslipidemia[88,97,98]	5%-15%	>15%
Hepatic steatosis[5,99-101]	5%-10%	>10%
MASH[66,102-106]	≥10% (may vary if medication has benefits independent of weight loss)	≥15% (may vary if medication has benefits independent of weight loss)
OSA[107-110]	7%-10%	>10%
OA[5]	5%-10%	>10%
Stress incontinence[111-114]	5%-10%	>10%
GERD[115-117]	5%-10%	>10%
PCOS[118-123]	5%-15%	>15%
Cancer prevention[124-128]	Requires additional research	
ASCVD and MACE[90,129-139]	10% (may vary if medication has benefits independent of weight loss)	>10% (may vary if medication has benefits independent of weight loss)

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; GERD = gastroesophageal reflux disease; MACE = major adverse cardiovascular events; MASH = metabolic dysfunction-associated steatohepatitis; OA = osteoarthritis; OSA = obstructive sleep apnea; PCOS = polycystic ovary syndrome; T2D = type 2 diabetes.

In addition to obesity medications and surgical procedures, lifestyle interventions are essential to optimize health outcomes for people with ABCD. Algorithm 7 shows nonpharmacologic interventions involving nutrition, physical activity, and sleep, while reducing stress and implementing individualized behavioral therapy.

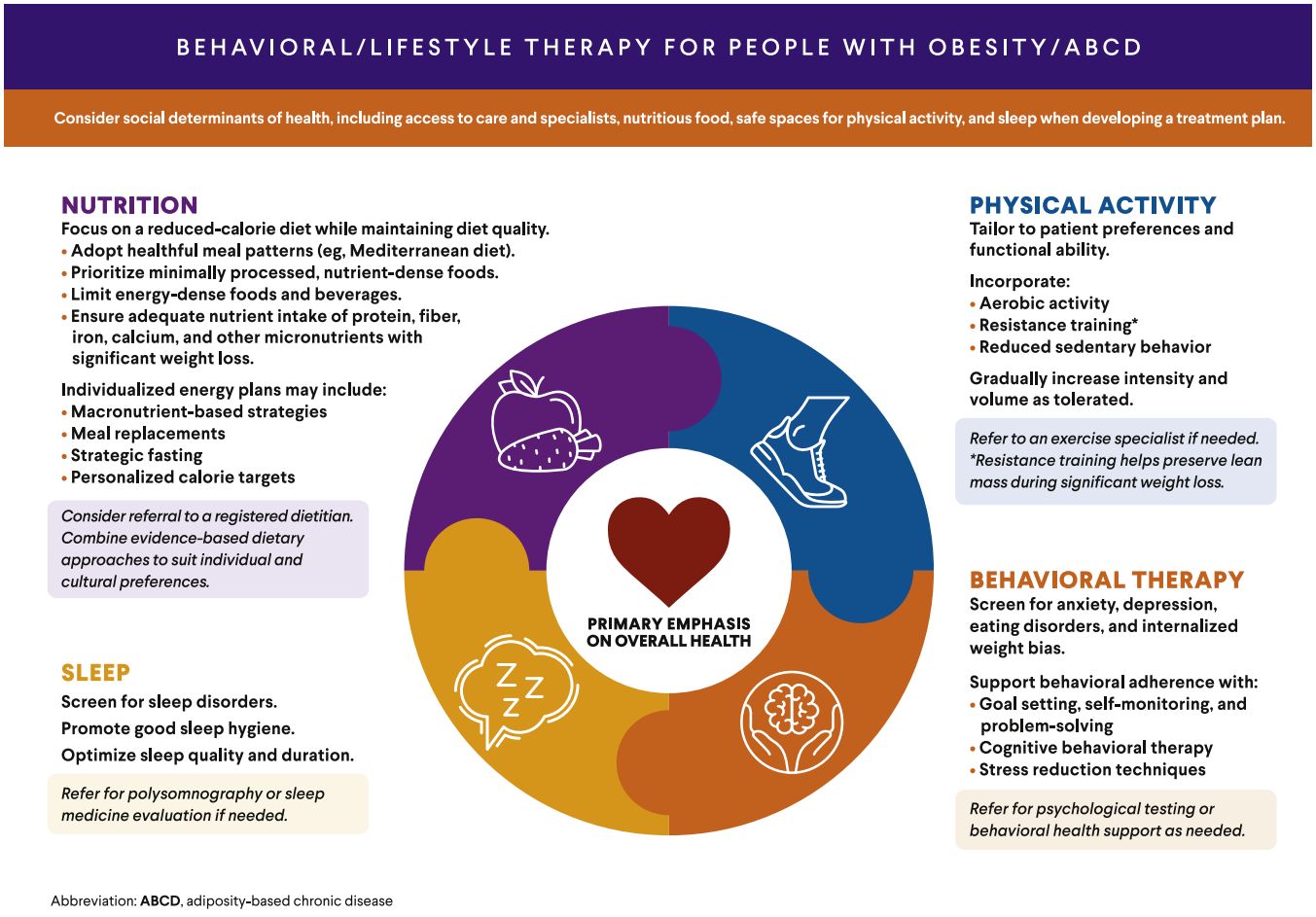
Nutrition

Nutrition and energy intake are critical components in the regulation of energy balance affecting the degree of adiposity. Exclusively focusing on "calories in, calories out" undermines the complexity of obesity pathophysiology and potentiates stigmatization. While weight reduction requires a change in energy balance to use stores greater than those replaced by dietary intake,[155,156] a healthy intake of macro- and micronutrients remains important and can help retain muscle and bone mass and promote health.

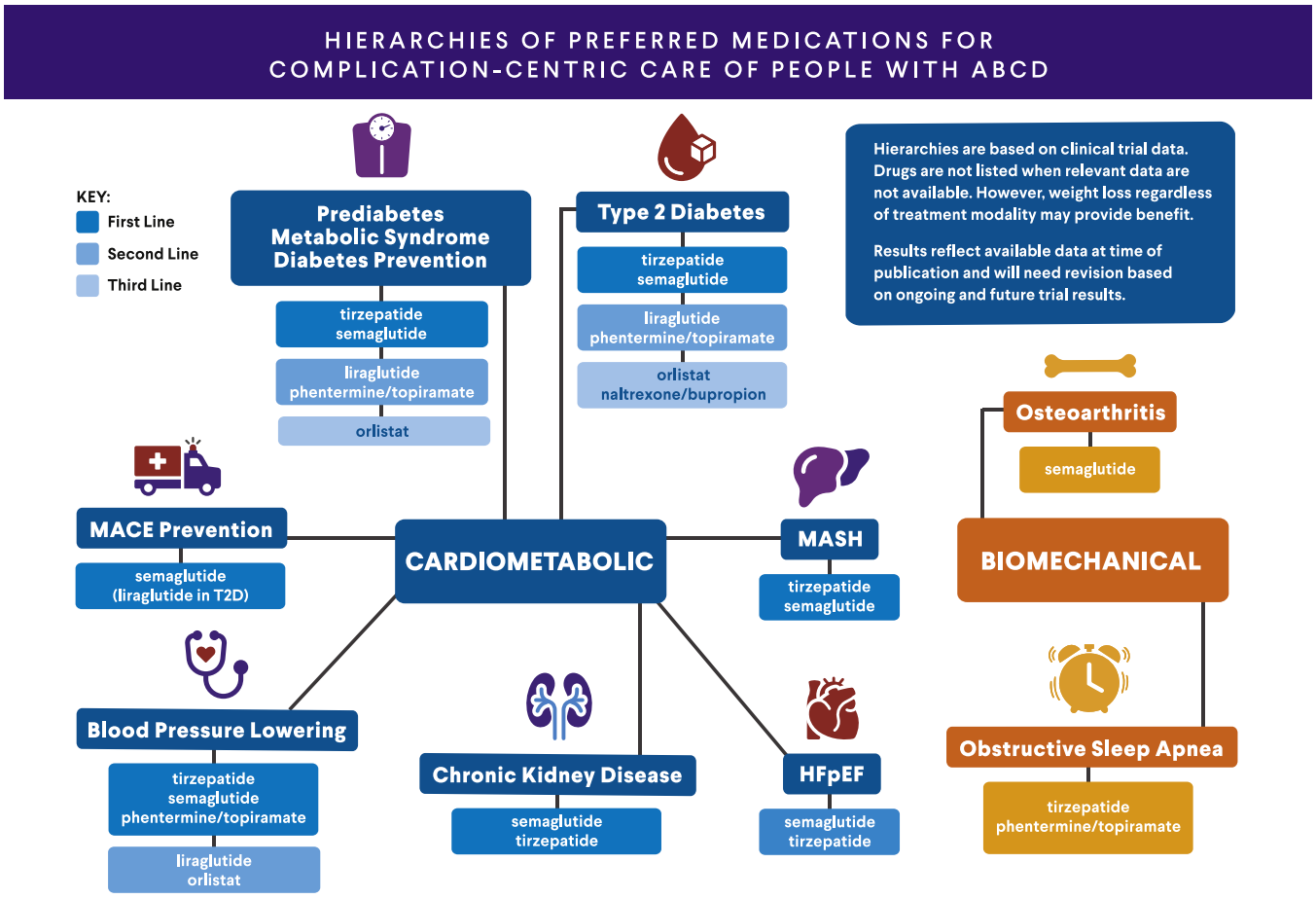
Nutritional interventions should focus on the quality and nutrient density of food consumed, while minimizing ultra-processed and energy-dense food intake, within the context of psychosocial cultural norms and preferences. Nutritional interventions must create an energy deficit for weight reduction but can be challenging to sustain long-term in the absence of medical or surgical therapies. Despite efforts at adherence to dietary prescriptions, many people experience weight regain because of maladaptive responses after weight loss that are integral to the pathophysiology of obesity. Achieving an energy deficit for weight loss can be accomplished through a variety of evidence-based dietary strategies that need not be mutually exclusive and can be combined or modified in a personalized manner for individuals. Dietary patterns should be optimized to achieve health benefits beyond weight reduction and should reflect individual preferences, cultural context, health goals, and access to food. Special attention to diet quality should be given to those experiencing pronounced weight loss (ie, taking second-generation obesity medications) to ensure adequate intake of macro- and micronutrients (eg, protein, fiber, iron, calcium).

Dietary Interventions

Individuals should receive counseling and support to create personalized nutrition plans in the context of autonomy accommodating dietary personal and cultural preferences while aligning with weight and health goals.[76,157-163] Numerous meal plans with variable macronutrient composition can be used in a



Algorithm 7. Behavioral/lifestyle therapy for people with obesity/adiposity-based chronic disease.



Abbreviations: **ABCD**, adiposity-based chronic disease; **HFpEF**, heart failure with preserved ejection fraction; **MACE**, major adverse cardiac events; **MASH**, metabolic dysfunction-associated steatohepatitis ; **T2D**, type 2 diabetes

Algorithm Figure 8 - Preferred Medications Hierarchies

Algorithm 8. Hierarchies of preferred medications for complication-centric care of people with adiposity-based chronic disease.

reduced-calorie format to safely promote weight reduction and health improvement. When lifestyle interventions are used as the single therapeutic modality, guidelines conventionally recommend caloric deficit plans of 500 to 750 kilocalories daily or estimated intakes of 1200 to 1500 kilocalories daily for women and men, respectively,[5,164-166] calculated based on the participants' baseline energy expenditure assessed at the time of randomization in trials (ie, using the National Institutes of Health calculator available at https://www.niddk.nih.gov/bwp).[167-173] When considering a broad range of meal plans (Mediterranean, Dietary Approaches to Stop Hypertension, complex carbohydrate, low-carbohydrate, plant-based, paleo, etc.), there is no macronutrient composition known to be superior to others; rather, the most effective dietary intervention depends upon an individual's ability to adhere to it over the long term.[174] That said, safety data beyond 2 to 3 years are unavailable for many of these meal plans and longer-term cardiovascular (CV) risk reduction has been demonstrated only for the Mediterranean diet.[175-178] Meal replacement plans and timing of eating or fasting also may be implemented in combination with any other personalized dietary interventions.[5,83,163,179-185]

During the dose-escalation phase of obesity medications and the hypocaloric period of active weight loss, it is important to ensure adequate nutrition as well as dietary practices to minimize adverse events. With the powerful anorexigenic effects of second-generation obesity medications, the emphasis shifts from promoting reduced caloric intake to assuring nutritive diet quality. Several key guiding points: (1) optimize and prioritize nutrient-dense carbohydrates such as vegetables, beans/pulses, and fruits; (2) prioritize lean protein; (3) consider multivitamin supplementation to include iron and calcium; and (4) flexible use of meal replacements. For mitigating gastrointestinal side effects of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and other obesity medications, patients can be counseled to: (1) eat slowly to mitigate side effects of medications; (2) eat more frequently but consume smaller portions; (3) lower intake of fatty foods or foods that may exacerbate side effects; (4) track foods that may exacerbate gastrointestinal side effects; and (5) maintain adequate hydration.[186]

Dietary protein is the critical macronutrient to prioritize during weight reduction to potentially mitigate muscle loss.[187-195] High protein consumption was previously hypothesized to accelerate CKD; however, protein restriction (<0.8 g/kg) has not been shown to slow renal decline.[196-198] Recent guidance suggests maintaining a protein intake of ≥1.2 grams of protein per kilogram of body mass

per day for most and ≥0.8 grams of protein per kilogram of body mass per day for those with diabetes mellitus and CKD not treated with dialysis.[198,199] Higher protein intakes (≥2.3 g/kg/day) may be needed to maximize the retention of lean body mass while prioritizing resistance training during hypocaloric periods.[194,200,201] Very high protein intake (>2 g/kg/day for prolonged periods) may not have adverse health effects, but the tolerable upper limit is thought to be ~3.5 grams per kilogram of body mass per day.[202]

Physical Activity

Physical activity, which includes aerobic activity, resistance/strength training, reduced sedentary time, and an increase in non–exercise activity thermogenesis, serves an important therapeutic role for people with obesity to improve overall health. Multiple guidelines for obesity and its complications, such as T2D, support physical activity prescription as an important part of therapy.[164,179,129,203-206] In particular, AACE suggests an individualized activity prescription in line with each individual's preferences and limitations (see Box B).[5] An eventual target of 150 minutes per week of moderate-intensity aerobic activity, divided into 3 or more days per week, is a general goal. Whole-body resistance training sessions at least 2 to 3 days per week are recommended and need to be prioritized, especially alongside intensive medical or surgical weight reduction, with the goal to maintain or improve lean muscle mass. Particular emphasis on higher-volume physical activity is needed for an individual to maintain weight after behavioral, medical, and/or surgical weight reduction; in general, this should involve 200 to 300 minutes weekly of moderate-intensity aerobic exercise, again with a priority placed on resistance training for the preservation of lean muscle mass.[207,208] Retention of lean mass via resistance training during active weight reduction serves to preserve resting metabolic rate and overall energy expenditure.[206,209-215] Elderly individuals or those at risk of frailty (sarcopenic obesity) especially need to prioritize resistance training accompanied by adequate protein intake, because the loss of lean mass in these populations can be particularly harmful both metabolically and in terms of decreased function and risk of falls or fractures.[212,216-218]

Physical activity goals recommended in various guidelines can be difficult to achieve for people with obesity, especially when they first begin this physical activity. It is important to individualize the physical activity prescription based on the preferences and capabilities of each patient. Two adages apply: first, begin at a low intensity level and increase slowly as tolerated; second, any activity is better than none.[1] It can be a challenge for clinicians to assist a patient with limited exercise experience or with disabilities to safely begin an appropriate activity regimen. A practical first step may be to encourage simple and brief bouts of activity, such as a short walk during their lunch break or trying to stand more often throughout the day. Chair- or water-based exercises and consideration for physical therapy referral may benefit those with significant functional limitations to help find activities they can safely perform. When available, medical fitness programs, such as Exercise is Medicine, can be beneficial to safely introduce patients to resistance training and various exercises.[219]

Box B

Physical Activity and Exercise Prescription for Obesity/Adiposity-Based Chronic Disease

- The exercise and physical activity prescription alone may result in modest (1% to 3%) weight reduction in some individuals or weight neutrality as individuals make up for expended calories with greater caloric ingestion. Nevertheless, exercise can have beneficial effects on insulin sensitivity, body composition, cardiometabolic risk factors, and sense of well-being, as well as help sustain weight loss in the weight-maintenance phase.
- Daily habits of "exercise" should be initiated at an individual's baseline ability and can include a variety of activities (eg, walking, swimming, biking, or other recreation).
- Frequency, intensity, and time duration should progress as a person is capable, which may include increasing speed, incline, and/or resistance. An eventual goal is ≥150 minutes per week of moderate-intensity physical activity, such as brisk walking, or ≥75 minutes per week of high-intensity physical activity, such as high-intensity interval training. Frequent and higher volumes of physical activity are required for maintenance of weight reduction.
- Strength/resistance training should be prioritized, especially in conjunction with highly effective obesity pharmacotherapy and/or surgery.

Sleep

Suboptimal sleep duration (<7-8 hours per night) and poor sleep quality can promote dysregulated energy intake, metabolic perturbations, and obesity.[220-224] Inadequate sleep and circadian disruption are associated with increased appetite, increased energy intake, decreased energy expenditure, and cardiometabolic disease risk.[225] For those with short sleep duration, individualized sleep hygiene counseling intended to extend sleep duration may reduce energy intake and increase weight reduction. OSA is a common obesity complication but remains underdiagnosed and often untreated.[226] The pathophysiological relationship between OSA and obesity is complex and multidirectional, and both are associated with insulin resistance and increased CV risks.[64,227] In the Sleep AHEAD (Action for Health in Diabetes) trial assessing a lifestyle intervention, weight reduction resulted in significant improvements in OSA and the apnea-hypopnea index among people with obesity and T2D.[228] Treating OSA with continuous positive airway pressure only, however, does not seem to improve weight reduction.[229,230] Sleep health is an important domain in the prevention and management of people with obesity and ORCD. People with obesity should be counseled about the importance of adequate sleep and circadian health. Screening for OSA is recommended in those with typical symptoms, high neck circumference (>17 inches in men and >16 inches in women), or high risk for OSA.[231]

Bias, Stigma, Psychological Disorders, and Behavioral Therapy

Weight bias is defined as negative ideologies toward people living with obesity, and weight stigma denotes thoughts and acts of discrimination toward people living with obesity as a result of weight bias.[26] Verbal and nonverbal communication of stigma impact medical care and highlight systematic barriers to health care.[232]

Weight bias and stigmatization lead to internalized weight bias (IWB), when people apply negative weight stereotypes to themselves and engage in self-devaluation.[24,26] IWB negatively affects the physical and mental components of health-related quality of life and can compromise the ability to adhere to the therapeutic

plan.[233] IWB is inversely related to motivation for healthy lifestyle behaviors and contributes to negative health outcomes.[234] For these reasons, AACE was the first to recommend taking IWB into account in the clinical evaluation and staging of people with obesity and in developing individualized treatment plans (Table 1).[26] The Weight Self-Stigma Questionnaire and the Weight Bias Internalization Scale are validated tools for assessing IWB in clinical settings.[235,236] IWB is the best predictor of stress, anxiety, depression, and body dissatisfaction.[237]

A person-centered approach to weight-based communication, using person-first language and conveying empathy when addressing health care concerns, is paramount.[238] Individuals should be presented with the full range of evidence-based medical and surgical treatment options in addition to lifestyle interventions.[232] Health care professionals should communicate the risks versus benefits of treating obesity by emphasizing benefits related to their health with messaging tailored to different degrees of health literacy.[179] Cognitive behavioral therapy can aid people with obesity in maintaining healthy lifestyle choices by fostering cognitive changes oriented toward supporting weight reduction while optimizing health.[239]

Health care professionals should consider the psychological overlay of overweight/obesity and possibility of psychological disorders in people with ABCD. Depression, anxiety, and binge-eating disorder are more prevalent among people with obesity compared with the general population.[240] These issues can require immediate intervention in some patients to assure that the therapeutic plan can be effective. Consultation with trained professionals for psychological screening and cognitive behavioral therapy should be considered as part of long-term follow-up for people with IWB. Collaboration with a psychological specialist by referral or as a member of the multidisciplinary obesity care team is important for the provision of holistic care for people with ABCD.[241]

Algorithm 8 provides guidance to assist clinicians as they personalize therapy based on complication-centric care targeting specific ORCD. Hierarchies of preferred medications are recommended based on clinical trial data. These hierarchies are supported by phase III clinical trials that have addressed the ability of obesity medications to treat ORCD as primary or predesignated outcome measures. This does not negate the possibility that weight loss regardless of treatment modality may provide benefit as indicated in the algorithm.

Cardiometabolic ORCD

Prediabetes Metabolic Syndrome and Diabetes Prevention

Semaglutide[242] or tirzepatide[243] are preferred medications for preventing progression to overt diabetes because of substantial weight loss and direct glycemic effects as incretins in addition to other clinically significant cardiometabolic benefits pertaining to improvements in lipids, BP, and inflammation.[5,28,83] Liraglutide[77] and phentermine/topiramate[59,78] are second-tier medications but highly effective in this regard. Orlistat is a third-tier medication.[244]

T2D

Tirzepatide[245] and semaglutide[246] are first-tier medications for treating people with T2D and obesity based on weight loss achieved, degree of lowering A1C to target, and low rates of hypoglycemia. Liraglutide[247] and phentermine/topiramate[78] are second-tier medications but effective in the treatment of these individuals. Orlistat[248] and naltrexone/bupropion[249] are considered third-tier medications.

Major Adverse Cardiovascular Event Prevention

Semaglutide is the only obesity medication, thus far, that has been shown to reduce risks of major adverse cardiovascular events (MACE) in a cardiovascular outcome trial (CVOT) involving secondary prevention in people with obesity and not diabetes.[130] Tirzepatide may also be efficacious for cardioprotection based on post hoc analyses of the SURMOUNT 1 extension trial, which showed reduced hazard ratios for MACE.[250] Liraglutide 1.8 mg per day demonstrated cardioprotection in people with obesity and T2D in the LEADER CVOT.[130,251] A morbidity and mortality outcome trial is ongoing for tirzepatide. Definitive data for cardioprotection are lacking for orlistat, naltrexone/bupropion, and phentermine/topiramate.

Metabolic Dysfunction-Associated Steatohepatitis

Semaglutide[102,252] and tirzepatide[103] are preferred medications for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) based on data showing improvements in hepatic histology and fibrosis.[66] Any weight-loss intervention that achieves 5% to 10% weight loss or more will predictably reduce hepatic steatosis.[5]

HTN/BP Lowering

Tirzepatide and semaglutide, followed by phentermine/topiramate extended release (ER) are preferred medications for those with ABCD complicated by HTN based upon improvement of BP in clinical trials.[95,253-259] Liraglutide[260] and orlistat are considered second-tier medications.[261,262]

CKD

Semaglutide is the preferred medication for treatment of CKD, based on clinical trial data in people with T2D showing that a dose of 1 mg per week will slow the rate of decline of estimated glomerular filtration rate and prevent renal outcomes.[263] Liraglutide in patients with T2D at a dose of 1.8 mg per day was also shown to be renal protective in a secondary analysis of the LEADER trial.[264] A clinical trial primarily assessing the impact of tirzepatide on renal function is ongoing, and a post hoc analysis of a previous trial in people with T2D supports the expectation that tirzepatide will show positive results.[265]

HFpEF

Tirzepatide has been shown to improve symptoms, physical function, and heart failure outcomes (eg, the need for urgent care visits or hospitalization) in people with HFpEF, and semaglutide to improve symptoms and physical function in these individuals.[266,267]

Biomechanical ORCD

OA

Semaglutide is the preferred medication for individuals with obesity complicated by OA of the knee based on clinical trial data.[268] Weight loss of >5% can improve symptoms of OA.[1]

OSA

Tirzepatide and phentermine/topiramate are preferred medications for the treatment of OSA in people with ABCD based on

clinical trial data that showed improvements in symptoms and the apnea-hypopnea index during polysomnography.[107,269-271] Tirzepatide is now approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate and severe OSA in adults with obesity.[272]

Dual Benefits Regarding Comorbidities

Clinicians should consider the dual benefits of obesity medications (eg, efficacy for weight loss and demonstrated ability to ameliorate specific complications or comorbidities unrelated to obesity), known adverse effects, and cost of available medications. When cost and coverage create barriers to access, consider off-label generic medications with evidence for therapeutic potential. In addition to ameliorating specific ORCD, topiramate, phentermine/topiramate, liraglutide, and semaglutide have shown benefits for binge-eating syndrome or food cravings, with likely beneficial, but mixed, results for naltrexone/bupropion.[273,274] Other indications to consider for specific medications include topiramate for migraines, naltrexone and GLP-1 RAs for alcohol use dependence, and bupropion for treatment of smoking cessation.[275-277] While pharmacotherapy to treat regain or achieve clinical goals after bariatric/metabolic surgery is not specifically addressed, it should be noted that obesity medications may be an effective tool to support patients postsurgery.[278,279]

Second-generation obesity medications are highly expensive, particularly in the United States, and people often lack insurance coverage and access to these evidence-based therapies.[280] It is important to keep in mind that first-generation medications (eg, phentermine, orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide) can effectively be used for weight loss and treatment of ORCD in many people. These medications are less expensive and more accessible and can be considered in people with stage 1 or 2 ABCD, although second-generation medications should be used whenever possible in stage 3 disease if needed for sufficient weight loss to treat more serious complications. First-generation medications have been demonstrated in clinical trials to effectively ameliorate certain obesity complications and can be used to benefit BP and lipids, hepatic steatosis, diabetes prevention (liraglutide and phentermine/topiramate), treatment of OSA (phentermine/topiramate), treatment of T2D (all first-generation medications), and cardioprotection and renal protection in those with T2D (liraglutide).[1] If weight loss is insufficient to achieve clinical goals, an alternative first-generation medication, intensification of behavioral or lifestyle interventions, or switch to a second-generation medication should be considered (see Algorithm 9). The health of an individual through the achievement of clinical goals in complication-centric care is critical. Complications and related diseases can also be treated with specific therapies that are not related to weight loss. In addition, a trial of first-generation medication to maintain weight loss after initial treatment using a second-generation medication can also be considered an option with better cost and access for long-term maintenance.

Algorithm 10 provides guidance to help individualize the choice of pharmacotherapy, taking into consideration ORCD, comorbidities, and potential adverse events, although the list of obesity-related conditions is not exhaustive. The table is color coded as follows: (1) blue: evidence of benefit; (2) gray: insufficient evidence, but obesity medication may still be considered; (3) yellow: caution or extra monitoring recommended; and (4) orange: known contraindications. Clinicians should refer to additional details in the FDA prescribing information.

Algorithm 11 provides key information for prescribing obesity medications that are currently approved by the FDA for obesity (ie, "chronic weight management"), including considerations involving age, dose, titration, observed efficacy, cost, and cautions or contraindications. Additional salient details for each medication are provided below, focusing on outcomes in individuals with obesity. Clinicians are encouraged to read and review FDA labels (package inserts) for each obesity medication for more detailed information.

Orlistat

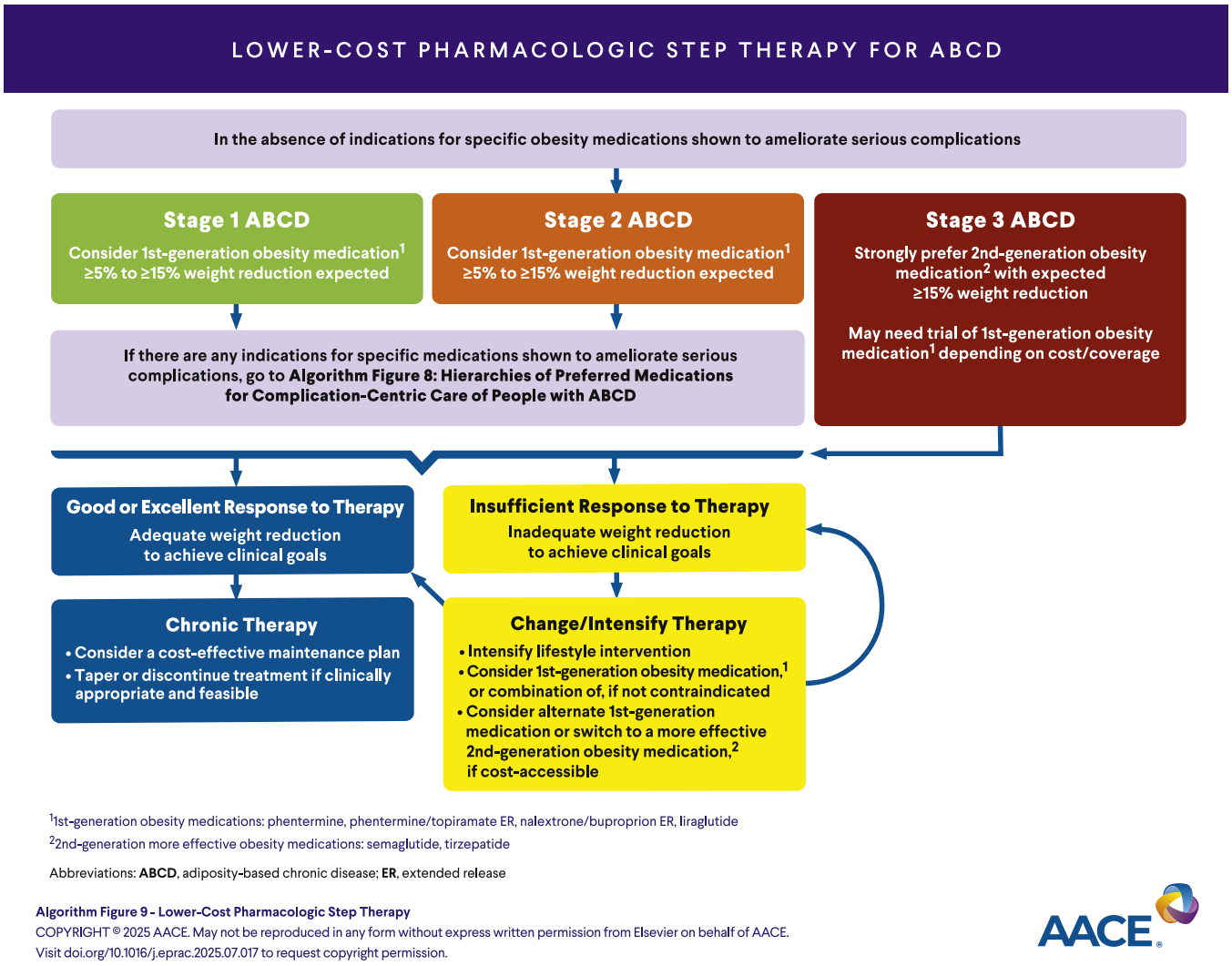
Orlistat was approved by the FDA for chronic weight management (obesity treatment) in 1999. It results in weight reduction by inhibiting pancreatic and gastric lipases and reducing fat absorption by approximately 30%. In the XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study, the mean weight reduction after 4 years was significantly greater in the orlistat group than with placebo (5.8 vs 3.0 kg, respectively).[244] Treatment with orlistat also resulted in a significant reduction in the cumulative incidence of T2D after 4 years of treatment (9.0% with placebo vs 6.2% with orlistat), corresponding to a risk reduction of 37.3%.[244] Other benefits of orlistat include a reduction in low-density lipoprotein cholesterol independent of that expected from change in body weight. Two doses for orlistat are currently approved by the FDA for obesity, 120 mg orally 3 times a day before meals (by prescription) and 60 mg orally 3 times a day before meals (over the counter).

Side effects of orlistat include steatorrhea, incontinence, oily spotting, frequent bowel movements, abdominal pain, flatulence with discharge, and fecal urgency, especially after high-fat dietary intake. Serum levels of fat-soluble vitamins (A, D, E, and K) have shown to be lower with orlistat than with placebo, so a fat-soluble vitamin supplement (including vitamins A, D, E, and K) is recommended at bedtime or $\geq$2 hours after orlistat dose.[281,282] Kidney and liver function should be monitored while taking orlistat. Serious but infrequent adverse events such as liver injury, cholelithiasis, nephrolithiasis, and kidney damage have been reported.[283,284] Orlistat is not recommended for patients with malabsorption disorders.[285,286]

Phentermine and Other Norepinephrine-Releasing Agents

Phentermine is a central norepinephrine-releasing agent approved in 1959 for short-term weight loss ("a few weeks," per the FDA label). As obesity is a chronic disease, phentermine is commonly prescribed off-label beyond 3 months and has been the most prescribed obesity medication in the United States.[287-290] Frequently raised concerns for long-term CV safety, with prospective CV safety data lacking, are now being addressed in the ongoing Long-term Effectiveness of the Anti-Obesity Medication Phentermine (LEAP) National Institutes of Health–funded trial (NCT05176626).[291] Studies of phentermine in adults have demonstrated only transient changes in BP, but retrospective data have demonstrated overall long-term safety and effectiveness.[292-294]

Phentermine is available as a tablet or capsule; the initial recommended dose is 8 mg or 15 mg with maximum dose of 37.5 mg taken once daily or 8 mg up to 3 times daily (24 mg total). Short-term studies ranging from 12 to 28 weeks have demonstrated average weight reduction of 5.45% to 7.7% with the use of phentermine.[295,296] Most longer-term data on the use of phentermine comes from trials using a combination of phentermine and topiramate, where medications were continued for up to 2 years.[260,292]



Algorithm 9. Lower-cost pharmacologic step therapy for adiposity-based chronic disease.

The most common side effects reported with phentermine include headaches, elevation of BP and heart rate, insomnia, dry mouth, constipation, and anxiety. Phentermine use is contraindicated in people with a history of CVD (coronary artery disease, uncontrolled HTN, arrythmias, stroke, congestive heart failure), hyperthyroidism, glaucoma, and a history of drug use disorder, or those who are pregnant or breastfeeding.[5,73] Included in the class of norepinephrine-releasing agents approved for obesity is diethylpropion (or amfepramone), phendimetrazine, and benzphetamine.

Phentermine and Topiramate ER

Phentermine and topiramate ER as a combination therapy was approved by the FDA for chronic weight management in 2012 and for adolescents ≥12 years of age in 2022 with its efficacy and safety studied in several randomized controlled trials.[167,260,295,297] The mechanism of action for weight reduction of topiramate is not well understood but is thought to be related to modulating gamma-aminobutyric acid release, blocking glutamate release.[298] Four different oral doses are available: the starting dose is 3.75/23 mg for 14 days followed by a maintenance dose of 7.5/46 mg daily, with 2 higher doses of 11/69 mg and 15/92 mg available if needed. Results from several clinical trials (EQUIP, CONQUER, and SEQUEL) demonstrated weight reduction in the treatment group (phentermine and topiramate ER), ranging from 7.8% to 10.7% compared with 1.2% to 2.2% in the placebo group on both completers and intent-to-treat groups.[167,260,299]

The side-effect profile of phentermine and topiramate ER is similar to phentermine with the addition of side effects from topiramate. Some of topiramate's common side effects include dysgeusia, paresthesia, cognitive side effects such as drowsiness or word aphasia, and constipation. Topiramate can also cause hypokalemia, metabolic acidosis, and nephrolithiasis as a carbonic anhydrase inhibitor. The combination of phentermine and topiramate ER is contraindicated in pregnancy (known teratogenicity) and breastfeeding, glaucoma, and untreated hyperthyroidism. A risk evaluation and mitigation strategy is required by the FDA for phentermine/topiramate ER to inform certified pharmacies and patients of reproductive potential about the increased risk of embryo-fetal toxicity with major congenital malformations. Pregnancy prevention is mandatory. A negative pregnancy test is recommended before initiating monthly monitoring. If pregnancy occurs, phentermine/topiramate ER must be discontinued immediately. People who receive higher doses are prone to more side effects. While the CV safety of phentermine and topiramate ER is not established, data from the phase III trials do not raise signal of concern.[300] Small

MEDICATIONS FOR OBESITY: INDIVIDUALIZATION OF THERAPY[a]

KEY: Preferred (evidence of benefit) | Insufficient evidence to prefer | Monitoring indicated | Contraindicated (evidence of risk/harm)

OBESITY-RELATED CONDITION	ORLISTAT	PHENTERMINE	PHENTERMINE/ TOPIRAMATE ER	NALTREXONE ER/ BUPROPION ER	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
DIABETES PREVENTION	Benefit via weight reduction		Benefit via weight reduction		Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect
TYPE 2 DIABETES	Benefit via weight reduction		Benefit via weight reduction	Benefit via weight reduction	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect
HYPERTENSION	Benefit via weight reduction	Monitor heart rate, BP Contraindicated in uncontrolled HTN	Monitor heart rate, BP; BP benefit observed in trials*	Monitor heart rate, BP Contraindicated in uncontrolled HTN	BP benefit observed in trials; Monitor heart rate	BP benefit observed in trials; Monitor heart rate	BP benefit observed in trials; Monitor heart rate
ASCVD		Contraindicated	Use with caution; Monitor heart rate, BP	Monitor heart rate, BP	Demonstrated prevention of ASCVD in T2D	Demonstrated prevention of ASCVD	Evidence in T2D and obesity pending
MASLD					Benefit observed in trials	Benefit observed in trials	Benefit observed in trials
DEPRESSION			Appropriate monitoring	Appropriate monitoring	Appropriate monitoring	Appropriate monitoring	Appropriate monitoring
ANXIETY		Appropriate monitoring	Appropriate monitoring	Appropriate monitoring			
CHRONIC KIDNEY DISEASE	Monitor for oxalate nephropathy		Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90mg twice a day	Benefit in T2D; Avoid vomiting and volume depletion	Benefit in T2D; Avoid vomiting and volume depletion	Benefit in T2D; Avoid vomiting and volume depletion
SEVERE KIDNEY IMPAIRMENT	Monitor for oxalate nephropathy	Urinary clearance of drug	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion	Avoid vomiting and volume depletion	Avoid vomiting and volume depletion
NEPHROLITHIASIS	Calcium oxalate stones		Calcium phosphate stones				
HEPATOBILIARY IMPAIRMENT	Monitor for cholelithiasis	Do not exceed 8 mg per day	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg daily	Monitor for cholelithiasis	Monitor for cholelithiasis	Monitor for cholelithiasis
SEVERE HEPATIC IMPAIRMENT	Not recommended						

[a]All medications are contraindicated in pregnancy and breastfeeding. *Blood pressures are significantly decreased in clinical trials.

Abbreviations: **ASCVD**, atherosclerotic cardiovascular disease; **BP**, blood pressure; **ER**, extended release; **HTN**, hypertension; **T2D**, type 2 diabetes

Algorithm Figure 10 - Medications for Obesity: Individualization of Therapy

Algorithm 10. Medications for obesity: individualization of therapy.

increases in heart rate are well balanced by decreases in BP such that the rate-pressure product is favorable. Phentermine and topiramate ER have been shown to effectively ameliorate OSA,[107] to prevent progression from metabolic syndrome or prediabetes to T2D,[59] and in T2D to promote weight loss and lower A1C with less need for conventional diabetes medications.[78]

Naltrexone/Bupropion ER

Naltrexone/bupropion ER is an ER combination of naltrexone, an opioid antagonist, and bupropion, a noradrenergic/dopaminergic reuptake inhibitor antidepressant, approved by the FDA in 2014 for chronic weight management in adults.[301] Although the exact mechanism of action is not fully understood, studies suggest that the combined action of naltrexone and bupropion leads to a synergistic effect in regulating food intake with effects on the hypothalamus (appetite regulatory centers) and on the mesolimbic dopamine circuit (reward system).[302]

Each tablet of naltrexone/bupropion ER contains 8 mg naltrexone and 90 mg bupropion. Dose escalation starts with 1 tablet once daily for the first 7 days, increased by 1 tablet weekly up to a final dose of 2 tablets twice daily (naltrexone 32 mg/bupropion ER 360 mg). Caution is advised for its use in patients >65 years of age as they may have increased sensitivity to naltrexone/bupropion's adverse effects on the central nervous system. There are no safety and efficacy data for patients <18 years of age, and this medication is not recommended for individuals <18 years of age.

In 4 56-week phase III trials,[168,249,303,304] treatment with naltrexone/bupropion 32 mg/360 mg led to clinically significant weight reduction, ranging from 5.9% to 11.5% compared with placebo among completers. The initial 3 trials focused on those with obesity alone or with obesity and controlled HTN and/or dyslipidemia. Participants of these trials lost nearly 12% on average if achieving 5% weight reduction in the first 3 months of full dosing.[305]

Naltrexone/bupropion ER should be avoided with fatty meals, as this can result in a significant increase in both drug levels systemically. There is a recommended dose adjustment for those with renal and hepatic impairment. The maximum dose of naltrexone/bupropion ER is 1 tablet twice daily for those with moderate to severe renal impairment/or moderate hepatic impartment. Naltrexone/bupropion ER is not recommended with end-stage renal disease or with severe hepatic impairment.

Common side effects include nausea, headache, constipation, dizziness, vomiting, and dry mouth, with occurrences ranging

MEDICATIONS FOR OBESITY APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION[a,b]

	ORLISTAT	PHENTERMINE[c]	PHENTERMINE/ TOPIRAMATE ER	NALTREXONE ER/ BUPROPION ER	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
CLASS/MECHANISM OF ACTION	Lipase Inhibitor	NE-releasing agent	NE-releasing agent GABA Receptor Modulation	Opioid-Receptor Antagonist DA-NE Reuptake Inhibitor	GLP-1 RA	GLP-1 RA	GIP/GLP-1 RA
AGE	≥12 years[d]	>16 years	≥12 years	≥18 years[d]	≥12 years[e]	≥12 years[e]	≥18 years[d]
DELIVERY	Oral	Oral	Oral	Oral	Subcutaneous Injection	Subcutaneous Injection	Subcutaneous Injection
STARTING DOSE	60 mg 3 times/day AC	8mg or 15mg QAM	3.75 mg/23 mg QAM	8 mg/90 mg QAM	0.6 mg QD	0.25 mg QWK	2.5 mg QWK
DOSE ESCALATION	Titrate up to needed dose Slow dose titration if side effects occur Formulations: 60 mg cap 120mg cap	Titrate up to needed dose Slow down dose titration if side effects occur Formulations: 8mg tab 15 mg cap 37.5mg tab	Titrate up bi-weekly to needed dose Slow down dose titration if side effects occur 3.75 mg/23 mg QAM x 2 wk 7.5 mg/ 46 mg QAM x 12 wk 11.25 mg / 69 mg QAM x 2 wk 15 mg/92 mg QAM	Titrate up weekly to needed dose Slow down dose titration if side effects occur 8 mg/90 mg QAM x 1wk 8 mg/90 mg twice daily x 1 wk 16 mg/90 mg QAM and 8 mg/90 mg QPM x 1 wk 16 mg/90 mg twice daily	Titrate up weekly to needed dose Slow down dose titration if side effects occur 0.6 mg QD x 1 wk 1.2 mg QD x 1 wk 1.8 mg QD x 1 wk 2.4 mg QD x 1 wk 3.0 mg QD	Titrate up monthly to needed dose Slow down dose titration if side effects occur 0.25 mg QWK x 4 wk 0.5 mg QWK x 4 wk 1.0 mg QWK x 4 wk 1.7 mg QWK x 4 wk 2.4 mg QWK	Titrate up monthly to needed dose Slow down dose titration if side effects occur 2.5 mg QWK x 4 wk 5.0 mg QWK x 4 wk 7.5 mg QWK x 4 wk 10 mg QWK x 4 wk 12.5 mg QWK x 4 wk 15 mg QWK
MAXIMUM DOSE	120 mg 3 times/day AC	37.5 mg QAM[f]	15 mg/92 mg QD	16mg/180mg twice daily	3.0 mg QD	2.4 mg QWK	15 mg QWK
WEIGHT REDUCTION[g]	4% (52 weeks)	5%-6% (28 weeks)	9.6%-9.9% (52 weeks) dose dependent	4.2%-5.2% (52 weeks)	9.2% (56 weeks)	16.9% (68 weeks)	22.5% (72 weeks)
POTENTIAL SIDE EFFECTS[h]	Flatulence Fecal Urgency Oily Stools Fat-Soluble Vitamin and Drug Malabsorption Potential Drug-Drug Interactions	Restlessness Insomnia Headache Dry Mouth Tachycardia BP Elevation	Paresthesia, Dizziness Dysgeusia, Insomnia Constipation, Dry Mouth Fatigue Blurred Vision Mental Clouding Mood Changes	Nausea, Constipation Headache Vomiting Dizziness Insomnia Dry Mouth, Diarrhea Anxiety	Nausea Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain GERD	Nausea, Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain Headache Fatigue	Nausea, Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain Headache Fatigue
CAUTIONS, RELATIVE AND ABSOLUTE CONTRAINDICATIONS[i]	Cholestasis Chronic Malabsorption Syndrome Nephrolithiasis Vitamin Malabsorption Encourage Supplementation Potential for Misuse	CAD, CVA, Arrythmias, CHF, Uncontrolled HTN* Hyperthyroidism Agitated States History of Drug Abuse MAOI Use Angle-Closure Glaucoma	MAOI Hyperthyroidism Angle-Closure Glaucoma Monitor for Increased Heart Rate Nephrolithiasis Metabolic Acidosis[c] Monitor for Worsening Anxiety or Depression[c]	Seizure Disorder Uncontrolled HTN Chronic Opioid Use Anorexia Nervosa Bulimia Nervosa MAOI Use Abrupt Drug or Alcohol Withdrawal Angle-Closure Glaucoma Monitor for Worsening Anxiety or Depression[c]	History or Family History MTC/MEN2 Gallbladder Disease Pancreatitis Increased Heart Rate	History or Family History MTC/MEN2 Gallbladder Disease Pancreatitis Diabetic Retinopathy[j]	History or Family History MTC/MEN2 Gallbladder Disease Diabetic Retinopathy[j]
ACCESS/COST	$$	$	$$	$$	$$$	$$$$	$$$$

[a]Monogenic obesity treatment, devices for weight reduction, and setmelanotide can be found in narrative. [b]FDA-approved for CWM. [c]This class of medications includes diethylpropion (or amfepramone), phendimetrazine, and benzphetamine. [d]EMA approved for age 18 years and above for CWM. [e]EMA approved for age 12 years and above for CWM. [f]Maximum dose allowed for phentermine; however, many patients will see results on 8 mg 3 times a day which is also considered a maintenance dose in patients with diabetes and obesity. [g]Percent body weight reduction in treatment in Phase 3 trial. [h]Complications requiring caution or monitoring in order of observed frequency. [i]All FDA-approved medications for obesity are contraindicated in individuals who are pregnant or breastfeeding; effective birth control should be recommended/prescribed. A negative pregnancy test is recommended before initiating, with monthly monitoring. [j]In patients with T2D and obesity. *Blood pressures are significantly decreased in clinical trials for phentermine/topiramate ER.

Abbreviations: **AC**, before meals; **BP**, blood pressure; **CAD**, coronary artery disease; **CHF**, congestive heart failure; **CVA**, cerebrovascular accident; **CWM**, chronic weight management; **DA**, dopamine; **EMA**, European Medicines Agency; **ER**, extended release; **FDA**, U.S. Food and Drug Administration; **GERD**, gastroesophageal reflux disease; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **HTN**, hypertension; **MAOI**, monoamine oxidase inhibitors; **MEN2**, multiple endocrine neoplasia, type 2; **MTC**, medullary thyroid cancer; **NE**, norepinephrine; **QAM**, every morning; **QD**, every day; **QPM**, every afternoon or evening; **QWK**, every week; **wk**, week(s)

Algorithm Figure 11 - FDA-Approved Medications for Obesity: Prescribing Information

Algorithm 11. Medications for obesity approved by the U.S. Food and Drug Administration.

from approximately 4% to 32%.[301] A slight elevation in BP and heart rate have been observed, so it is important to monitor BP and heart rate at the start of therapy and at regular intervals. A CVOT was initiated for naltrexone/bupropion ER, but the trial was terminated because of public compromise of the data; thus, CV safety has not been determined.[306] Use caution with patients taking beta blockers, as naltrexone/bupropion ER may increase levels of beta blockers; consider starting the medication at a lower dose while closely monitoring heart rate. Contraindications include uncontrolled HTN; seizure disorders (can lower seizure threshold); anorexia nervosa or bulimia; abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs; use of other bupropion-containing products; chronic opioid use; during or within 14 days of taking monoamine oxidase inhibitors; known allergies to any of the drug's ingredients; and pregnancy.

Liraglutide

Liraglutide is a daily injectable GLP-1 RA. Originally approved by the FDA for T2D in 2010 at a dose of 1.8 mg per day, liraglutide was the first GLP-1 RA approved by the FDA for chronic weight management (obesity) treatment (2014) in adults and in adolescents (2020) at a dose of 3.0 mg per day. In addition to its well characterized incretin effect, endogenous GLP-1 impacts weight homeostasis by acting centrally in various regions of the brain, including in the hypothalamus, directly activating proopiomelanocortin (POMC)/cocaine- and amphetamine-regulated transcript neurons and indirectly inhibiting the neuropeptide Y/agouti-related peptide neurons,[307-309] as well as having action in the brain stem.

Liraglutide has a half-life of 13 hours, allowing it to be given once daily. It is titrated up weekly as tolerated by the patient from a starting dose of 0.6 mg. Liraglutide is approved by the FDA for obesity (chronic weight management) for patients ≥12 years of age at a dose of 3.0 mg daily.[310] Efficacy and safety in adults were examined in the SCALE Obesity and Prediabetes trial, in which liraglutide 3 mg daily resulted in a mean weight reduction of 8.0% compared with 2.6% with placebo after 56 weeks of treatment.[311] A total of 63.2% of participants in the liraglutide group, compared with 27.1% of participants in the placebo group, lost ≥5% of their body weight.[311] Liraglutide 3 mg also prevented progression of prediabetes to T2D.[77]

In people with obesity and T2D, the SCALE Diabetes trial demonstrated a mean weight change of -5.8% for liraglutide 3.0 mg versus -1.5% with placebo after 56 weeks of treatment.[247] With liraglutide 3.0 mg, 51.8% of individuals achieved ≥5% weight

reduction versus 24.0% of individuals with placebo.[247] Liraglutide also resulted in significant improvements in A1C (mean change -1.3% vs -0.3% with placebo), fasting and postprandial glucose levels, and fasting glucagon levels.[247] Weight reduction of ≥4% at 16 weeks best predicted weight reduction after 56 weeks (10.8% vs 3.0% [without T2D] and 8.5% vs 3.1% [T2D]).[312]

The LEADER trial demonstrated that a 1.8-mg dose of liraglutide significantly reduced rates of MACE (CV death, nonfatal myocardial infarction, or nonfatal stroke) in people with T2D and elevated CV risk factors.[251] There is no CVOT with liraglutide in individuals with obesity without T2D.

The main side effects and mitigation strategies of liraglutide are included in the section below as they pertain to the class of GLP-1 RA–based therapies approved by the FDA for treatment of obesity, inclusive of liraglutide, semaglutide, and tirzepatide.

Semaglutide

Semaglutide is a second-generation GLP-1 RA formulated as both a once-weekly subcutaneous (SC) injection ($t_{½}$ 183 hours) and as a daily oral tablet. The SC formulation at 2.4 mg per week was approved by the FDA for the treatment of obesity in adults in 2021 and for adolescents ≥12 years of age in 2022,[166,246,313] and for adults with T2D in 2017 at doses of 1 mg and 2 mg SC each week.[314-327] More recently, semaglutide 2.4 mg per week was approved for secondary CV risk reduction.[130,328] Semaglutide SC for obesity is titrated up from a starting or initial dose of 0.25 mg weekly and titrated monthly as tolerated up to a maximum dose of 2.4 mg weekly for treatment of obesity.[166] The oral formulation of this peptide is approved by the FDA for people with T2D at a dose of 14 mg per day and has been shown to be effective in phase III trials in people with obesity at doses of 25 mg and 50 mg per day.[329]

The Semaglutide Treatment Effect in People with Obesity (STEP 1) trial investigated the efficacy and safety of semaglutide 2.4 mg versus placebo in adults with obesity demonstrating an average percent weight reduction of 16.9% from baseline with 68 weeks of treatment.[166] The STEP 5 trial demonstrated that with a second year of treatment a majority of the weight reduction (16.7%) was maintained.[330] The OASIS-1 investigated the efficacy of daily oral semaglutide at a dose of 50 mg and demonstrated that 68 weeks of therapy resulted in an average percent weight reduction of 17.1%.[331] Currently, higher doses of SC semaglutide (7.2 mg/week) are being tested in phase III trials for individuals with obesity and T2D.[332] In the SUSTAIN-FORTE trial, A1C reduction of 2.2% was demonstrated with SC semaglutide 2.0 mg compared with 1.9% for 1.0 mg in participants with T2D.[333]

Semaglutide had previously been shown to reduce the composite MACE outcome (driven by a reduction in nonfatal stroke) in those with obesity and T2D and with established or at high risk of CVD.[334] The SELECT trial was the first CVOT investigating secondary prevention of CV events in people with established CVD with obesity and without T2D. Treatment with semaglutide 2.4 mg SC resulted in a 20% reduction in 3-point MACE (nonfatal myocardial infarction, nonfatal stroke, and CV death) over a mean exposure duration of 34 months and a mean follow-up of 40 months,[130] garnering semaglutide approval by the FDA for secondary CVD risk reduction. Semaglutide 2.4 mg also has been shown to prevent progression from prediabetes to T2D[242,335] to prevent the decline in renal function in T2D at doses used to treat diabetes,[263] to ameliorate OA[268] and HFpEF,[267] and to improve MASH histology and fibrosis.[102]

The main side effects and mitigation strategies of semaglutide are included in the section below as they pertain to the class of GLP-1 RA–based therapies approved by the FDA for obesity treatment, inclusive of liraglutide, semaglutide, and tirzepatide.

Tirzepatide

Tirzepatide is a second-generation obesity medication and is the first dual-hormone receptor agonist approved by the FDA; it is a single molecule engineered from the native glucose-dependent insulinotropic polypeptide (GIP) sequence, with action on both the GIP and GLP-1 receptors, thus a dual GIP/GLP-1 RA. As with other nutrient-stimulated hormone-based therapies, tirzepatide impacts weight by acting centrally.

Tirzepatide is formulated as a once-weekly SC injection ($t_{½}$ 116.7 hours) titrated up monthly from a starting dose of 2.5 mg weekly to a maximum dose of 15 mg weekly.[336,337] Tirzepatide was approved by the FDA at doses of 5, 10, and 15 mg per week for the treatment of both obesity in 2023 and T2D in 2022.[338] The SURMOUNT trials investigated the efficacy, safety, and tolerability of tirzepatide in obesity.[339-343] In the SURMOUNT-1 trial, the highest dose (15 mg) of tirzepatide resulted in an average weight reduction of 22.5% at 72 weeks, with nearly 40% of participants losing ≥25% of their body weight.[165] In addition, SURMOUNT-3 and SURMOUNT-4 demonstrated that combining tirzepatide with intensive lifestyle intervention or continuing treatment for 88 weeks, respectively, resulted in weight reduction up to 26.6% and 26%, respectively, in individuals with obesity.[165,344] As with other obesity medications, the weight-reduction efficacy is dampened in individuals with T2D compared with individuals with obesity alone. But, notably, in the SURMOUNT-2 trial, tirzepatide reduced weight by an average of 12.8% and 14.7% on 10- and 15-mg doses, respectively, and led to a 2.2% reduction in A1C with nearly half of participants achieving normal A1C values (<5.7%) while experiencing only uncommon episodes of level 2 or no level 3 hypoglycemia.[245] In the SURPASS-1 trial involving people with T2D, tirzepatide demonstrated an A1C reduction of 1.9% to 2% with >87% reaching the A1C target of <7%.[343]

In a prespecified post hoc analysis, tirzepatide did not increase the risk of MACE in participants with T2D compared with control individuals; the CVOT in individuals with T2D is ongoing (SURPASS CVOT, NCT04255433).[250,345-347] In addition, SURMOUNT-MMO is an ongoing CVOT investigating both primary and secondary CV risk prevention in individuals with obesity without diabetes (NCT05556512).[348] Tirzepatide has been shown to prevent progression from prediabetes to T2D[243] and to ameliorate OSA,[269] HFpEF,[266] and MASH histology and fibrosis.[103] In December 2024, the FDA approved tirzepatide as the first prescription medicine for the treatment of moderate-to-severe OSA in adults with obesity.[272]

The main side effects of tirzepatide and strategies to mitigate them are included in the section below as they pertain to the class of GLP-1 RA-based therapies inclusive of liraglutide, semaglutide, and tirzepatide.

Mitigating Side Effects of Nutrient-Stimulated Hormone-Based Therapies

The most common side effects of GLP-1 RA–based medications, such as liraglutide, semaglutide, and tirzepatide, are gastrointestinal in nature, occurring most commonly during dose escalation.[186,286] In people who are naïve to these medications, starting with the lowest dose is essential to prevent clinically significant side effects, and slow dose up-titration is vital in mitigating potential side effects if they occur. In addition, individuals benefit from monitoring which foods may exacerbate side effects (eg, fatty foods), not eating past the point of fullness, and eating smaller amounts at a given time but more

frequently if needed. Patients should be counseled that if they discontinue or pause treatment for a length of time, they will need to restart at a low dose and titrate up to enable the body time to acclimate to the medication.[186] GLP-1 RAs also cause a modest increase in heart rate, and those with vomiting or diarrhea should be monitored for dehydration and renal impairment. Therapy is also associated with elevations in lipase and amylase in the absence of pancreatitis. While weight loss from any modality increases risk of gall bladder disease, treatment with GLP-1 RAs appears to augment this risk. The FDA still recommends close monitoring for mood changes, emerging or worsening depression, or suicidal behavior during treatment with GLP-1 RA despite their findings, along with the European Medicines Agency, that evidence is insufficient to support a causal association.[349-351]

Setmelanotide

Setmelanotide is a melanocortin 4 receptor (MC4R) agonist administered daily by SC injection for the treatment of certain rare genetic disorders of obesity. It received breakthrough drug designation from the FDA in 2020 for chronic weight management in people ≥6 years of age with obesity caused by POMC, proprotein convertase 1, or leptin receptor deficiency. In June 2022, it was also approved by the FDA for the chronic treatment of Bardet-Biedl syndrome (BBS) and has efficacy in those with hypothalamic obesity.

Setmelanotide targets the MC4R, which is pivotal in controlling appetite and maintaining energy balance. Individuals with genetic mutations impacting the MC4R pathway often exhibit early onset of severe obesity (before 5 years of age), hyperphagia (uncontrollable hunger), and a positive family history of obesity.

Given the rarity of these genetic mutations, the initial regulatory approval of setmelanotide was based on studies that included 21 participants.[352-355] The findings demonstrated that for the 10 participants with POMC or proprotein convertase 1 deficiency, 8 of 10 patients met the primary outcome of ≥10% weight loss at 1 year; among all enrollees, mean weight reduction was -25.6%. For the 11 participants with leptin receptor deficiency, the response to setmelanotide was more variable. Of those 11, only 5 (45%) achieved the primary outcome of ≥10% weight loss at 1 year. For the BBS studies, 16 participants ≥12 years of age were treated with setmelanotide. Among them, 32.3% experienced a significant reduction of ≥10% in body weight after 52 weeks. Furthermore, quality of life studies involving 20 participants with BBS revealed meaningful improvements across various health-related quality of life measures after 1 year of setmelanotide treatment.[356] People with hypothalamic obesity have also been shown to benefit from treatment with setmelanotide.[357]

The most common adverse events of setmelanotide are injection site reactions, skin hyperpigmentation (which improved after stopping the medication), nausea, vomiting, and diarrhea. Other side effects include spontaneous penile erections and spontaneous female arousal, depression, and suicidal thoughts.

Cellulose and Citric Acid Hydrogel

The combination product of cellulose and citric acid hydrogel differs from other available products because it is not a medication but rather a matrix that is not absorbed, occupying volume in the stomach with the goal to promote fullness. It is considered a medical device with FDA clearance for weight management. In the GLOW and GLOW-EX studies, 59% of participants achieved 5% weight reduction.[358] This product should be avoided in those with a history of gastrointestinal disorders and may impact the absorption of other medications. Plenity was discontinued by the manufacturer in 2023 for financial reasons. Another hydrogel, Epitomee, is approved for treating people with obesity over the BMI range of 25.0 kg/m^2 to 40.0 kg/m^2 and produced a 4.5% weight loss in a clinical trial after 12 weeks with reductions in BP and triglycerides.[359,360]

Online Prescriptions for Obesity Medications and Compounded, Nutrient-Stimulated, Hormone-Based Peptides

It should be clear that online prescriptions for obesity medications, unless accompanied by clinical evaluation by a health care professional, would not provide for assessment of ORCD. Without the clinical component of diagnosis and the evaluation for ORCD, complication-centric care is not possible, and the principles defining quality care for people with ABCD in Algorithm 1 could not be operative. Furthermore, people with ABCD require long-term follow-up for evaluating response to therapy regarding ORCD and the maintenance of health benefits. Individuals should also be supported and managed to assure adequate nutrition, mitigation of side effects, avoidance of unhealthy excessive weight loss and inadequate nutrition (particularly on second-generation obesity medications), and establishment of safe long-term maintenance therapy which may differ from interventions first used for active weight loss. There are opportunities for telemedicine and telehealth strategies in the care of people with ABCD. Whether follow-up involves in-person visits or telehealth, the involvement of trained health care professionals is required to achieve these aspects of care. Online prescription of obesity medications per se, operating without involvement of health care professions for initial evaluation and follow-up, represents substandard care and places individuals at risk.

Compounded alternatives to FDA-approved semaglutide and tirzepatide are often dispensed via online pharmacies. AACE advises against the use of these agents. Several factors led to the demand for compounded medications, including the unprecedented efficacy of semaglutide and tirzepatide combined with the high cost, inadequate insurance coverage, and limited supply of the preparations approved by the FDA.

Both tirzepatide and semaglutide have periodically been in shortage because of the imbalance between supply and demand. Compounders may prepare compounded versions of a drug on FDA's list of drug shortages if the compounded drug meets certain conditions detailed in federal law. Compounded drugs, however, are not approved by the FDA; thus, without verification of safety, effectiveness, or quality before they are marketed, they pose a higher risk to individuals than drugs approved by the FDA. An analysis of compounded preparations has demonstrated inaccurately labeled concentrations, impurities, other high molecular weight peptides, trace metals, residual solvents, and neopeptides (compounded semaglutide is usually manufactured using peptide synthesis and not by recombinant DNA) with potential immunogenicity.[361] The FDA has recommended caution over the use of compounded semaglutide and tirzepatide because of overdosing that has led to hospitalizations.[362] Involved pharmaceutical companies have asked the FDA to place tirzepatide and semaglutide on its demonstrable difficulties for compounding lists, and this designation has recently been approved. Drug products or categories that present "demonstrable difficulties for compounding" under sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act would prohibit compounding those medications.

Conclusions

Obesity is a chronic, heterogeneous, neuroendocrine, progressive and/or relapsing disease impacted by the obesogenic environment

2025

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGY

AACE ALGORITHM

FOR THE EVALUATION AND TREATMENT OF ADULTS WITH OBESITY/ADIPOSITY-BASED CHRONIC DISEASE

Algorithm Title Page

TABLE OF CONTENTS

Abbreviations: **ABCD**, adiposity-based chronic disease; **FDA**, U.S. Food and Drug Administration

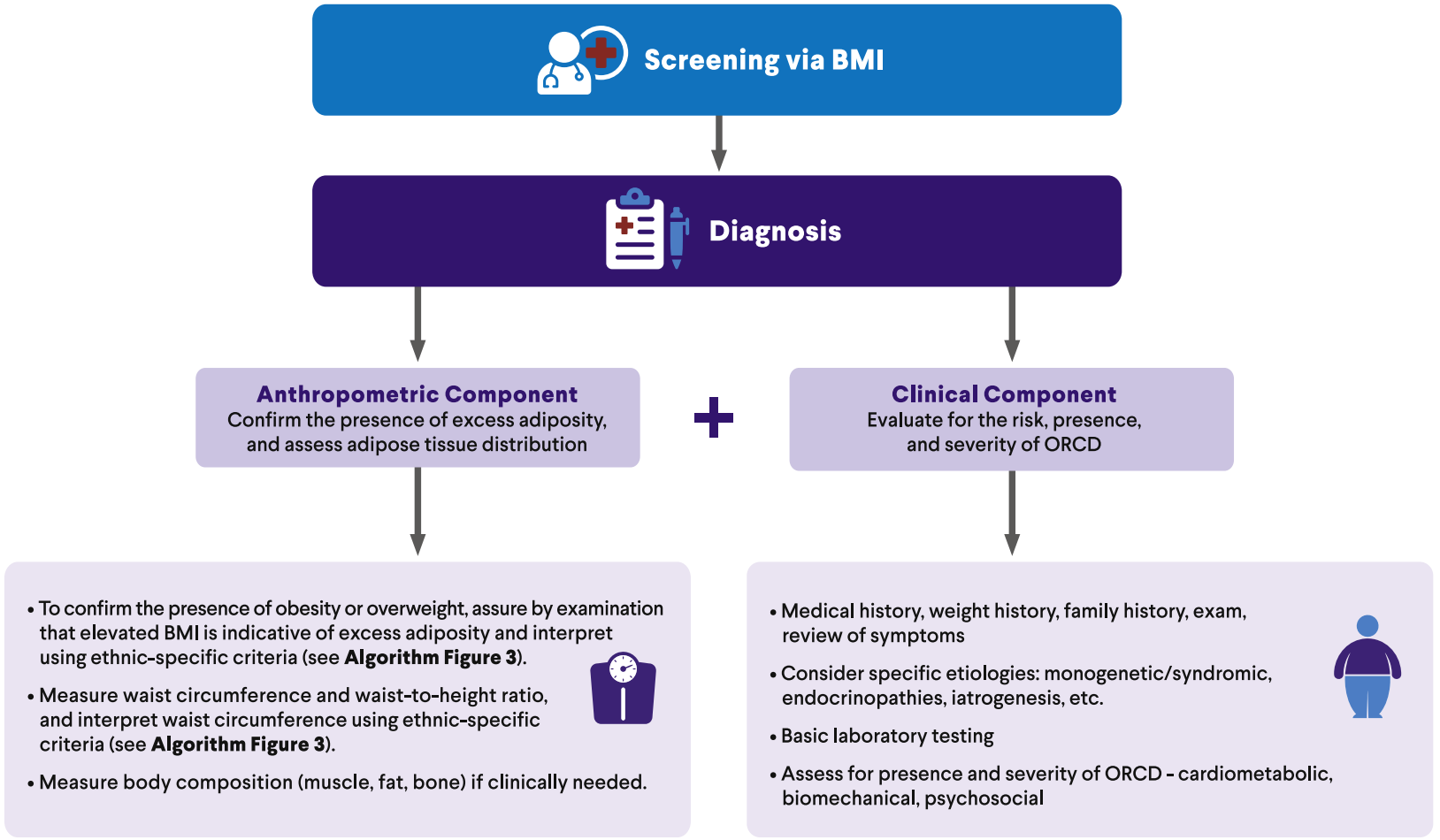
PRINCIPLES OF PERSON-CENTERED AND COMPLICATION-CENTRIC MANAGEMENT OF OBESITY/ABCD

1.	Emphasize whole-person health and de-emphasize BMI and weight-centric approaches in the treatment of individuals with obesity/ABCD.
2.	People with obesity/ABCD should be evaluated by an empathetic trained health care professional to include both the anthropometric and clinical components of the diagnosis and should be followed long-term by a health care professional who will manage weight loss and assure that treatment goals for optimizing health are achieved.
3.	For the anthropometric component of the diagnosis, obesity is evaluated using BMI with clinical confirmation of excess adiposity, waist circumference, waist-to-height ratio, and assessment of body composition when clinically needed.
4.	For the clinical component of the diagnosis and disease staging of ABCD, assess the risk, presence, and severity of ORCD. Include internalized weight bias and impact of stigmatization as part of clinical staging.
5.	Involve the individual in shared decision-making to determine personalized health goals while targeting sufficient weight loss to achieve clinical treatment goals for health.
6.	Develop treatment plans involving lifestyle, pharmacologic, and surgical options using an individualized approach that considers complications and their severity, patient preferences, social determinants of health, psychological disorders, and access to care.
7.	The goals of therapy are to improve health and the quality of life by preventing or treating ORCD, not solely defined by the loss of a specific amount of weight.
8.	Therapy, beyond behavioral/lifestyle alone, should be considered at all stages of ABCD (stages 1, 2, or 3) when needed to improve the health of patients.
9.	Implement a plan for long-term follow-up with each patient to monitor maintenance of healthy goals, clinical outcomes, and treatment modifications as needed.

Abbreviations: **ABCD**, adiposity-based chronic disease; **BMI**, body mass index; **ORCD**, obesity-related complications and diseases

Algorithm Figure 1 - Guiding Principles

CARE MODEL FOR PEOPLE WITH OBESITY/ABCD: SCREENING AND DIAGNOSIS



Abbreviations: **ABCD**, adiposity-based chronic disease; **BMI**, body mass index; **ORCD**, obesity-related complications and diseases

Algorithm Figure 2 - Screening and Diagnosis

DIAGNOSIS: ANTHROPOMETRIC COMPONENT

Anthropometric Screening & Classification

Measure BMI
Clinically examine and confirm excess adiposity

+

Measure Waist Circumference
for BMI <35.0 kg/m^2, and
Calculate Waist-to-Height Ratio
for classifying abdominal obesity and cardiometabolic risk

Class	WHO BMI Classification
Overweight*	25.0 – 29.9 kg/m^2
Class I Obesity*	30.0 – 34.9 kg/m^2
Class II Obesity	≥35.0 – 39.9 kg/m^2
Class III Obesity	≥40.0 kg/m^2

*In the Asia-Pacific region, the BMI threshold for obesity is generally considered to be ≥25 kg/m^2 and for overweight 23 kg/m^2 to 24.9 kg/m^2. See text for additional information.

+

Assess Body Composition
Using, for example, bioelectrical impedance analysis or DXA if clinically needed and available

International Diabetes Federation Waist Circumference Criteria for Cardiometabolic Risk[d]			National Institute for Health and Care Excellence, and World Health Organization
Region/Ethnic Background[e]	**Sex**	**Waist Circumference[f]**	**Waist-to-Height Ratio**
Europe, Sub-Saharan Africa, and Middle East	Male	≥94 cm	≥0.5
	Female	≥80 cm	≥0.5
United States & Canada	Male	≥102 cm	≥0.5
	Female	≥88 cm	≥0.5
Asia, South & Central America	Male	≥90 cm	≥0.5
	Female	≥80 cm	≥0.5

[d]Darbandi M et al. Discriminatory Capacity of Anthropometric Indices for Cardiovascular Disease in Adults: A Systematic Review and Meta-Analysis. Prev Chronic Dis. 2020 Oct 22;17:E131.

[e]See text for additional information.

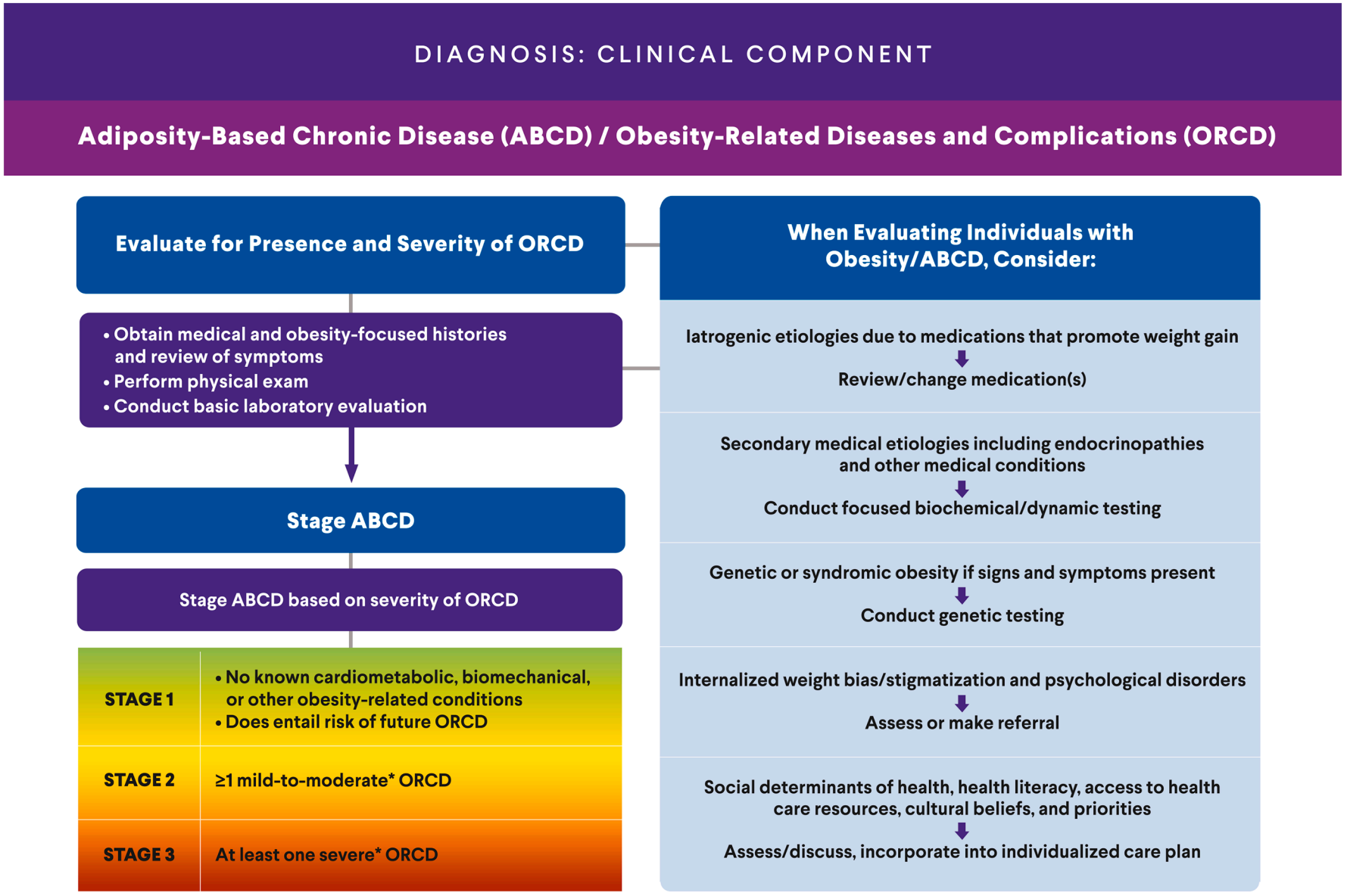
[f]Increasing waist circumference correlates with increased severity of obesity.

Obesity: identification, assessment and management. NICE Guideline, No. 189.

London: National Institute for Health and Care Excellence (NICE); 2023 Jul 26. Recommendations 1.2.11 and 1.2.12

Abbreviations: **BMI**, body mass index; **DXA**, dual-energy X-ray absorptiometry; **WHO**, World Health Organization

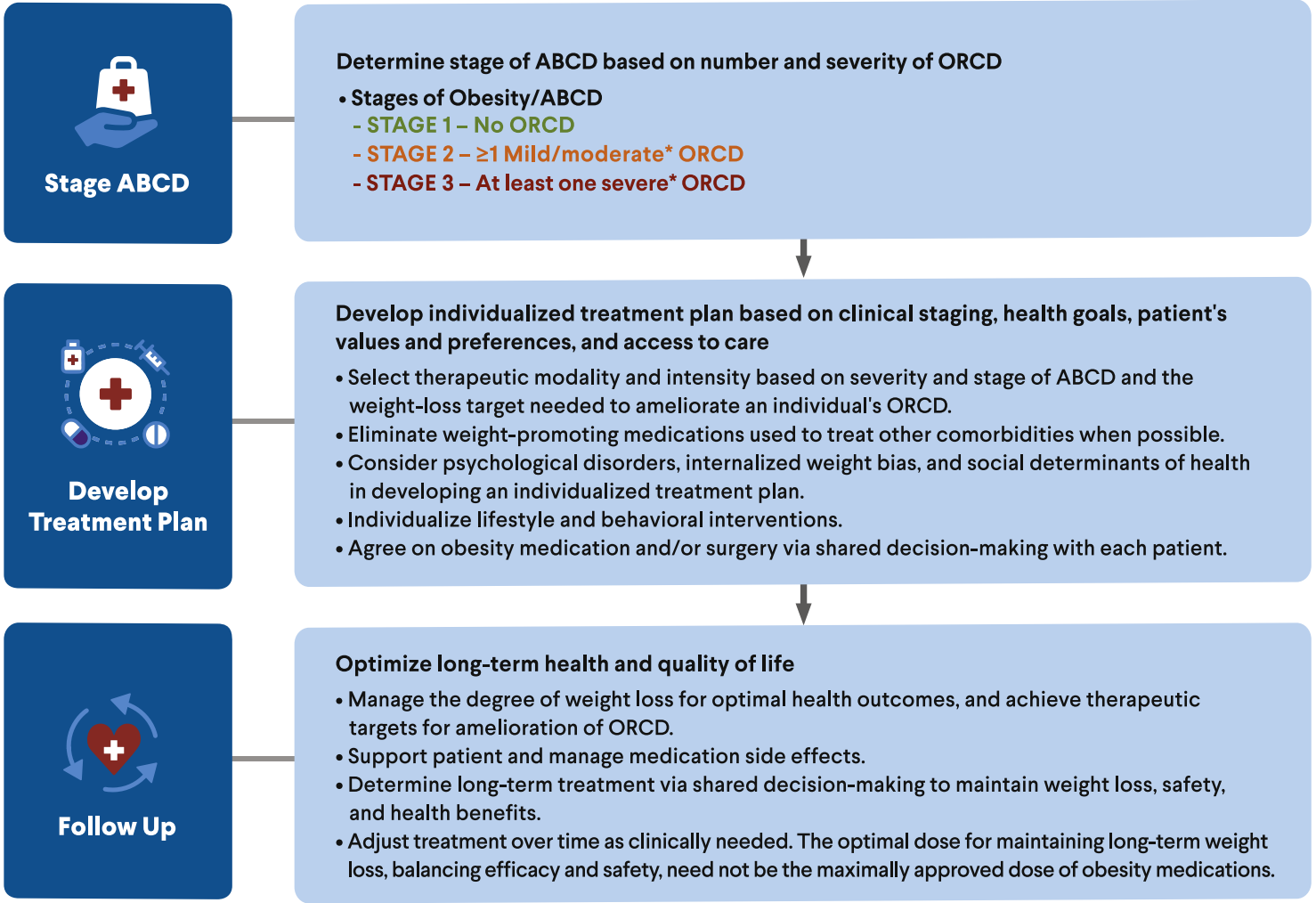
Algorithm Figure 3 - Diagnosis: Anthropometric Component



*The degree of severity for ORCD is based on clinical judgment, incorporating findings from physical examination, laboratory testing, and/or other diagnostic procedures, as well as a person's symptomatology, in ways that apply to each individual complication.

Algorithm Figure 4 - Diagnosis: Clinical Component

INDIVIDUALIZED TREATMENT PLAN, THERAPEUTIC GOALS, AND FOLLOW-UP

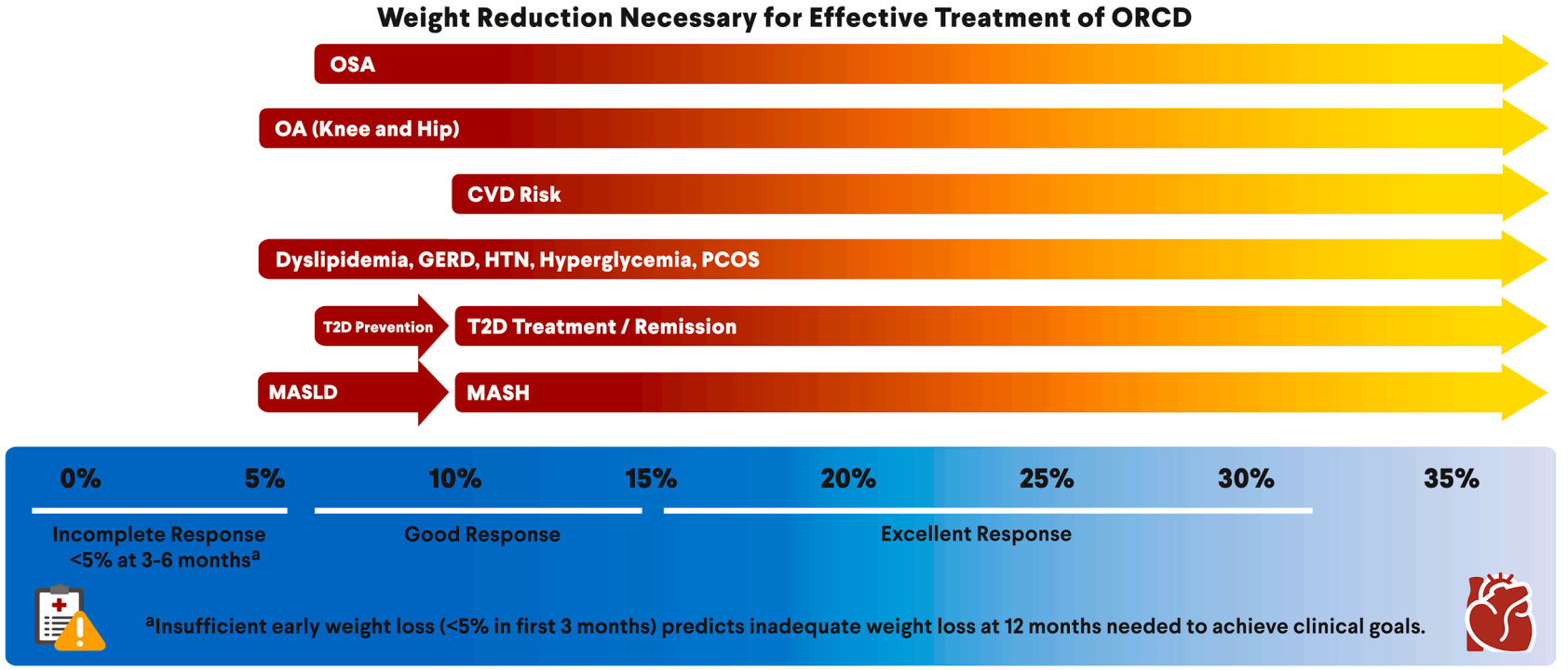


*The degree of severity for ORCD is based on clinical judgment, incorporating findings from physical examination, laboratory testing, and/or other diagnostic procedures, as well as a person's symptomatology, in ways that apply to each individual complication.

Abbreviations: **ABCD**, adiposity-based chronic disease; **ORCD**, obesity-related complications and diseases

Algorithm Figure 5 - Treatment Plan, Therapeutic Goals, and Follow-Up

RESPONSE TO THERAPY AND WEIGHT-LOSS TARGETS FOR PEOPLE WITH ABCD



Abbreviations: **ABCD**, adiposity-based chronic disease; **BMI**, body mass index; **CVD**, cardiovascular disease; **GERD**, gastroesophageal reflux disease; **HLD**, hyperlipidemia; **HTN**, hypertension; **MASH**, metabolic dysfunction-associated steatohepatitis; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **OA**, osteoarthritis; **ORCD**, obesity-related complications and diseases; **OSA**, obstructive sleep apnea; **PCOS**, polycystic ovary syndrome; **T2D**, type 2 diabetes

Algorithm Figure 6 - Response to Therapy and Weight-Loss Targets

BEHAVIORAL/LIFESTYLE THERAPY FOR PEOPLE WITH OBESITY/ABCD

Consider social determinants of health, including access to care and specialists, nutritious food, safe spaces for physical activity, and sleep when developing a treatment plan.

NUTRITION

Focus on a reduced-calorie diet while maintaining diet quality.

- **Adopt healthful meal patterns (eg, Mediterranean diet).**
- **Prioritize minimally processed, nutrient-dense foods.**
- **Limit energy-dense foods and beverages.**
- **Ensure adequate nutrient intake of protein, fiber, iron, calcium, and other micronutrients with significant weight loss.**

Individualized energy plans may include:

- **Macronutrient-based strategies**
- **Meal replacements**
- **Strategic fasting**
- **Personalized calorie targets**

Consider referral to a registered dietitian. Combine evidence-based dietary approaches to suit individual and cultural preferences.

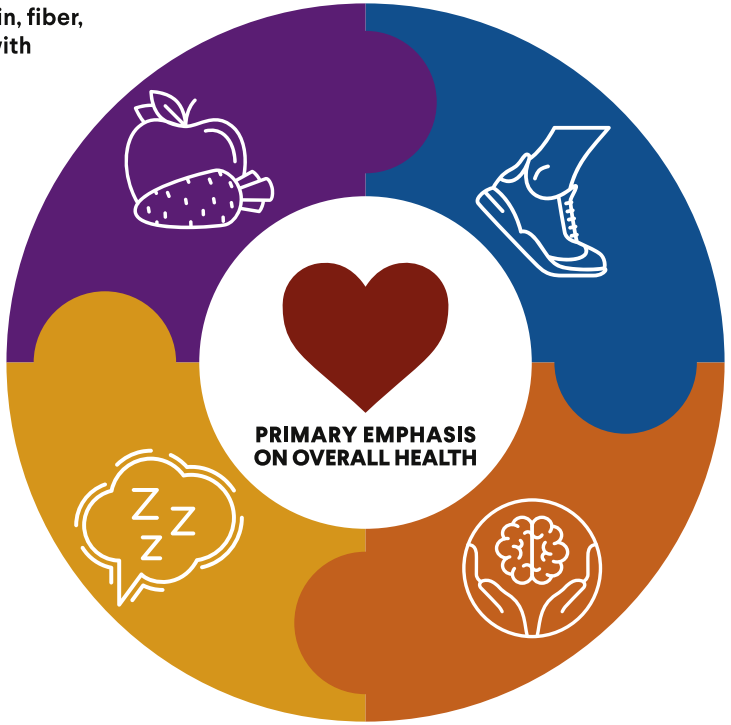
SLEEP

Screen for sleep disorders.

Promote good sleep hygiene.

Optimize sleep quality and duration.

Refer for polysomnography or sleep medicine evaluation if needed.



PHYSICAL ACTIVITY

Tailor to patient preferences and functional ability.

Incorporate:

- **Aerobic activity**
- **Resistance training***
- **Reduced sedentary behavior**

Gradually increase intensity and volume as tolerated.

Refer to an exercise specialist if needed.
**Resistance training helps preserve lean mass during significant weight loss.*

BEHAVIORAL THERAPY

Screen for anxiety, depression, eating disorders, and internalized weight bias.

Support behavioral adherence with:

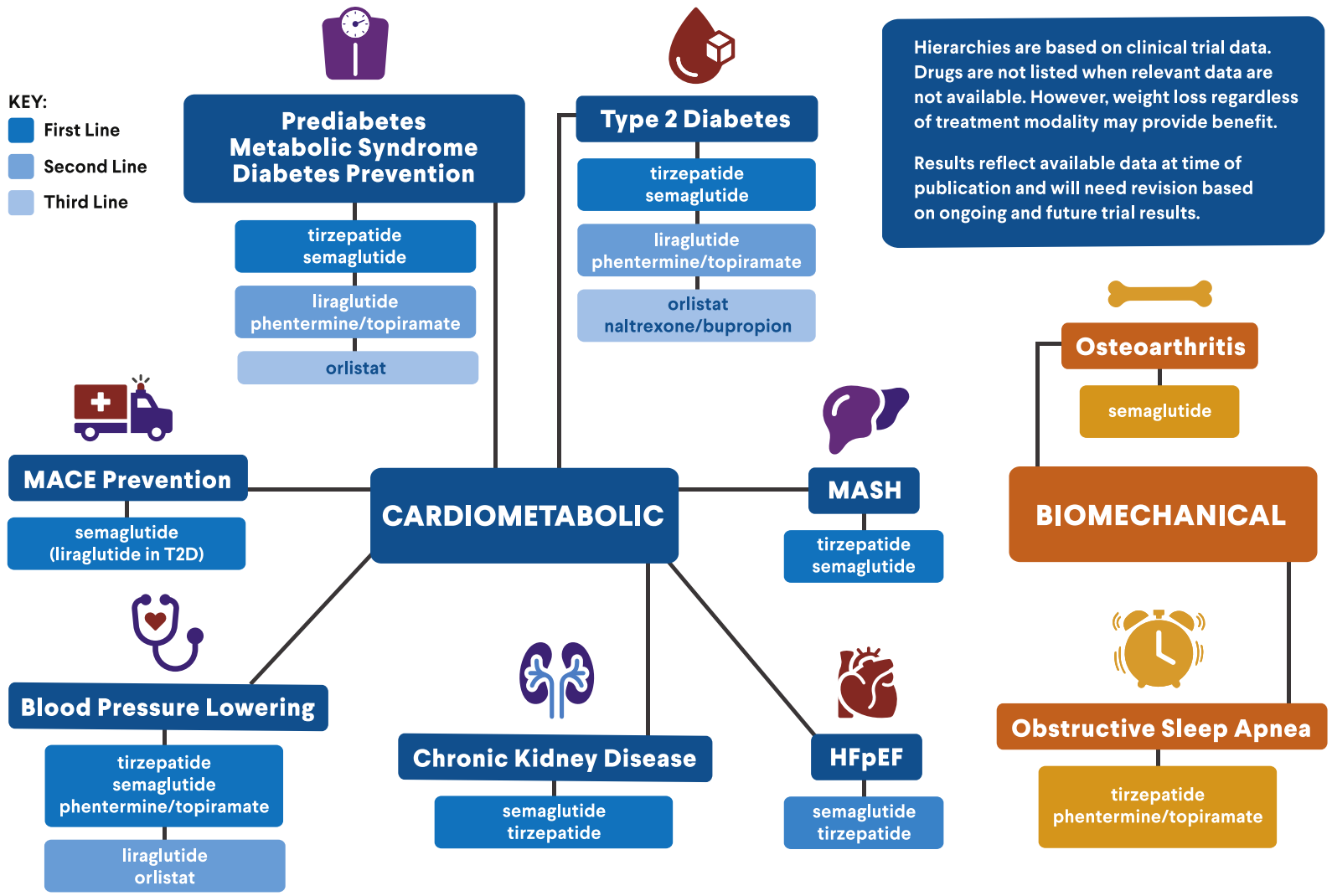
- **Goal setting, self-monitoring, and problem-solving**
- **Cognitive behavioral therapy**
- **Stress reduction techniques**

Refer for psychological testing or behavioral health support as needed.

Abbreviation: **ABCD**, adiposity-based chronic disease

Algorithm Figure 7 - Behavioral/Lifestyle Therapy

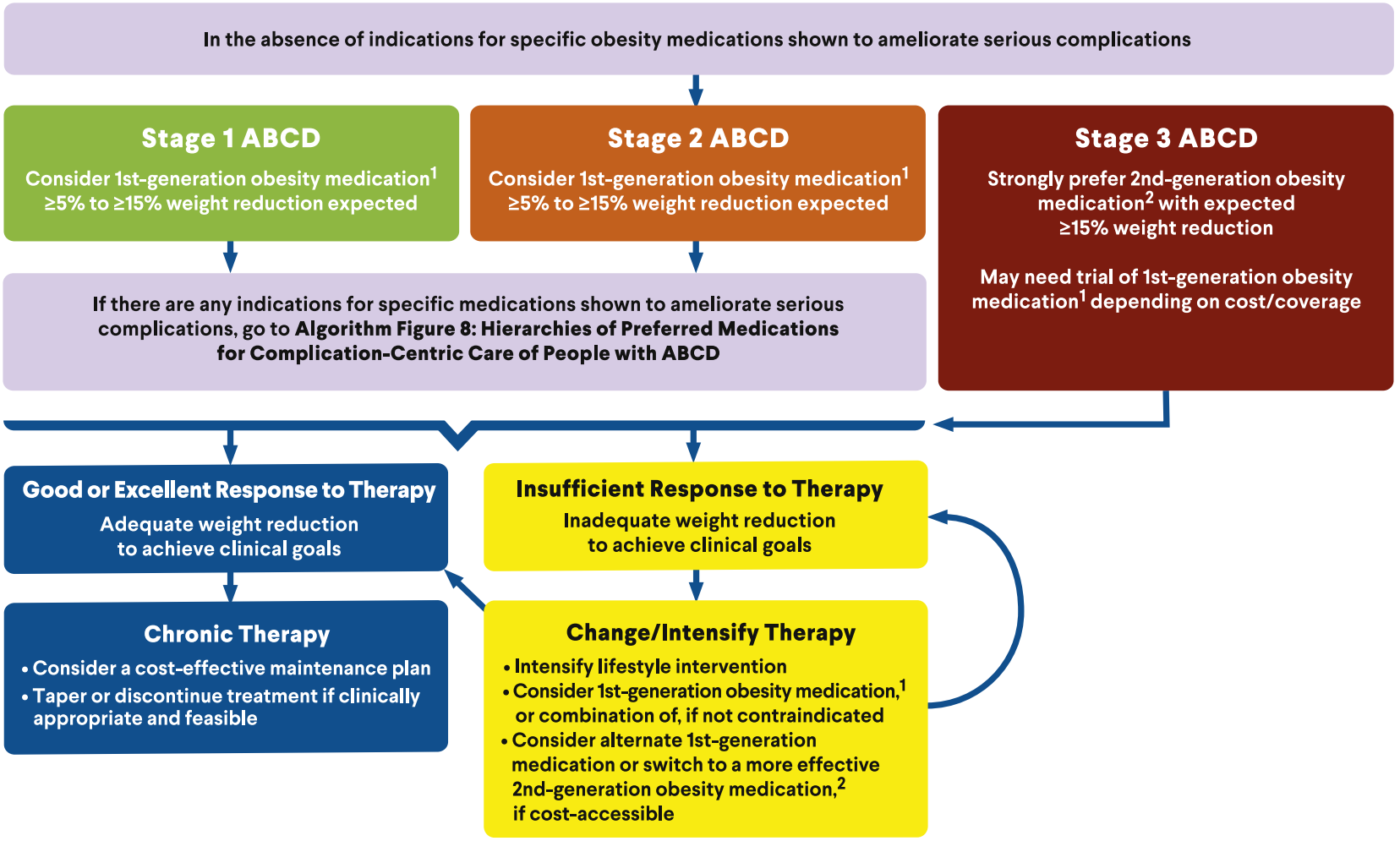
HIERARCHIES OF PREFERRED MEDICATIONS FOR COMPLICATION-CENTRIC CARE OF PEOPLE WITH ABCD



Abbreviations: **ABCD**, adiposity-based chronic disease; **HFpEF**, heart failure with preserved ejection fraction; **MACE**, major adverse cardiac events; **MASH**, metabolic dysfunction-associated steatohepatitis ; **T2D**, type 2 diabetes

Algorithm Figure 8 - Preferred Medications Hierarchies

LOWER-COST PHARMACOLOGIC STEP THERAPY FOR ABCD



[1]1st-generation obesity medications: phentermine, phentermine/topiramate ER, nalextrone/buproprion ER, liraglutide

[2]2nd-generation more effective obesity medications: semaglutide, tirzepatide

Abbreviations: **ABCD**, adiposity-based chronic disease; **ER**, extended release

Algorithm Figure 9 - Lower-Cost Pharmacologic Step Therapy

MEDICATIONS FOR OBESITY: INDIVIDUALIZATION OF THERAPY[a]

KEY: Preferred (evidence of benefit) | Insufficient evidence to prefer | Monitoring indicated | Contraindicated (evidence of risk/harm)

OBESITY-RELATED CONDITION	ORLISTAT	PHENTERMINE	PHENTERMINE/ TOPIRAMATE ER	NALTREXONE ER/ BUPROPION ER	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
DIABETES PREVENTION	Benefit via weight reduction		Benefit via weight reduction		Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect
TYPE 2 DIABETES	Benefit via weight reduction		Benefit via weight reduction	Benefit via weight reduction	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect	Benefit via weight reduction and incretin effect
HYPERTENSION	Benefit via weight reduction	Monitor heart rate, BP Contraindicated in uncontrolled HTN	Monitor heart rate, BP; BP benefit observed in trials*	Monitor heart rate, BP Contraindicated in uncontrolled HTN	BP benefit observed in trials; Monitor heart rate	BP benefit observed in trials; Monitor heart rate	BP benefit observed in trials; Monitor heart rate
ASCVD		Contraindicated	Use with caution; Monitor heart rate, BP	Monitor heart rate, BP	Demonstrated prevention of ASCVD in T2D	Demonstrated prevention of ASCVD	Evidence in T2D and obesity pending
MASLD					Benefit observed in trials	Benefit observed in trials	Benefit observed in trials
DEPRESSION			Appropriate monitoring	Appropriate monitoring	Appropriate monitoring	Appropriate monitoring	Appropriate monitoring
ANXIETY		Appropriate monitoring	Appropriate monitoring	Appropriate monitoring			
CHRONIC KIDNEY DISEASE	Monitor for oxalate nephropathy		Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90mg twice a day	Benefit in T2D; Avoid vomiting and volume depletion	Benefit in T2D; Avoid vomiting and volume depletion	Benefit in T2D; Avoid vomiting and volume depletion
SEVERE KIDNEY IMPAIRMENT	Monitor for oxalate nephropathy	Urinary clearance of drug	Urinary clearance of drug	Urinary clearance of drug	Avoid vomiting and volume depletion	Avoid vomiting and volume depletion	Avoid vomiting and volume depletion
NEPHROLITHIASIS	Calcium oxalate stones		Calcium phosphate stones				
HEPATOBILIARY IMPAIRMENT	Monitor for cholelithiasis	Do not exceed 8 mg per day	Do not exceed 7.5 mg/46 mg per day	Do not exceed 8 mg/90 mg daily	Monitor for cholelithiasis	Monitor for cholelithiasis	Monitor for cholelithiasis
SEVERE HEPATIC IMPAIRMENT	Not recommended						

[a]All medications are contraindicated in pregnancy and breastfeeding. *Blood pressures are significantly decreased in clinical trials.

Abbreviations: **ASCVD**, atherosclerotic cardiovascular disease; **BP**, blood pressure; **ER**, extended release; **HTN**, hypertension; **T2D**, type 2 diabetes

Algorithm Figure 10 - Medications for Obesity: Individualization of Therapy

MEDICATIONS FOR OBESITY APPROVED BY THE U.S. FOOD AND DRUG ADMINISTRATION[a,b]

	ORLISTAT	PHENTERMINE[c]	PHENTERMINE/ TOPIRAMATE ER	NALTREXONE ER/ BUPROPION ER	LIRAGLUTIDE	SEMAGLUTIDE	TIRZEPATIDE
CLASS/MECHANISM OF ACTION	Lipase Inhibitor	NE-releasing agent	NE-releasing agent GABA Receptor Modulation	Opioid-Receptor Antagonist DA-NE Reuptake Inhibitor	GLP-1 RA	GLP-1 RA	GIP/GLP-1 RA
AGE	≥12 years[d]	>16 years	≥12 years	≥18 years[d]	≥12 years[e]	≥12 years[e]	≥18 years[d]
DELIVERY	Oral	Oral	Oral	Oral	Subcutaneous Injection	Subcutaneous Injection	Subcutaneous Injection
STARTING DOSE	60 mg 3 times/day AC	8mg or 15mg QAM	3.75 mg/23 mg QAM	8 mg/90 mg QAM	0.6 mg QD	0.25 mg QWK	2.5 mg QWK
DOSE ESCALATION	Titrate up to needed dose Slow dose titration if side effects occur Formulations: 60 mg cap 120mg cap	Titrate up to needed dose Slow down dose titration if side effects occur Formulations: 8mg tab 15 mg cap 37.5mg tab	Titrate up bi-weekly to needed dose Slow down dose titration if side effects occur 3.75 mg/23 mg QAM x 2 wk 7.5 mg/ 46 mg QAM x 12 wk 11.25 mg / 69 mg QAM x 2 wk 15 mg/92 mg QAM	Titrate up weekly to needed dose Slow down dose titration if side effects occur 8 mg/90 mg QAM x 1wk 8 mg/90 mg twice daily x 1 wk 16 mg/90 mg QAM and 8 mg/90 mg QPM x 1 wk 16 mg/90 mg twice daily	Titrate up weekly to needed dose Slow down dose titration if side effects occur 0.6 mg QD x 1 wk 1.2 mg QD x 1 wk 1.8 mg QD x 1 wk 2.4 mg QD x 1 wk 3.0 mg QD	Titrate up monthly to needed dose Slow down dose titration if side effects occur 0.25 mg QWK x 4 wk 0.5 mg QWK x 4 wk 1.0 mg QWK x 4 wk 1.7 mg QWK x 4 wk 2.4 mg QWK	Titrate up monthly to needed dose Slow down dose titration if side effects occur 2.5 mg QWK x 4 wk 5.0 mg QWK x 4 wk 7.5 mg QWK x 4 wk 10 mg QWK x 4 wk 12.5 mg QWK x 4 wk 15 mg QWK
MAXIMUM DOSE	120 mg 3 times/day AC	37.5 mg QAM[f]	15 mg/92 mg QD	16mg/180mg twice daily	3.0 mg QD	2.4 mg QWK	15 mg QWK
WEIGHT REDUCTION[g]	4% (52 weeks)	5%–6% (28 weeks)	9.6%–9.9% (52 weeks) dose dependent	4.2%–5.2% (52 weeks)	9.2% (56 weeks)	16.9% (68 weeks)	22.5% (72 weeks)
POTENTIAL SIDE EFFECTS[h]	Flatulence Fecal Urgency Oily Stools Fat-Soluble Vitamin and Drug Malabsorption Potential Drug-Drug Interactions	Restlessness Insomnia Headache Dry Mouth Tachycardia BP Elevation	Paresthesia, Dizziness Dysgeusia, Insomnia Constipation, Dry Mouth Fatigue Blurred Vision Mental Clouding Mood Changes	Nausea, Constipation Headache Vomiting Dizziness Insomnia Dry Mouth, Diarrhea Anxiety	Nausea Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain GERD	Nausea, Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain Headache Fatigue	Nausea, Diarrhea Constipation Dyspepsia Vomiting Abdominal Pain Headache Fatigue
CAUTIONS, RELATIVE AND ABSOLUTE CONTRAINDICATIONS[i]	Cholestasis Chronic Malabsorption Syndrome Nephrolithiasis Vitamin Malabsorption Encourage Supplementation Potential for Misuse	CAD, CVA, Arrythmias, CHF, Uncontrolled HTN* Hyperthyroidism Agitated States History of Drug Abuse MAOI Use Angle-Closure Glaucoma	MAOI Hyperthyroidism Angle-Closure Glaucoma Monitor for Increased Heart Rate Nephrolithiasis Metabolic Acidosis[c] Monitor for Worsening Anxiety or Depression[c]	Seizure Disorder Uncontrolled HTN Chronic Opioid Use Anorexia Nervosa Bulimia Nervosa MAOI Use Abrupt Drug or Alcohol Withdrawal Angle-Closure Glaucoma Monitor for Worsening Anxiety or Depression[c]	History or Family History MTC/MEN2 Gallbladder Disease Pancreatitis Increased Heart Rate	History or Family History MTC/MEN2 Gallbladder Disease Pancreatitis Diabetic Retinopathy[j]	History or Family History MTC/MEN2 Gallbladder Disease Diabetic Retinopathy[j]
ACCESS/COST	$$	$	$$	$$	$$$	$$$$	$$$$

[a]Monogenic obesity treatment, devices for weight reduction, and setmelanotide can be found in narrative. [b]FDA-approved for CWM. [c]This class of medications includes diethylpropion (or amfepramone), phendimetrazine, and benzphetamine. [d]EMA approved for age 18 years and above for CWM. [e]EMA approved for age 12 years and above for CWM. [f]Maximum dose allowed for phentermine; however, many patients will see results on 8 mg 3 times a day which is also considered a maintenance dose in patients with diabetes and obesity. [g]Percent body weight reduction in treatment in Phase 3 trial. [h]Complications requiring caution or monitoring in order of observed frequency. [i]All FDA-approved medications for obesity are contraindicated in individuals who are pregnant or breastfeeding; effective birth control should be recommended/prescribed. A negative pregnancy test is recommended before initiating, with monthly monitoring. [j]In patients with T2D and obesity. *Blood pressures are significantly decreased in clinical trials for phentermine/topiramate ER.

Abbreviations: **AC**, before meals; **BP**, blood pressure; **CAD**, coronary artery disease; **CHF**, congestive heart failure; **CVA**, cerebrovascular accident; **CWM**, chronic weight management; **DA**, dopamine; **EMA**, European Medicines Agency; **ER**, extended release; **FDA**, U.S. Food and Drug Administration; **GERD**, gastroesophageal reflux disease; **GIP**, glucose-dependent insulinotropic polypeptide; **GLP-1 RA**, glucagon-like peptide-1 receptor agonist; **HTN**, hypertension; **MAOI**, monoamine oxidase inhibitors; **MEN2**, multiple endocrine neoplasia, type 2; **MTC**, medullary thyroid cancer; **NE**, norepinephrine; **QAM**, every morning; **QD**, every day; **QPM**, every afternoon or evening; **QWK**, every week; **wk**, week(s)

Algorithm Figure 11 - FDA-Approved Medications for Obesity: Prescribing Information

and genetic susceptibility factors resulting in excess or abnormally distributed adiposity which impairs overall health. This algorithm guides clinicians in the decision-making process with their patients for the medical treatment of ABCD using a complication-centric approach and provides supportive guidance for personalized lifestyle and behavioral interventions. Anthropometric and clinical evaluation provides the basis for diagnosis and disease staging, which informs decisions regarding therapy intensity and the setting of individualized therapeutic goals. The evaluation requires a general medical and obesity-focused history, obesity-oriented review of systems, a physical examination, and key laboratory testing by a trained health care professional. In addition, an individualized care plan requires patient engagement in decision making and consideration of bias and stigmatization, psychological disorders, and social determinants of health. Clinical goals extend beyond weight reduction and maintenance to a primary focus on amelioration of ORCD, improved health outcomes, and a better quality of life consistent with a complication-centric approach to care.

Lifestyle interventions remain an important component for optimizing health in individuals with ABCD. This includes personalized medical nutrition therapy, prescribed physical activity, and behavioral interventions to help optimize healthful eating and integrate movement into daily life. It is key that individuals with ABCD incorporate these lifestyle and behavioral efforts alongside initiation and continuation of pharmacotherapeutic interventions for improvement of overall health.

Medications have variable mechanisms of actions, side effects, and clinical outcomes. Shared decisionmaking should be used to individualize care, matching a person with the pharmacotherapeutic interventions that may optimally treat their disease, improve quality of life, and treat or prevent ORCD. The algorithm for the first time establishes hierarchies of preferred medications in complication-centric care based on evidence for amelioration of specific ORCD. Importantly, as for any complex, chronic disease, it is critical to provide lifelong care, adjusting obesity treatment interventions to the needs of each person with the goal of optimizing overall health over their lifetime.

Review Process

Drafts of this consensus statement were reviewed and approved by all task force members, the AACE Clinical Practice Guidelines Oversight Committee, the AACE Board of Directors, and peer reviewers for *Endocrine Practice.*

Disclosures

The task force was empaneled in accordance with the 2019 AACE Conflicts of Interest Policy. Disclosures were updated and reviewed annually at a minimum and as necessary to maintain accuracy. See Appendix A for a full list of disclosures.

Acknowledgments

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Panel Composition

This consensus statement was developed by a task force of credentialed medical professionals in the fields of endocrinology, obesity medicine, primary care, and nutrition who are current AACE members in good standing.

Document Retirement Date: November 2030

AACE reviews and updates or retires its guidance documents every 5 years following publication or sooner if significant scientific developments or change in public policy occurs.

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