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EXPERT PANEL

Obesity Pharmacotherapy

An Urgent Need for Progressing Science, Access, and Equity—*JACC: Advances* Expert Panel

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ABSTRACT

The Duke Clinical Research Institute hosted a think tank, "Anti-Obesity Pharmacotherapy: Need for Guidance, Access, and Equity" in October 2024. This brought together multi-industry stakeholders to align and advance the field of obesity medications (OMs). Key themes included the need for an evidence-based, patient-centric definition of obesity incorporating alternative measures of excess or dysfunctional adiposity, obesity symptoms, and obesity-related complications; barriers to OM access (cost and availability) that perpetuate inequalities in care; ambiguity in optimal clinical OM use; challenges of novel clinical trial designs; and ethics of placebo-controlled trials. Action items included a cross-stakeholder obesity research roadmap, standardized obesity measures inclusive of and beyond body mass index, strategies to ensure equitable OM access, and a forum to address regulatory and payer challenges. The complex, rapidly developing field of obesity research and OM development requires a strategy to ensure equitable, streamlined research and access to OMs. (JACC Adv. 2026;■:102713) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Obesity and overweight impact the lives of approximately 172 to 205 million adults in the United States.[1,2] At a societal level, obesity is estimated to cost ~425 billion U.S. dollars annually,[3,4] and the prevalence of overweight and obesity is expected to reach over 50% of the U.S. population by 2030,[5] further increasing the potential financial burden.

Multifaceted strategies involving a wide range of stakeholders are essential to combat rising obesity rates and associated comorbidities. Recent developments in obesity medications (OMs) have proven effective in treating obesity;[6-8] however, these developments have resulted in unique implementation challenges. In early days, manufacturers struggled to keep up with unexpected demand,

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

GLP-1 = glucagon-like peptide-1

OM = obesity medication

leading to drug shortages that made it difficult for health care systems to meet patient demands, and the cost of OMs continue to make them unattainable for many. Additional challenges include identifying patients most likely to benefit from OMs, ensuring equitable access, determining strategies for long-term weight maintenance, identifying relevant nonweight-based endpoints, and developing clinical trial designs to efficiently address these unknowns and elucidate the optimal use of OMs in chronic disease treatment and the prevention of obesity-related complications. The navigation of current and upcoming challenges will shape the field of obesity care for decades, highlighting the importance of coordinated, equitable, and efficient actions from multiple stakeholders. This report has been compiled with the goal of identifying concrete action items to advance this field (**Central Illustration**).

METHODS

The Duke Clinical Research Institute hosted a think tank titled "Anti-Obesity Pharmacotherapy: An Urgent Need for Guidance, Access, and Equity" on October 16 to 17, 2024. The think tank comprised thought leaders and experts across the spectrum of the clinical research enterprise. The think tank organizers (P.G., C.H., J.J., A.J., and N.P.) developed an outline for topics of interest related to antiobesity pharmacotherapy that were purposefully matched to potential speakers across stakeholder groups, leveraging pre-existing relationships and prior think tank participation. This structured, multistakeholder approach was intended to ensure that the perspectives and recommendations presented would reflect practical considerations across clinical care, trial design, regulatory science, and payer decision-making rather than the views of any single discipline. As such, the themes outlined in this manuscript are meant to complement existing empirical evidence by highlighting cross-cutting challenges and opportunities that are difficult to capture through traditional single-stakeholder studies alone. Participants were subsequently invited with the possibility of recommending additional speakers and fine-tuning discussion topics. All meeting sessions were recorded and summarized at the end of each session, with specific themes and potential action items identified. These summaries were presented at the end of each day to participants to ensure that they were representative of the discussion and to provide an opportunity for clarification. Following the meeting, a meeting brief was created that outlined key concepts and action items with iterative feedback from participants. The key themes and actionable items that emerged from the discussions are outlined within this manuscript.

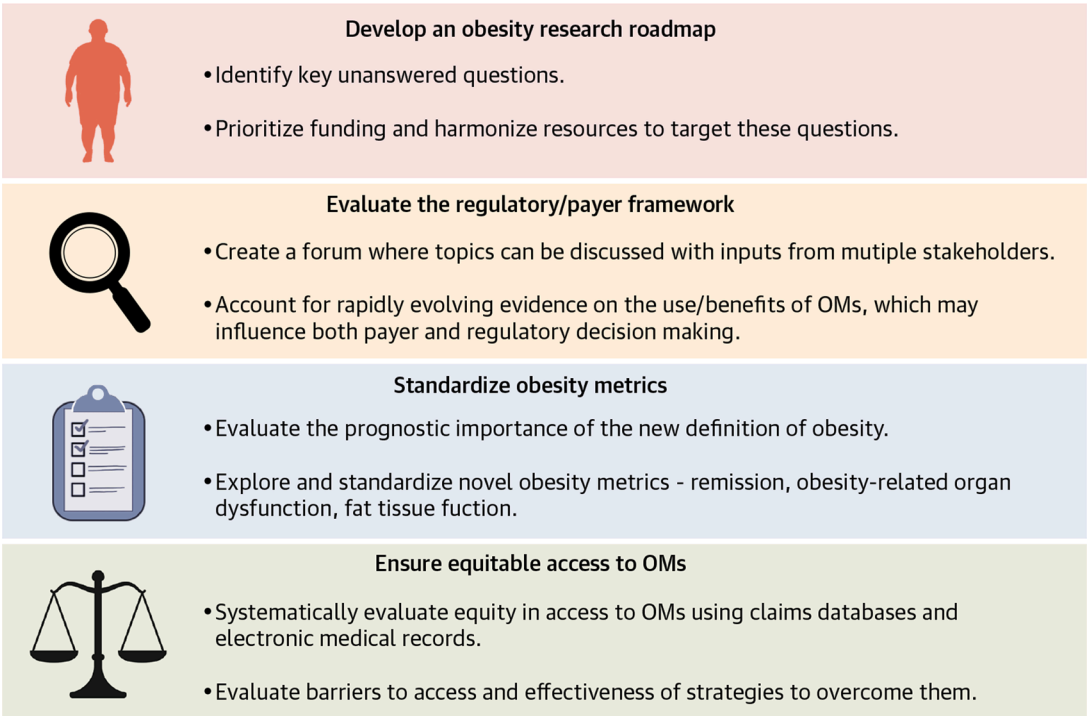
HIGHLIGHTS

- The Duke Clinical Research Institute brought together stakeholders to participate in a think tank titled "Anti-Obesity Pharmacotherapy: An Urgent Need for Guidance, Access, and Equity" to align on actionable action items to advance the field of obesity medications.
- Key actionable items include the development of a roadmap for obesity research, standardization of obesity metrics and endpoints, ensuring equitable access to obesity medications, and evaluation of the regulatory and payer framework.
- Key components of the obesity research roadmap should include further understanding of the lifelong epidemiology and pathophysiology of obesity, an evidence-based approach to the definition of obesity and obesity outcomes, enhanced understanding of role of obesity medication, and efforts to improve education and health literacy among patients and providers alike.

KEY THEMES

DEFINING OBESITY. The definition of obesity has been long debated, but there has been agreement that obesity is a chronic disease. Obesity has an underlying neurometabolic biology that results in excess body fat accumulation. Although obesity can be quantified with the use of body mass index (BMI), BMI is a calculated measure that was designed to be a screening tool, not a diagnostic tool. Obesity has historically been defined as having a BMI of $\geq$30 kg/m^2 and overweight as having a BMI $\geq$25 kg/m^2.[9] However, due to a lack of diversity in the populations studied to create these BMI criteria, sex and racial and ethnic variations are not captured accurately in historic categorizations of BMI.[10] Recognizing these limitations, prior guidelines have introduced waist circumference as a complementary measure of central adiposity and incorporated BMI, adiposity distributions, and obesity-related comorbidities into a risk-stratified framework to guide clinical assessment

CENTRAL ILLUSTRATION **Action Items to Address Challenges With Obesity Medications**



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Key actions items identified included the development of an obesity research roadmap with input from all stakeholders, the standardization of current and novel obesity metrics, development of a regular process to evaluate the regulatory and payer framework with regards to obesity medications, and development of strategies to ensure and measure equitable access to obesity medications.

and treatment decisions.[11] Together, BMI and waist circumference demonstrate a predictable relationship with total and central adiposity across a population.[12,13] These anthropometric measurements remain easy, cost-effective measurements that may be leveraged to monitor trends on a population level or as a screening tool. However, the definition of obesity needs to advance beyond these 2 anthropological measurements.

Consensus was reached by the think tank participants that the definition of obesity should evolve to more accurately capture various aspects of obesity, including metrics of adiposity (central and visceral adiposity and imaging metrics), functional limitations (joint/muscle pain, mobility, fatigue, sleep, and strength), psychological symptoms (stress, nociception, depression, anxiety, and cognitive impairment), complications of obesity (arthritis, obstructive sleep apnea, hypertension, metabolic dysfunction-associated steatotic liver disease, heart disease, and glucose dysregulation, including type 2 diabetes), and concomitant comorbidities/manifestations.[14] In January 2025, the Lancet Commission on Obesity proposed new diagnostic criteria for obesity,[15] re-emphasizing the importance of confirming obesity with an additional anthropometric measurement such as waist circumference or direct fat measurement. The diagnosis of obesity should also require the presence of either signs or symptoms of organ dysfunction secondary to obesity or limitations of mobility or activities of daily living due to obesity.

To translate an expanded definition of obesity into clinical practice, a pragmatic, tiered approach will be required. In routine care, BMI may continue to function as an initial screening tool, with confirmation of clinical obesity based on readily obtainable adjunctive measures (such as waist circumference and body fat composition) and screening for obesity-related symptoms or complications. In parallel, further studies will be required to identify which individuals are most likely to benefit from

pharmacologic therapy based on these new criteria. Such an approach provides a transparent framework for payers by linking treatment eligibility to demonstrable disease burden and anticipated clinical benefit rather than anthropometry alone. For clinical trials and regulatory programs, sponsors could operationalize this definition through standardized inclusion criteria for obesity incorporating measures of adiposity and functional or organ-level impairment and through the incorporation of endpoints that extend beyond weight loss to include improvements in physical function, metabolic health, and obesity-related complications. These measures could align trial design, health benefit design, reimbursement decisions, and real-world effectiveness.

COMPREHENSIVE APPROACHES TO OBESITY MANAGEMENT. A core principle of obesity management centers around empowering patients to make lifestyle changes. Numerous studies have demonstrated that individualized nutrition consultation with a focus on creating a sustained energy deficit is an effective method of weight loss.[16] Similarly, enabling patients to achieve 30 to 60 minutes of moderate aerobic activity accentuates weight loss in addition to improving a range of cardiovascular outcomes.[17,18] Despite their proven effectiveness, access to these services and to obesity services in general remains a major barrier.[19,20] A holistic approach to obesity management requires the concurrent assessment and management of mental health, with a known bidirectional relationship between mental health and obesity.[21] Improving access to multidisciplinary, comprehensive obesity care that emphasizes nutrition, physical activity, and mental health remains a strategic priority to improve obesity-related outcomes. While these comprehensive approaches are effective, their resource-intensive nature highlights the need for the complementary integration of pharmacological therapy. The integration of pharmacological therapy in the primary care setting with multidisciplinary care models requires clear clinical pathways, appropriate provider education, and alignment of the reimbursement structure to support long-term, coordinated care.

THE VALUE AND COST OF OBESITY MEDICATIONS. At the time of the think tank, several therapies had been approved for obesity-management (phentermine/topiramate [2012], naltrexone/bupropion [2014], liraglutide [2014], semaglutide [2021], tirzepatide [2023]);[6-8,22,23] these therapies have been shown to lead to a mean weight loss ranging from −8% to −23% of baseline body weight over approximately 1.5 years. Several of these therapies also have additional benefits. The 2 most effective agents, semaglutide and tirzepatide, have demonstrated improved outcomes related to cardiovascular health,[24-26] diabetes prevention,[27] osteoarthritis,[28] obstructive sleep apnea,[29] and metabolic dysfunction-associated steatohepatitis[30] among individuals with obesity. Although these therapies can be expensive,[31] the cost-effectiveness of these therapies on an individual and societal level is unknown. Microsimulation models estimate the cost-effectiveness ratios of OMs to range from 237,000 (semaglutide) to 483,000 (liraglutide) U.S. dollars per quality-of-life year gained,[32] which would suggest that these therapies are not cost-effective. However, these models have fundamental flaws in that they do not account for the cost savings associated with improvements in obesity-related conditions such as cardiovascular outcomes, osteoarthritis, or sleep apnea, as supportive data are lacking. Importantly, a comprehensive assessment of the societal value of OMs must account for their potential lifetime, multiorgan system benefits, as current cost-effectiveness analyses are largely derived from time-limited, single-disease trial data and therefore systematically underestimate their true preventive and economic impact. Data from employer-sponsored insurance programs suggest that employees with obesity who reduced their BMI by >5% demonstrated a 7% decrease in health care spending.[33] The most recent draft report from the Institute of Clinical and Economic Review highlights that when accounting for obesity-related complications, semaglutide and tirzepatide are highly cost effective, with the cost per quality-adjusted life-year ranging from 53,400-69,300 U.S. dollars,[34] but further data from real-world effectiveness are still required.

IMPROVING EQUITY WITH OBESITY MEDICATIONS. Obesity does not affect all populations equally. Obesity prevalence differs markedly by race, ethnicity, and geographic location.[35] These disparities are exacerbated because rural-dwelling, older, lower-socioeconomic status, and non-White individuals are less likely to receive appropriate treatment for obesity,[36-38] translating into disparities in obesity-related complications and mortality.[39] The use of OMs can be harnessed to minimize these disparities but requires representation in clinical trials and equitable access. For instance, even though obesity disproportionately impacts Black individuals, especially Black women, obesity clinical trials are largely (74%) composed of non-Hispanic White participants.[40] To date, recent trials have not

consistently achieved population-level representation, underscoring the need for diversity plans to ensure that obesity clinical trial populations mirror real-world demographics. In terms of access, non-White individuals are 30 to 60% less likely to be started on a glucagon-like peptide-1 (GLP-1) receptor agonist,[41] largely due to financial barriers.[42] The financial burden (including co-payments) may lead to a disproportionate increase in the use of unregulated compounded OMs among marginalized populations; unregulated compounded OMs are not studied in clinical trials or Food and Drug Administration approved, and they have been associated with significant adverse effects.[43]

INITIATION, MAINTENANCE, AND DISCONTINUATION OF OBESITY MEDICATIONS. Guidelines typically recommend the initiation of OMs in adults with a BMI of ≥30 kg/m^2 or a BMI of ≥27 kg/m^2 with at least 1 obesity-related comorbidity or complication after assessment of readiness/barriers to lifestyle changes.[44,45] However, the observed variability in effectiveness of OMs highlights the need for studies that evaluate phenotype-driven (metabolic vs behavioral) and personalized approaches to OMs.[46,47] One of the critical unresolved questions in this field is the long-term management of obesity. There is a significant need to develop an evidence-based definition of "weight maintenance" and to determine whether weight maintenance is associated with improved outcomes and improved long-term body composition parameters. Another critical question centers on the duration of therapy with OMs. Studies have shown significant weight regain when incretin-based OMs like semaglutide[48] and tirzepatide[49] are stopped, which is expected, as obesity requires long-term therapy akin to any other chronic disease.[50] Whether strategies such as a reduced-dose maintenance phase, gradual withdrawal of OMs, or intermittent "booster periods" with short-term OM use are effective remains to be investigated. Importantly, any such studies should consider whether such changes in intervention have been effective in the setting of other chronic diseases. Harnessing real-world data to understand what occurs when patients start and stop these OMs as part of routine care will be important.

An additional and increasingly salient consideration in long-term obesity pharmacotherapy is the potential for adverse effects related to body composition, particularly loss of lean skeletal muscle mass and the downstream risk of sarcopenia. Emerging imaging-based and body composition analyses from clinical trials of GLP-1-based therapies demonstrate that a meaningful proportion of total weight loss may derive from lean mass, with substantial interindividual variability.[51] These changes may have important implications for physical function, frailty, metabolic resilience, and long-term cardiovascular risk, particularly among older adults and individuals with established cardiovascular disease. Accordingly, the cardiometabolic community has increasingly recognized the need to contextualize pharmacologically induced weight loss within broader frameworks of muscle health and functional outcomes.[52]

Concerns regarding potential long-term effects on muscle mass and physical function are commonly encountered in clinical discussions and reflect the chronic nature of obesity treatment. Interventions to minimize muscle loss during pharmacologic weight reduction will likely require deliberate cointerventions, including resistance exercise, adequate protein intake, and periodic assessment of strength and physical performance.[53] Several "muscle-sparing" agents are currently being evaluated to explore the utility of these agents in preserving lean muscle mass during weight loss. Bimagrumab is an activin type II receptor blocker that has demonstrated the ability to increase lean mass by 3.6% while decreasing body weight by 6.5% in a phase 2 weight loss intervention study in patients with diabetes.[54] A phase 2 study exploring the utility of bimagrumab in conjunction with tirzepatide among patients without diabetes is currently underway, with results expected by the end of 2026 (NCT06643728). Two additional agents (trevogrumab, a human monoclonal antibody targeting myostatin, and garetosmab, a human IgG4 monoclonal antibody that targets activin A) are being explored in a variety of combinations in addition to semaglutide in an ongoing phase 2 trial (NCT06299098). Enobosarm, a selective androgen receptor modulator that mimics testosterone, is also being evaluated in combination with GLP-1 receptor agonists (NCT06282458). Overall, the regulatory path forward with these agents remains unclear. Further clarity is required to define who should be considered for these agents, which may include all-comers or target those who are at highest risk of sarcopenia. In addition, the recommended timing of the use of these interventions, that is, whether they should be initiated at the time of weight loss therapy initiation or when there is objective evidence of sarcopenia, remains unknown. To clarify these aspects, collaboration between clinicians, researchers, industry, regulators, and patient advocates will be required.

Future long-term trials and postmarketing surveillance should therefore incorporate standardized

measures of body composition, muscle strength, and functional status to better characterize benefit-risk trade-offs and to guide durable, patient-centered treatment strategies. Such an approach is particularly important given the emerging recognition of sarcopenic obesity as a clinically relevant phenotype rather than a theoretical construct.[55]

CLINICAL TRIAL DESIGN. Clinical trials in the field of obesity should evolve to include pragmatic study designs and the recruitment of a more diverse and generalizable population. Adopting platform study designs could improve trial efficiency, particularly when multiple indications are sought for a single drug, by enabling the concurrent use of clinical trial sites and shared control groups. Unlike traditional trials, platform trials allow simultaneous investigation of multiple interventions with the flexibility to add or remove therapies as new evidence emerges.

Another pragmatic element of interest includes the use of digital technologies to enable virtual or remote follow-up. All study designs, including basket/platform trials, have inherent advantages and limitations, which require careful consideration on a case-by-case basis.[56,57] A promising new model for obesity research is exemplified by the American Heart Association's Healthy Living BEYOND Weight Study (NCT07075341), a nationwide observational cohort study designed to capture long-term, real-world health experiences of adults living with overweight or obesity and those engaged in weight management, including medication use or bariatric procedures. Unlike traditional clinic-based trials, this study will recruit participants directly through digital platforms and use app-based surveys and optional electronic health record linkage to longitudinally assess lifestyle, treatment exposures, health behaviors, and outcomes across a broad spectrum of individuals. By prioritizing large-scale, direct-to-participant engagement and repeated remote assessments, Healthy Living BEYOND Weight has the potential to generate highly generalizable data on the effectiveness, tolerability, and real-world impact of weight management strategies outside of controlled settings. This approach may accelerate understanding of how emerging therapies and integrated lifestyle factors influence cardiovascular, metabolic, and quality-of-life outcomes over time, offering insights that can complement traditional randomized trials and inform both clinical practice and public health strategy.

The use of placebo arms is also increasingly becoming an ethical issue in the obesity space now that there are several effective and safe products on the market.[6-8] The decision to switch from placebo to an active comparator is nuanced. On one side, there may be clinicians who believe that given currently available evidence, it would be unethical to randomize an individual to placebo when non-investigational, proven efficacious therapies are available. Conversely, current access to OMs remains complicated, and patients may not have access to them without participating in a trial. An additional challenge with the use of placebo is retention; due to the unique, visible effects of active OM drugs, when patients realize they are on placebo, they may discontinue the trial and pursue alternative OM access routes, therefore affecting the data quality. This phenomenon is now increasingly being observed in the placebo-treated arms of studies of obesity. One potential solution to address this concern is to offer all participants access to the investigational drug in long-term extension phases following study completion, contingent on the drug demonstrating safety and efficacy. An alternative to this approach that is being used in obesity pharmacotherapy trials is the use of a putative placebo.[58] In obesity research, a putative placebo refers to an externally derived estimate of expected weight change in the absence of active pharmacologic therapy informed by prior randomized placebo-controlled trials, run-in periods, or historical control data. This approach may be useful in active-comparator or pragmatic study designs to contextualize observed weight loss and to assess whether treatment effects exceed those plausibly attributable to placebo response alone.

This strategy was employed in the SURPASS-CVOT (Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes), which allowed the trial to simultaneously assess superiority of tirzepatide against a putative placebo benchmark and noninferiority against dulaglutide.[58,59] However, putative placebo comparisons rely on strong assumptions of exchangeability across trials and populations and are highly sensitive to differences in background lifestyle intervention, follow-up duration, baseline BMI, metabolic status, and secular trends in weight management. Importantly, a putative placebo does not represent a randomized counterfactual or a formal estimand and therefore cannot support confirmatory inference, control of type I error, or causal attribution of treatment effects.

Accordingly, comparisons against a putative placebo should be interpreted as contextual or descriptive rather than inferential. Clear prespecification of the data sources, assumptions, and uncertainty underlying any putative placebo estimate (including

FIGURE 1 Obesity Research Roadmap

Epidemiology and Pathophysiology

1. What is the prevalence and rate of progression in the spectrum of obesity?
2. What are predictive factors of progression?
3. What are genetic/environmental risk factors for obesity?

Definition of Obesity and Outcomes

1. What are thresholds for anthropometric measures of obesity that correlate with obesity-related outcomes?
2. What is the significance of various types of obesity-related organ dysfunction?
3. What is the optimal method of staging obesity severity?
4. How do we define control/relapse of obesity?
5. What degree of weight loss is associated with improvements in obesity outcomes?
6. What are alternative metrics (fat tissue function, biomarkers) to quantify/characterize subtypes of obesity?
7. What is the cost-effectiveness of OM in various obesity subgroups?

Obesity Management

1. How effective are OMs at improving "clinical" obesity rather than solely weight loss?
2. Should OMs be used differently during a "maintenance" phase or in the event of disease progression?
3. What is the optimal pathway/combination of various obesity treatments (bariatric surgery, OMs, lifestyle interventions)? Does it vary by stage/severity/complications of obesity?
4. What are the disparities and barriers to obesity therapy access? What are evidence-based mechanisms to overcome them?

Education and Health Literacy

1. What are effective strategies to reframe obesity as a disease rather than the results of lifestyle choices?
2. What are effective strategies to improve physician knowledge and engagement with obesity management?

Key components of an obesity research roadmap will require enhanced understanding of the lifelong epidemiology (patient journey) and pathophysiology of obesity, improvements of various definitions used to describe obesity and obesity outcomes, further data regarding the utility of obesity medications in different stages of obesity and how they should be used long term, and development of initiatives to improve education and health literacy among the general public and healthcare providers. OM = obesity medication.

sensitivity analyses across plausible benchmark scenarios) is essential, particularly when such comparisons are used to support claims of clinical relevance or to inform regulatory, payer, or clinical decision-making.

ACTIONABLE ITEMS

DEVELOP AN OBESITY RESEARCH ROADMAP. The field of obesity research would benefit from an obesity research roadmap that would highlight key challenges and unanswered questions that need to be addressed and prioritized by researchers and funders. Establishing these priorities would simultaneously allow for harmonization of obesity research across all stages of drug development, from preclinical to postapproval studies (Figure 1).

STANDARDIZE OBESITY METRICS. There is a need for standardization in the field of obesity research, including an evidence-based approach for defining obesity and treatment success. Standardization of these definitions will allow for data sharing across clinical trials and real-world registries. The January 2025 Lancet Commission on the Diagnostic Criteria of Obesity began the process of updating and moving toward standardization of the definition of obesity on a population/epidemiological level[15] by requiring an additional anthropometric criterion or direct body fat measurement as well as the presence of obesity-related organ dysfunction or significant limitations in daily activities or mobility due to obesity. These definitions, when applied to retrospective and prospective clinical trials, will provide additional data on the prognostic importance of these changes. However, the commission concomitantly highlights that the absence of data adequately characterizing obesity and other obesity-related metrics (such as criteria for disease control) will need to be evaluated as new evidence becomes available. Going forward, it will be important for sponsors to establish consensus on the most critical data elements to capture in clinical trials, such as changes in fat and lean mass, physical function, and other relevant biomarkers. Aligning on these priorities will enable more precise characterization of obesity, support the development of personalized treatment strategies, and ultimately impact clinical outcomes.

ENSURE EQUITABLE ACCESS TO OBESITY MEDICATIONS. As with all novel pharmacotherapies, disparities exist in the utilization of OMs. As such, understanding the use of OMs throughout the United States will be the key to understanding the changing landscape of obesity. These evaluations could provide insights on differences in utilization across sexes, visible minorities, socioeconomic statuses, and rural/urban populations. Any observed disparities should trigger deeper qualitative evaluations to understand their underlying causes, inform strategies to address identified barriers, and assess the effectiveness of resulting interventions and programs. These

assessments should harness generalizable, population-wide databases, including claims databases, electronic health records from a variety of health systems, and registries. This evidence will further support development of precision medicine and provide clarity into its impact on clinical outcomes and health utilization.

EVALUATE THE REGULATORY/PAYER FRAMEWORK. Collectively, the think tank recognized that the field of OMs is rapidly evolving; as such, a forum where regulators, payers, and employers can meet with other stakeholders (clinicians, industry, and patient/advocacy organizations) to routinely evaluate topics of interest and debate would be of great use. Topics that may require regular re-evaluation include reimbursement standards in special populations, class indications for labeling, use of innovative clinical trial designs, novel endpoints in obesity trials, and the need for continued use of placebo-controlled trials. This forum will serve as a facilitator of policy changes and accelerate implementation in the field of obesity.

CONCLUSIONS

Obesity science is evolving at an unprecedented pace, and the introduction of novel OMs demonstrates both great potential as well as significant challenges. In the face of the global health crisis that is obesity, the speed and effectiveness with which these challenges are navigated will have significant implications for population health. Amid these uncertainties, the think tank participants underscore the need for increased attention and prioritization of obesity research across a broad spectrum of stakeholders to ensure that innovation translates into meaningful health outcomes.

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