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SPECIAL ARTICLE

Leveraging Real-World Evidence to Inform Regulatory, Clinical, and Coverage Decisions Related to Glucagon-Like Peptide-1–Based Therapies: Synopsis of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have transformed obesity and diabetes management, with rapidly expanding indications and use among U.S. adults. Despite their promise, key questions remain about optimal treatment pathways, long-term safety, effectiveness across diverse populations, adherence, and economic impact. Real-world evidence (RWE) derived from electronic health records, claims, and other data sources could address these gaps, but unique challenges complicate its use, such as inconsistent insurance coverage, high discontinuation rates, medication shortages, compounded formulations, and off-label prescribing. To explore these issues, the National Institute of Diabetes and Digestive and Kidney Diseases convened a workshop in May 2025 with experts from regulatory agencies, guideline committees, payers, and academia. Discussions focused on identifying knowledge gaps in GLP-1RA use, evaluating how RWE informs practice, assessing limitations of real-world data, and strategies to reduce bias in RWE. Presentations emphasized RWE's potential to complement randomized trials by capturing rare adverse events, long-term outcomes, and effectiveness in routine care. However, persistent challenges include data reliability, confounding, and incomplete capture of medication use and outcomes, particularly in pediatric and underserved populations. Coverage decisions remain heterogeneous across Medicare, Medicaid, and private payers and across time, underscoring the need for rigorous cost–benefit analyses. The workshop concluded that robust RWE is essential for developing value-based coverage policies and optimizing GLP-1RA use. Continued investment in high-quality data infrastructure and analytic methods will be critical to inform regulatory, clinical, and economic decisions as utilization expands.

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Glucagon-like peptide-1 (GLP-1)–based medications have transformed the treatment landscape for obesity and diabetes and may reduce long-term complications (1, 2). Growing evidence also suggests their potential use for prevention and/or treatment of osteoarthritis, neurodegenerative disorders, substance or alcohol use disorders, binge eating, and obesity-associated cancer (3).

As of 2025, about 12% of U.S. adults had taken a GLP-1 receptor agonist (GLP-1RA), including 20% of women aged 50 to 64 years (4), and use is expected to increase as new agents become available and indications expand (5). Yet many questions remain about treatment pathways, adherence, heterogeneity of response, outcomes outside clinical trials, the effect of GLP-1RAs on health care costs, and the incidence of rare adverse effects (6).

Real-world data (RWD) sources, including electronic health records (EHRs) and claims data, could answer many of these questions, but using these sources to generate real-world evidence (RWE) presents many challenges that are unique to GLP-1RAs. On 7 and 8 May 2025, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored a workshop, "Leveraging Real-World Evidence to Assess Benefits and Risks of GLP-1–Based Therapies," to better understand these challenges and potential approaches to mitigate them (7).

Workshop Goals and Structure

The workshop had 2 goals: to identify knowledge gaps in optimal GLP-1RA use and how RWE informs practice, and to describe RWD limitations and methods to mitigate biases. This article summarizes the day 1 sessions on "Real-World Evidence to Inform Regulatory Decisions and Clinical Practice" and "Real-World Evidence for Public and Private Payer Coverage Decisions." A companion article covers sessions 3 and 4 (7).

See also:

Related article

The Incretin Effect: From Physiology to Model Therapeutic

Dr. Kimberly Narain, an internal medicine physician and obesity medicine specialist at the University of California, Los Angeles, began by moderating a keynote presentation by Dr. David D'Alessio, Chief of the Endocrinology and Metabolism Division at Duke University, on the transition of incretin-based therapies from bench to bedside.

Incretin-based therapies have been a major development in diabetes therapeutics in the 21st century. The term *incretin* was coined almost a century ago to describe factors secreted from endocrine cells in the gastrointestinal tract after eating that stimulate insulin secretion (8). Although it has long been known that glucose ingestion stimulates more insulin secretion than intravenous infusion of glucose, the specific hormones involved were not discovered until the 1970s and 1980s. Two small peptides, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, each produced by specific enteroendocrine cells in the small intestine, were isolated and shown to act as incretins (that is, released into circulation after eating and stimulating insulin secretion only when blood glucose is elevated) (9, 10).

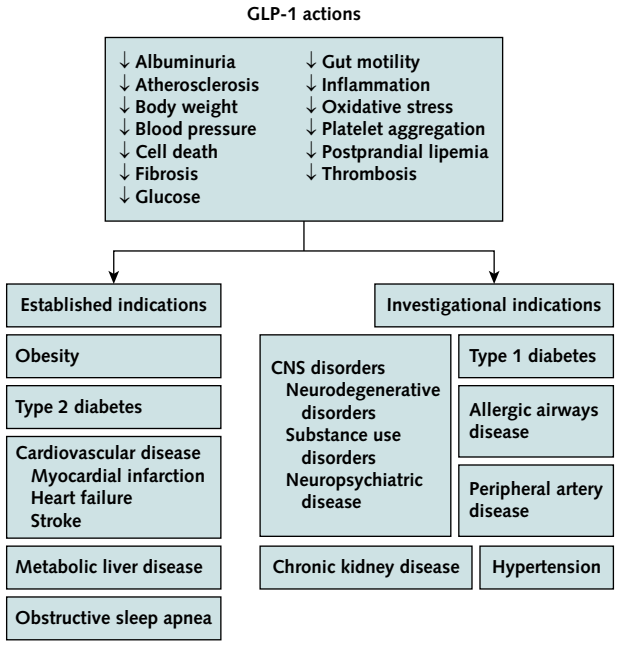
Although the 2 incretins share several key features, initial studies suggested that their potential as therapeutics differed. GIP provided a strong stimulus for glucose-stimulated insulin secretion in healthy persons, but this effect was attenuated in people with diabetes (11, 12). In contrast, the early studies in which GLP-1 was infused into persons with type 2 diabetes (T2D) showed marked enhancement of β-cell secretion (12). Moreover, hyperglycemic persons with T2D given infusions of GLP-1 showed normalization of their blood glucose levels over several hours (13). These results demonstrated the clear potential of the GLP-1 receptor as a drug target. However, parallel studies indicated that native GLP-1 was rapidly degraded in the circulation by the enzyme dipeptidyl peptidase-4 (DPP4), constraining the half-life of active peptide to just 1 to 2 minutes (14). Consequently, the application of the GLP-1 system for therapeutic ends required development of compounds resistant to DPP4 with extended circulating half-life.

Development of GLP-1RAs with pharmacokinetic profiles allowing intermittent dosing proceeded rapidly, with drugs available for clinical use within 15 years of the discovery that GLP-1 was an active incretin (15). The first agent, exenatide, was based on a molecule produced in Gila monster saliva, exendin-4, which shares considerable homology with mammalian GLP-1, is resistant to DPP4, and is a potent GLP-1RA. This was followed by other compounds, including lixisenatide, which is also based on exendin, and liraglutide and dulaglutide, which are based on modified GLP-1 sequences. These agents were effective for reducing hyperglycemia in patients with T2D, and long-term treatment also caused weight loss in most persons. This latter effect was of great interest, drove extensive research into the role of central nervous system GLP-1 receptors to mediate satiety, and prompted the development of liraglutide into an approved therapy for weight loss (16). The pharmacology of GLP-1RAs was revolutionized with the advent of semaglutide, a GLP-1–based molecule similar to liraglutide but with greater potency. Whereas the first generation of GLP-1RAs caused average reductions in hemoglobin A_{1c} (HbA_{1c}) of about 1% and weight loss of 5% to 6%, semaglutide decreased HbA_{1c} levels by 1.5% to 2.0% and body weight by 10% to 15% (17); mean weight loss of up to 20% was seen with a higher-dose formulation approved for weight loss in people without diabetes (18). The most recent advance in incretin-based therapies has been the development of multireceptor agonists (MRAs), unimolecular compounds that activate multiple receptor targets (19). Tirzepatide, a GLP-1/GIP receptor co-agonist, is the most effective U.S. Food and Drug Administration (FDA)–approved agent in the incretin class, with average HbA_{1c} reductions of about 2% and weight loss of 20% to 25% (20).

Of critical importance to the treatment of people with T2D and obesity are effects of incretin-based drugs on several comorbidities of metabolic disease. Most patients treated with GLP-1RAs or tirzepatide have associated reductions in blood pressure and circulating lipids (21). Semaglutide reduced an incident composite of cardiovascular events (myocardial infarction, stroke, and cardiovascular death) in high-risk persons without T2D (22). Moreover, GLP-1RAs have been shown to reduce the rate of decrease in renal function in persons with diabetic nephropathy as well as people with overweight and vascular disease (23). Finally, both semaglutide and tirzepatide cause histologic improvement in persons with metabolic dysfunction–associated steatotic liver disease (24) and improvement in symptoms of moderate-to-severe obstructive sleep apnea (25).

Because of the broad and potent pharmaceutical effects of incretin-based drugs (**Figure 1**), research in this area remains active. MRAs are one area of intense interest, with double- and triple-receptor agonists in the pipeline. A second area of development is in the application of small molecules that interact with incretin receptors (26). It is still unclear whether small molecules can be engineered as MRAs, but advances in receptor biology and computer modeling of receptor structures have sped progress in this approach to creating incretin-based drugs. The expansion of genomic databases, the discovery of common variants in incretin receptors, and the understanding of their function in signaling support the eventual potential for personalized use of incretin-based drugs.

Figure 1. Systemic and localized actions of GLP-1 medications, indications, and disorders with established benefit and indications under investigation in clinical trials.



CNS = central nervous system; GLP-1 = glucagon-like peptide-1. (Adapted from Drucker DJ, GLP-1–based therapies for diabetes, obesity and beyond, *Nature Reviews Drug Discovery*, 2025, vol. 24, pp. 631-650, with permission.)

RWE to Inform Regulatory Decisions and Clinical Practice

Dr. Christina Wee, Senior Deputy Editor at *Annals of Internal Medicine*, moderated a panel presentation by Drs. Marie Bradley, John Wong, and Asheley Skinner that focused on the role of RWE in informing regulatory decisions and clinical practice.

Dr. Bradley, Senior Advisor for Real World Evidence in the FDA's Office of Medical Policy, Center for Drug Evaluation and Research, described how the FDA actively uses and evaluates RWE to support regulatory decision making, including evaluating new indications and postapproval safety monitoring. The FDA's RWE program, established in response to the 21st Century Cures Act of 2016 (27), is specifically designed to facilitate the integration of RWE into regulatory decision making (28), and the FDA has issued 8 guidance documents covering data, study design, regulatory, and procedural issues (29).

The FDA's approach to evaluating RWE submissions focuses on 3 areas: fitness for use of the RWD, adequacy of the study design to answer regulatory questions, and compliance with FDA regulatory requirements. The FDA has already relied on RWE for several drug and biological approvals (30, 31) and routinely uses RWD within the Sentinel System to monitor safety signals (32), including for GLP-1RAs (33, 34). However, the use of RWD and RWE in regulatory decision making has challenges, such as issues with data reliability and relevance, missing or mistimed data, exposure misclassification, unmeasured confounding, and limited clinical detail in claims data, that must be addressed for RWE to be considered credible and actionable.

Next, Dr. Wong, Vice-Chair of the U.S. Preventive Services Task Force (USPSTF) and Associate Editor for Methods at *Annals of Internal Medicine*, described how clinical guidelines are grounded in systematic evaluation of scientific evidence to improve care and outcomes. He highlighted how organizations such as the USPSTF, the American Diabetes Association (ADA), and the American Academy of Pediatrics (AAP) span the guideline spectrum across adult and pediatric populations (**Appendix Tables 1** and **2**, available at Annals.org), reflecting distinct missions and evidentiary standards (35–37).

The USPSTF is an independent volunteer panel that makes recommendations about preventive services for asymptomatic people, including screening, counseling, and preventive medications (38), using grades ranging from A to D and I statements (39). A and B grades require moderate-to-high certainty of moderate-to-substantial net benefit, preferably based on data from randomized controlled trials (RCTs), and indicate recommended services ("do") (40); C grades indicate small net benefit and call for shared decision making; D grades indicate zero or negative net benefit ("don't"); and I statements reflect insufficient evidence. For the USPSTF, benefit must reflect patient-perceptible outcomes rather than intermediate outcomes alone, such as weight loss (41). Although RWE may inform harms, benefits, epidemiology, and modeling, it is generally used for context rather than as primary evidence (42).

The USPSTF last evaluated weight loss pharmacotherapy in 2018 in a review of 34 RCTs of 5 medications, including 4 trials of liraglutide (43). Trials showed modest short-term weight loss (−1.0 to −5.8 kg at 12 to 18 months) with high attrition, limited data on durability, variable outcome reporting, and limited generalizability to primary care populations (43, 44). Given these limitations and the lack of long-term outcome data, the USPSTF did not recommend pharmacotherapy for weight loss at that time and instead recommended intensive behavioral interventions for adults with a body mass index (BMI) of 30 kg/m^2 or higher (Grade B) (43). Going forward, Dr. Wong further emphasized the importance of patient preferences, treatment durability, and the need for longer-term studies evaluating cardiovascular, metabolic, psychosocial, quality of life, and other patient-centered outcomes (45).

The ADA Standards of Care, developed annually by a 20-member professional practice committee, use a graded evidence framework (46). Evidence levels range from A (high-quality RCTs or meta-analysis) to C

(poorly controlled or uncontrolled studies), with E reflecting expert consensus (46). In 2025, the ADA reported progressively greater weight loss with GLP-1RAs versus older drugs, with liraglutide, semaglutide, and tirzepatide achieving weight loss of about 5% to 15% (47). Interventions achieving weight loss of 3% to 7% were rated as level A for improved glycemia and intermediate cardiovascular risk factors and level B for possible T2D remission and long-term cardiovascular benefit (47). The ADA calls for further research on durability and long-term cardiovascular, mortality, and health system effects of sustained weight loss exceeding 10% (46, 47).

Dr. Skinner, lead methodologist for the AAP obesity guidelines, summarized key considerations for pharmacologic treatment in children. In 2023, the AAP published its first evidence-based guideline for obesity recommending motivational interviewing and intensive health behavior and lifestyle treatment (IHBLT) to children aged 6 years or older with obesity (BMI ≥95th percentile) (48). For adolescents aged 12 years or older with obesity, the AAP recommends offering weight loss pharmacotherapy with IHBLT, and for those aged 13 years or older with severe obesity (BMI ≥120% of the 95th percentile), referral for bariatric surgery may be considered (48). Evidence suggests meaningful efficacy with phentermine–topiramate and semaglutide (49–53). However, important differences in route of administration and gaps in evidence on adherence, safety, and long-term outcomes remain, with the longest trial thus far (for semaglutide) lasting 68 weeks (50). Ultimately, selection of agents involves shared decision making between the clinician and the family.

Additional factors influencing pediatric obesity pharmacotherapy include coverage, uncertain optimal clinical management, and potential harms. Because Medicaid covers a higher proportion of children (41%) than adults (15%) (54), access to treatment is often constrained by state Medicaid policy, which frequently excludes or restricts coverage for obesity treatment, particularly GLP-1RAs and bariatric surgery. Evidence is sparse on the optimal clinical management approaches for children; trials of GLP-1RAs in pediatric populations are limited, evaluate the short term, and include homogeneous populations with few data on how long to continue treatment, how to modify treatment, or how to discontinue treatment (55). Children with comorbid mental health conditions and eating disorders—often linked to obesity (56)—are frequently excluded from trials, resulting in uncertainty about eligibility and safety. These medications may also affect a child's social development, as weight loss is visible and could alter relationships with their peers.

Dr. Skinner noted that research using RWE could play a vital role in filling these evidence gaps despite challenges in using such data when studying obesity. One important data challenge is misclassification due to unobserved exposure. For example, medications received through compounding pharmacies are often not captured in EHRs. In addition, pediatric populations may disproportionately receive medications from specialists, and those data may be housed in different, unlinked EHR systems. Finally, many factors outside the health care system affect obesity and related outcomes, and these exposures cannot be ascertained from clinical data. Despite these data limitations, Dr. Skinner believes that RWD present major opportunities to fill important evidence gaps, including on long-term outcomes; potential effects on mental health, eating behaviors, and social development; and identifying the optimal clinical management strategies, including medication dose and duration, and strategies to mitigate weight regain.

During the question-and-answer session, Dr. Skinner advocated for registries and insurer incentives to identify pediatric populations in which GLP-1–based therapies are effective. She also suggested increased postmarketing surveillance to fill evidence gaps related to long-term outcomes.

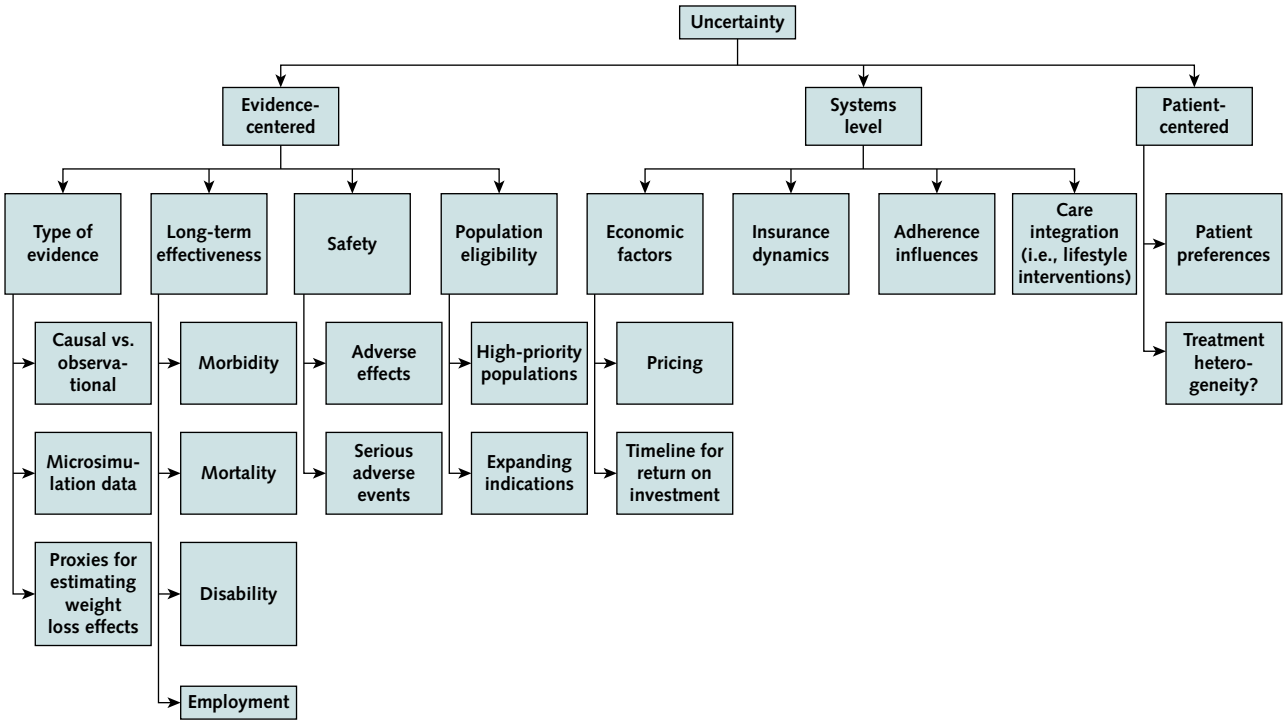
RWE for Public and Private Payer Coverage Decisions: A National and Public Payer Perspective

Dr. Davene Wright, from the Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, moderated a panel presentation by Dr. Anand Parekh, Mr. David Hines, and Dr. Noelia Duchovny highlighting different payer perspectives on the challenges of coverage decisions for GLP-1RAs.

Dr. Parekh, former chief medical advisor for the Bipartisan Policy Center, began by acknowledging the heterogeneous approach public payers currently use to evaluate coverage of GLP-1–based therapies. Given that private payers often follow suit, understanding Medicare coverage of obesity pharmacotherapy is an important starting point. Medicare currently covers GLP-1RAs for T2D, sleep apnea, and cardiovascular disease concomitant with obesity but does not cover medications specifically for obesity due to a 2004 statutory prohibition of cosmetic "weight loss drugs" (57). The Treat and Reduce Obesity Act of 2023 would support obesity pharmacotherapy coverage under Medicare; however, legislation was still pending at the time of the presentation.

Executive branch actions could also facilitate Medicare coverage of obesity pharmacotherapy. During the Biden administration, the Centers for Medicare & Medicaid Services (CMS) proposed Medicare Part D and Medicaid coverage of obesity pharmacotherapy, estimated by the Assistant Secretary for Planning and Evaluation (58) to cost an additional $24.8 billion to Medicare and $14.8 billion to Medicaid to cover 3.4 million Medicare and 4 million Medicaid beneficiaries over a 10-year period, respectively;

Figure 2. Existing types of uncertainty around GLP-1–based therapies from the national and public payer perspective.



GLP-1 = glucagon-like peptide-1. (Adapted from Han PK, Klein WM, Arora NK, Varieties of uncertainty in health care: a conceptual taxonomy, *Medical Decision Making*, 2011, vol. 31, pp. 828-838, with permission.)

however, the proposal was not finalized by the Trump administration.

Under the Inflation Reduction Act, CMS has selected semaglutide—including Ozempic, Wegovy, and Rybelsus—for Medicare price negotiations, and the negotiated prices are expected to take effect in 2027 (59, 60). On 6 November 2025, after the NIDDK workshop, the White House announced an agreement with Eli Lilly and Novo Nordisk to substantially reduce prices for various GLP-1RAs in Medicare and Medicaid and through TrumpRx, a new website that launched in early 2026 (61).

Medicare's approach to coverage of GLP-1–based therapies contrasts with other federal government programs, including TRICARE, the U.S. Department of Veterans Affairs (VA), and the Office of Personnel Management (OPM). The Department of Defense and the VA cover GLP-1–based obesity pharmacotherapy subject to prior authorization criteria, including a BMI threshold, previous engagement in lifestyle therapy, and step-up therapy using generic alternative medications (such as phentermine) (62). The OPM requires that all health benefits carriers cover at least one GLP-1RA for weight loss (63).

Medicaid coverage is also highly heterogeneous; 14 states covered GLP-1–based obesity pharmacotherapy at the time of the workshop (64). Many Medicaid programs eschew obesity pharmacotherapy coverage, primarily due to cost but also due to potential adverse effects, adherence concerns (65), and the need for legislative action.

Policy experts have proposed several market strategies and federal actions to increase obesity pharmacotherapy access (66). Given the large gap between those who could benefit from obesity pharmacotherapy and those who currently receive it, researchers should identify high-priority subgroups for whom expanded access would be most beneficial (67). This "rationing" should ideally be paired with an aggressive approach to negotiate prices of these therapies to expand access in the long term.

David Hines, Executive Director of Benefits for Metro Nashville Public Schools, provided context on state and private payer decision making on covering GLP-1RAs for obesity. In recent years, aggressive fee negotiations by medical professionals combined with a dramatic uptick in the volume and cost of catastrophic claims (claims $\geq$\$100 000) have resulted in average annual increases in health care premiums of 8% to 9% (68). Payers are therefore seeking to cut or divert costs rather than add coverage for medications like GLP-1RAs that would increase overall costs by an additional 3 to 4 percentage points.

The volatility and unpredictability of costs also influence payers' coverage philosophies, driving them to become more conservative in benefit offerings (69).

Table. Summary of Research Gaps and Opportunities

Theme Area	Research Gaps and Opportunities
Long-term outcomes	Data on the long-term metabolic, body composition, and behavioral effects of stopping use of these medications Whether benefits wane over time, even with continuation of the maximum dose Subsets of patients who derive the most benefit from GLP-1RAs Understanding which comorbidities or BMI ranges see the largest health benefit and/or medical cost savings Identifying factors that contribute to heterogeneity of response and what more can be done to improve response Developing EHR-integrated clinical decision support tools to predict pharmacotherapy outcomes using real-world data How much social determinants of health confound results of RWE studies Evaluating off-label use of GLP-1RAs using target trials Whether stepped-care therapy is more effective or cost-effective than going straight to GLP-1RA therapy Whether a defined period of treatment with GLP-1RAs followed by cessation of therapy may be associated with a legacy-like effect of continuing improvements in health, as has been described for glucose-lowering agents in people with diabetes
Maintenance/adherence/dosing	Impact of adverse effects on discontinuation rates vs. economic/coverage issues Best practices for tapering off GLP-1RAs with lifestyle intervention Effective off-ramping/deprescription regimens after weight loss Identifying patients for long-term GLP-1RA use vs. tapering/discontinuation Evidence-based recommendations for long-term microdosing Barriers to receiving and continuing GLP-1RA prescriptions
Economics/coverage	Significant cost offsets (savings) from GLP-1RA use Affordability of long-term treatment Reconciling upfront costs with long-term savings Pricing strategies and cost-sharing effects System-level changes to reduce gaps in care quality and outcomes Microsimulation research for fiscal effects of public policy changes Identifying subpopulations for increased AOM access Benefits of combining AOMs with lifestyle programs Near- and longer-term effects, natural experiments, and observational studies
Pragmatic trials	Comparing alternative AOMs head-to-head in diverse health care settings Testing strategies for tapering AOMs with lifestyle interventions Comparative effectiveness of various medications and interventions Cost-effectiveness of stepped-care therapy Decision-making process for switching patients for whom one AOM fails Intensity and type of lifestyle interventions needed for weight loss Approaches for long-term weight loss maintenance Comparing alternative titration schedules for adherence and weight loss outcomes
Pediatric and pregnancy outcomes	Effect of GLP-1RA–related weight loss on growth and development in pediatric patients Administration of drugs to teenagers or young adults to prevent chronic diseases Inclusion of pediatric patients in cost-effectiveness simulation studies Tracking outcomes for people with GLP-1RA exposure from childhood through adulthood Effectiveness of GLP-1RAs in treating monogenic/genetic obesity in pediatric patients Reluctance of primary care physicians to prescribe AOMs in adolescents Use of GLP-1RA/multiple agonist during pregnancy
Possible harms of GLP-1RAs	Effect of discontinuation on weight and health outcomes Prevalence of suicidal thoughts or actions in patients treated with GLP-1RAs Investigating harms (mental health risks, eating disorders, social development in pediatric populations)
Co–lifestyle interventions	Best practices for behavioral lifestyle interventions with GLP-1RAs Necessary amount of co–lifestyle intervention Optimal pairing of nutritional and physical activities Nutritional counseling and surveillance for patients using GLP-1RAs
Outside-the-box questions	Developing a more robust data aggregating and sharing platform for rapidly evaluating GLP-1RA medications

AOM = antiobesity medication; BMI = body mass index; EHR = electronic health record; GLP-1RA = glucagon-like peptide-1 receptor agonist; RWE = real-world evidence.

Value statements are scrutinized, and positive return on investment on GLP-1–based obesity treatment must be realized within a relatively short timeline of 12 to 24 months, especially considering workforce attrition and drug nonadherence (70). Other concerns include the idea that obesity pharmacotherapy requires ongoing treatment, uncertainty about adverse effects, challenges in identifying high-priority populations (vs. those using GLP-1RAs for "cosmetic" weight loss), and a lack of transparency about the true net price of GLP-1RAs amidst a complicated and opaque system of rebates that flow through pharmacy benefit managers.

As a result, in 2024 only 18% of large firms had expanded GLP-1RA coverage to treat obesity, and many organizations were retreating from coverage (71). Some payers have imposed restrictive clinical eligibility criteria (for example, minimum BMI or comorbidities), cover only specific GLP-1RAs due to perceived cost-effectiveness, and have moved some medications to excluded formulary tiers. Mr. Hines highlighted that the approach being

implemented by his Nashville-area school system (an early adopter of GLP-1RA coverage for obesity) was to combine obesity pharmacotherapy with a comprehensive lifestyle intervention and surgical weight loss support. Despite sustained improvements in weight loss and treatment engagement, the program was terminated due to a sharp increase in overall health plan costs.

Mr. Hines concluded that although many payers and benefit professionals understand the value of GLP-1RAs in combating obesity, many believe that their work resides in promoting lifestyle modifications, not medical or surgical interventions. He believes that sustainable GLP-1–based obesity treatment can only be achieved through lower medication prices, integration with behavioral treatment programs, and limiting access to high-priority candidates who are highly likely to succeed and contribute to a shorter timeline from investment to return that can motivate payer support.

RWE for Public and Private Payer Coverage Decisions: Challenges With Assumptions for Economic Analyses and How RWE May Inform Them

Dr. Noelia Duchovny, a principal analyst at the Congressional Budget Office, presented cost projections for Medicare obesity pharmacotherapy coverage from 2026 to 2034 (58). Despite potential savings from reduced obesity-related health issues, the expected use of obesity pharmacotherapy is projected to result in about $38.8 billion in federal health care spending after rebates, subsidies, and premium income are accounted for (58).

Dr. Duchovny emphasized that these estimates are highly uncertain and sensitive to expectations about obesity pharmacotherapy use, savings from improved health, pricing, and eligibility for treatment. For example, the Congressional Budget Office's estimates of savings were based on indirect evidence from bariatric surgery studies (72–78) and microsimulation models (79, 80). She noted that savings could be greater if, for example, research found that use of obesity pharmacotherapy resulted in sizable savings in health care costs among current Medicare beneficiaries and those who will eventually age into Medicare. Savings could be smaller than estimated if real-world effectiveness is lower than in RCTs or if weight loss leads beneficiaries to seek or receive additional medical services, thus increasing health care use.

This uncertainty can be reduced by analyzing RWD that shed light on short- and long-term changes in health care spending, especially given the variability in adherence and effectiveness. RWD could also inform the effect of obesity pharmacotherapy on mortality, disability, and employment.

Summary

Despite the transformative effect of GLP-1–based medications on obesity and related chronic conditions, important gaps remain in our understanding of their optimal use, long-term safety, clinical effectiveness, and cost-effectiveness as well as their effect on nonhealth outcomes such as workforce productivity and retention. These gaps limit availability of reliable data inputs for use in robust cost–benefit analyses (**Figure 2**). RWE offers a critical pathway to address these knowledge gaps across diverse populations and clinical settings and to help identify which subgroups benefit most and under what conditions, as well as to inform the development of tailored coverage policies that maximize value and access. Throughout the course of the workshop, the organizers gathered feedback from presenters and participants and identified the major gaps and opportunities for research to help advance the generation of RWE for GLP-1–based therapies. These were organized into 8 key themes, including long-term outcomes; maintenance, adherence, and dosing; economics and coverage; pragmatic trials; pediatric and pregnancy outcomes; possible harms of GLP-1–based therapies; co–lifestyle interventions; and outside-the-box considerations (**Table**). By illuminating patterns of medication adherence, discontinuation, and long-term outcomes, including economic impacts, RWE can support more accurate cost–benefit projections and policy coverage decisions that maximize population benefit at acceptable costs.

From Kaiser Permanente Washington Health Research Institute, Seattle, Washington (D.A.); Duke University School of Medicine, Durham, North Carolina (L.H.C., D.D., A.S.); Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (S.T., D.R.W.); U.S. Food and Drug Administration, Washington, DC (M.C.B.); Congressional Budget Office, Washington, DC (N.D.); Metro Nashville Public Schools, Nashville, Tennessee (D.H.); University of California, Los Angeles, Los Angeles, California (K.N.); University of Michigan School of Public Health, Ann Arbor, Michigan (A.P.); *Annals of Internal Medicine* and American College of Physicians, Philadelphia, Pennsylvania (C.C.W.); Tufts University School of Medicine, Boston, Massachusetts (J.B.W.); and National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland (S.K.O., C.H.).

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views expressed in this article may not represent the views of all named authors, nonauthor contributors, or organizations included. Throughout the text, the authors made every effort to indicate people to whom the content may be attributed. Summaries of the summit discussion were prepared by Drs. Arterburn, Hales, Osganian, Curtis, Toh, and Wee, based in part on authors' notes and the workshop transcript.

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Author contributions are available at Annals.org.

References

1. **Gilden AH, Catenacci VA, Taormina JM.** Obesity. Ann Intern Med. 2024;177:ITC65-ITC80. [PMID: 38739920] doi:10.7326/AITC202405210
2. **Ali SMJ, Lai M.** Metabolic dysfunction–associated steatotic liver disease. Ann Intern Med. 2025;178:ITC1-ITC16. [PMID: 39805112] doi:10.7326/ANNALS-24-02933
3. **Betensky DJ, Smith KC, Katz JN, et al.** The cost-effectiveness of semaglutide and tirzepatide for patients with knee osteoarthritis and obesity. Ann Intern Med. 2025;178:1549-1560. [PMID: 40953447] doi:10.7326/ANNALS-24-03609
4. **Bozick R, Donofry SD, Rancaño KM.** New Weight Loss Drugs: GLP-1 Agonist Use and Side Effects in the United States. RAND Corporation; 6 August 2025. Accessed at https://www.rand.org/pubs/research_reports/RRA4153-1.html on 4 December 2025.
5. **Kushner RF, Jastreboff AM, Ryan DH.** Current and future medications for obesity treatment. JAMA. 2025;334:1551-1552. [PMID: 40932726] doi:10.1001/jama.2025.13665
6. **U.S. Food and Drug Administration**. FDA Adverse Event Monitoring System (AEMS) Public Dashboard. Accessed at https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard on 4 December 2025.
7. **Curtis LH, Arterburn D, Toh S, et al.** Methodological approaches to real-world evidence generation for glucagon-like peptide-1–based therapies: synopsis of a National Institute of Diabetes and Digestive and Kidney Diseases workshop. Ann Intern Med. 30 June 2026. [Epub ahead of print]. doi:10.7326/ANNALS-26-00202
8. **Rehfeld JF.** The origin and understanding of the incretin concept. Front Endocrinol (Lausanne). 2018;9:387. [PMID: 30061863] doi:10.3389/fendo.2018.00387
9. **Kieffer TJ, Habener JF.** The glucagon-like peptides. Endocr Rev. 1999;20:876-913. [PMID: 10605628] doi:10.1210/edrv.20.6.0385
10. **Campbell JE, Drucker DJ.** Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab. 2013;17:819-837. [PMID: 23684623] doi:10.1016/j.cmet.2013.04.008
11. **Dupre J, Ross SA, Watson D, et al.** Stimulation of insulin secretion by gastric inhibitory polypeptide in man. J Clin Endocrinol Metab. 1973;37:826-828. [PMID: 4749457] doi:10.1210/jcem-37-5-826
12. **Nauck MA, Heimesaat MM, Orskov C, et al.** Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 1993;91:301-307. [PMID: 8423228] doi:10.1172/JCI116186
13. **Nauck MA, Kleine N, Orskov C, et al.** Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36:741-744. [PMID: 8405741] doi:10.1007/BF00401145
14. **Deacon CF, Johnsen AH, Holst JJ.** Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. J Clin Endocrinol Metab. 1995;80:952-957. [PMID: 7883856] doi:10.1210/jcem.80.3.7883856
15. **Drucker DJ, Nauck MA.** The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696-1705. [PMID: 17098089] doi:10.1016/S0140-6736(06)69705-5
16. **McLean BA, Wong CK, Campbell JE, et al.** Revisiting the complexity of GLP-1 action from sites of synthesis to receptor activation. Endocr Rev. 2021;42:101-132. [PMID: 33320179] doi:10.1210/endrev/bnaa032
17. **Petri KCC, Ingwersen SH, Flint A, et al.** Exposure-response analysis for evaluation of semaglutide dose levels in type 2 diabetes. Diabetes Obes Metab. 2018;20:2238-2245. [PMID: 29748996] doi:10.1111/dom.13358
18. **Kumar N, D'Alessio DA.** Slow and steady wins the race: 25 years developing the GLP-1 receptor as an effective target for weight loss. J Clin Endocrinol Metab. 2022;107:2148-2153. [PMID: 35536590] doi:10.1210/clinem/dgac276
19. **Campbell JE, Müller TD, Finan B, et al.** GIPR/GLP-1R dual agonist therapies for diabetes and weight loss-chemistry, physiology, and clinical applications. Cell Metab. 2023;35:1519-1529. [PMID: 37591245] doi:10.1016/j.cmet.2023.07.010
20. **Fan C, Wang J, Guo B, et al.** Exploring the causal relationships between anxiety, obesity, and hypertension: a two-sample Mendelian randomization study. Am J Hypertens. 2025;38:852-858. [PMID: 40357578] doi:10.1093/ajh/hpaf072
21. **Ussher JR, Drucker DJ.** Glucagon-like peptide 1 receptor agonists: cardiovascular benefits and mechanisms of action. Nat Rev Cardiol. 2023;20:463-474. [PMID: 36977782] doi:10.1038/s41569-023-00849-3
22. **Lincoff AM, Brown-Frandsen K, Colhoun HM, et al; SELECT Trial Investigators.** Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med. 2023;389:2221-2232. [PMID: 37952131] doi:10.1056/NEJMoa2307563
23. **Abasheva D, Ortiz A, Fernandez-Fernandez B.** GLP-1 receptor agonists in patients with chronic kidney disease and either overweight or obesity. Clin Kidney J. 2024;17:19-35. [PMID: 39583142] doi:10.1093/ckj/sfae296
24. **Newsome PN, Loomba R.** Therapeutic horizons in metabolic dysfunction–associated steatohepatitis. J Clin Invest. 2025;135:e186425. [PMID: 40590228] doi:10.1172/JCI186425

25. **Malhotra A, Grunstein RR, Fietze I, et al; SURMOUNT-OSA Investigators.** Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024;391:1193-1205. [PMID: 38912654] doi:10.1056/NEJMoa2404881
26. **Rosenstock J, Hsia S, Nevarez Ruiz L, et al; ACHIEVE-1 Trial Investigators.** Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes. N Engl J Med. 2025;393:1065-1076. [PMID: 40544435] doi:10.1056/NEJMoa2505669
27. **U.S. Food and Drug Administration**. 21st Century Cures Act. Accessed at https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act on 4 December 2025.
28. **U.S. Food and Drug Administration**. Framework for FDA's Real-World Evidence Program. December 2018. Accessed at https://www.fda.gov/media/120060/download?attachment on 4 December 2025.
29. **U.S. Food and Drug Administration**. Real-World Evidence. Accessed at https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence on 4 December 2025.
30. **U.S. Food and Drug Administration**. FDA approves new use of transplant drug based on real-world evidence. 16 July 2021. Accessed at https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-new-use-transplant-drug-based-real-world-evidence on 4 December 2025.
31. **RECOVERY Collaborative Group.** Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397:1637-1645. [PMID: 33933206] doi:10.1016/S0140-6736(21)00676-0
32. **Maro JC, Nguyen MD, Kolonoski J, et al.** Six years of the US Food and Drug Administration's postmarket Active Risk Identification and Analysis System in the Sentinel Initiative: Implications for real world evidence generation. Clin Pharmacol Ther. 2023;114:815-824. [PMID: 37391385] doi:10.1002/cpt.2979
33. Intentional self-harm following glucagon-like peptide-1 receptor agonists (GLP-1 RA) use in patients with diabetes: an inverse probability of treatment weighting analysis. Accessed at https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/intentional-self-harm-following-glucagon-peptide-1-receptor on 4 December 2025.
34. Intentional self-harm following glucagon-like peptide-1 receptor agonists (GLP-1 RA) use in patients with obesity: a descriptive analysis. Accessed at https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/intentional-self-harm-following-glucagon-peptide-1-0 on 4 December 2025.
35. **U.S. Preventive Services Task Force**. About the USPSTF. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf on 22 October 2025.
36. **American Diabetes Association**. Who We Are. Accessed at https://diabetes.org/about-us on 22 October 2025.
37. American Academy of Pediatrics website. Accessed at https://www.aap.org/en on 22 October 2025.
38. **U.S. Preventive Services Task Force**. Task Force at a Glance. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/task-force-at-a-glance on 22 October 2025.
39. **U.S. Preventive Services Task Force**. Procedure Manual. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual on 7 July 2025.
40. **U.S. Preventive Services Task Force.** Grade Definitions. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions on 22 October 2025.
41. **U.S. Preventive Services Task Force**. Procedure Manual Section 3. Topic Work Plan Development. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-section-3-topic-work-plan-development on 22 October 2025.
42. **U.S. Preventive Services Task Force**. Procedure Manual Section 4. Evidence Review Development. Accessed at https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-section-4-evidence-review-development on 22 October 2025.
43. **Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force.** Behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults: US Preventive Services Task Force recommendation statement. JAMA. 2018;320:1163-1171. [PMID: 30326502] doi:10.1001/jama.2018.13022
44. **LeBlanc ES, Patnode CD, Webber EM, et al.** Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2018;320:1172-1191. [PMID: 30326501] doi:10.1001/jama.2018.7777
45. **Davidson KW, Mangione CM, Barry MJ, et al; US Preventive Services Task Force.** Collaboration and shared decision-making between patients and clinicians in preventive health care decisions and US Preventive Services Task Force recommendations. JAMA. 2022;327:1171-1176. [PMID: 35315879] doi:10.1001/jama.2022.3267
46. **American Diabetes Association Professional Practice Committee.** 1. Improving care and promoting health in populations: Standards of Care in Diabetes–2025. Diabetes Care. 2025;48:S14-S26. [PMID: 39651974] doi:10.2337/dc25-S001
47. **American Diabetes Association Professional Practice Committee.** 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of Care in Diabetes–2025. Diabetes Care. 2025;48:S167-S180. [PMID: 39651976] doi:10.2337/dc25-S008
48. **Hampl SE, Hassink SG, Skinner AC, et al.** Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics. 2023;151:e2022060640. [PMID: 36622115] doi:10.1542/peds.2022-060640
49. **Kelly AS, Bensignor MO, Hsia DS, et al.** Phentermine/topiramate for the treatment of adolescent obesity. NEJM Evid. 2022;1:EVIDoa2200014. [PMID: 36968652] doi:10.1056/evidoa2200014
50. **Weghuber D, Barrett T, Barrientos-Pérez M, et al; STEP TEENS Investigators.** Once-weekly semaglutide in adolescents with obesity. N Engl J Med. 2022;387:2245-2257. [PMID: 36322838] doi:10.1056/NEJMoa2208601
51. **Ryder JR, Kaizer A, Rudser KD, et al.** Effect of phentermine on weight reduction in a pediatric weight management clinic. Int J Obes (Lond). 2017;41:90-93. [PMID: 27773937] doi:10.1038/ijo.2016.185
52. **Chanoine J-P, Hampl S, Jensen C, et al.** Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. JAMA. 2005;293:2873-2883. [PMID: 15956632] doi:10.1001/jama.293.23.2873
53. **Kelly AS, Auerbach P, Barrientos-Perez M, et al; NN8022-4180 Trial Investigators.** A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med. 2020;382:2117-2128. [PMID: 32233338] doi:10.1056/NEJMoa1916038
54. **Desilver D**. What the Data Says About Medicaid. Pew Research Center; 24 June 2025. Accessed at https://www.pewresearch.org/short-reads/2025/06/24/what-the-data-says-about-medicaid/#how-many-people-have-medicaid-coverage on 2 November 2025.
55. **Alorfi NM, Alshehri FS.** Usage of glucagon-like peptide-1 for obesity in children; updated review of ClinicalTrials.gov. J Multidiscip Healthc. 2023;16:2179-2187. [PMID: 37547806] doi:10.2147/JMDH.S419245
56. **Sarwer DB, Polonsky HM.** The psychosocial burden of obesity. Endocrinol Metab Clin North Am. 2016;45:677-688. [PMID: 27519139] doi:10.1016/j.ecl.2016.04.016
57. **Hoagland GW, Lovegrove M, Parekh A, et al**. Expanding Access to Obesity Treatments for Older Adults. Bipartisan Policy Center; February 2022. Accessed at https://bipartisanpolicy.org/wp-content/uploads/2022/02/BPC_ExpandingAccessToObesityFinal.pdf on 29 August 2025.
58. **Congressional Budget Office**. How Would Authorizing Medicare to Cover Anti-Obesity Medications Affect the Federal Budget?

October 2024. Accessed at https://www.cbo.gov/publication/60816 on 4 December 2025.
59. **Department of Health and Human Services**. Medicare and Medicaid Programs; Contract Year 2026 Policy and Technical Changes to the Medicare Advantage Program, Medicare Prescription Drug Benefit Program, Medicare Cost Plan Program, and Programs of All-Inclusive Care for the Elderly. Accessed at https://www.govinfo.gov/content/pkg/FR-2024-12-10/pdf/2024-27939.pdf on 4 December 2025.
60. **The White House**. Delivering Most-Favored-Nation Prescription Drug Pricing to American Patients. 12 May 2025. Accessed at https://www.whitehouse.gov/presidential-actions/2025/05/delivering-most-favored-nation-prescription-drug-pricing-to-american-patients on 4 December 2025.
61. **The White House**. Fact Sheet: President Donald J. Trump Announces Major Developments in Bringing Most-Favored-Nation Pricing to American Patients. 6 November 2025. Accessed at https://www.whitehouse.gov/fact-sheets/2025/11/fact-sheet-president-donald-j-trump-announces-major-developments-in-bringing-most-favored-nation-pricing-to-american-patients on 11 December 2025.
62. **TRICARE**. Does TRICARE cover Wegovy, Ozempic, and Mounjaro? Accessed at https://tricare.mil/FAQs/Pharmacy/PharmProg_Wegovy on 4 December 2025.
63. **Moss K**. Feds with Benefits: Does FEHB cover weight loss medications? Federal News Network; 11 September 2024. Accessed at https://federalnewsnetwork.com/feds-with-benefits/2024/09/feds-with-benefits-does-fehb-cover-weight-loss-medications on 4 December 2025.
64. **Ingmire B**. GLP-1 Weight Loss Drugs: Coverage Under Medicaid and Other Health Plans. MultiState; 17 March 2025. Accessed at https://www.multistate.us/insider/2025/3/17/glp-1-weight-loss-drugs-coverage-under-medicaid-and-other-health-plans on 4 December 2025.
65. **Williams E, Rudowithz R, Bell C**. Medicaid Coverage of and Spending on GLP-1s. Accessed at https://www.kff.org/medicaid/medicaid-coverage-of-and-spending-on-glp-1s on 4 December 2025.
66. **Pearson SD, Whaley CM, Emond SK**. Affordable Access to GLP-1 Obesity Medications: Strategies to Guide Market Action and Policy Solutions. Institute for Clinical and Economic Review; 9 April 2025. Accessed at https://icer.org/wp-content/uploads/2025/04/Affordable-Access-to-GLP-1-Obesity-Medications-_-ICER-White-Paper-_-04.09.2025.pdf on 4 December 2025.
67. **Dellgren J, Emanuel E, Persad G.** Ethical approaches to limiting overall costs for glucagon-like peptide-1 receptor agonists for weight management. Ann Intern Med. 2025;178:119-121. [PMID: 39586102] doi:10.7326/ANNALS-24-01317
68. **Hunzinger G, Skoog D, Sclafani P, et al**. No let up in sight. Medical cost trend set to grow at 8.5%. Is your playbook ready? Behind the Numbers 2026. PwC; 16 July 2025. Accessed at https://www.pwc.com/us/en/industries/health-industries/library/behind-the-numbers.html on 4 December 2025.
69. **Milanette T**. Healthcare Volatility Wreaks Havoc on Predicting Risk and Managing Costs. Accessed at https://www.iqvia.com/-/media/iqvia/pdfs/us/white-paper/2023/iqvia-hcs-risk-article-2023.pdf on 14 April 2026.
70. **Cotter L, Rae M, McGough M, et al**. Perspectives from employers on the costs and issues associated with covering GLP-1 agonists for weight loss. Peterson-KFF Health System Tracker; 22 October 2025. Accessed at https://www.healthsystemtracker.org/brief/perspectives-from-employers-on-the-costs-and-issues-associated-with-covering-glp-1-agonists-for-weight-loss on 14 April 2026.
71. **KFF**. 2024 Employer Health Benefits Survey. 9 October 2025. Accessed at https://www.kff.org/health-costs/2024-employer-health-benefits-survey on 4 December 2025.
72. **Smith VA, Zepel L, Kawatkar AA, et al.** Health expenditures after bariatric surgery: a retrospective cohort study. Ann Surg. 2024;280:e8-e16. [PMID: 38726675] doi:10.1097/SLA.0000000000006333
73. **Shambhu S, Ma Q, Gordon AS, et al.** Long term cost outcomes among commercially insured patients undergoing bariatric surgical procedures. Obes Sci Pract. 2024;10:e727. [PMID: 38187124] doi:10.1002/osp4.727
74. **Canakis A, Wall-Wieler E, Liu Y, et al.** Type 2 diabetes remission after bariatric surgery and its impact on healthcare costs. Obes Surg. 2023;33:3806-3813. [PMID: 37851285] doi:10.1007/s11695-023-06856-0
75. **Tarride J-E, Doumouras AG, Hong D, et al.** Association of Roux-en-Y gastric bypass with postoperative health care use and expenditures in Canada. JAMA Surg. 2020;155:e201985. [PMID: 32697298] doi:10.1001/jamasurg.2020.1985
76. **Xia Q, Campbell JA, Ahmad H, et al.** Bariatric surgery is a cost-saving treatment for obesity—a comprehensive meta-analysis and updated systematic review of health economic evaluations of bariatric surgery. Obes Rev. 2020;21:e12932. [PMID: 31733033] doi:10.1111/obr.12932
77. **Smith VA, Arterburn DE, Berkowitz TSZ, et al.** Association between bariatric surgery and long-term health care expenditures among veterans with severe obesity. JAMA Surg. 2019;154:e193732. [PMID: 31664427] doi:10.1001/jamasurg.2019.3732
78. **Weiner JP, Goodwin SM, Chang H-Y, et al.** Impact of bariatric surgery on health care costs of obese persons: a 6-year follow-up of surgical and comparison cohorts using health plan data. JAMA Surg. 2013;148:555-562. [PMID: 23426865] doi:10.1001/jamasurg.2013.1504
79. **Atlas SJ, Kim K, Beinfeld M, et al**. Medications for Obesity Management: Effectiveness and Value. Institute for Clinical and Economic Review; 31 August 2022. Accessed at https://icer.org/wp-content/uploads/2022/03/ICER_Obesity_Evidence_Report_083122.pdf on 4 December 2025.
80. **Ward AS, Tysinger B, Nguyen P, et al**. Benefits of Medicare Coverage for Weight Loss Drugs. Accessed at https://schaeffer.usc.edu/research/benefits-of-medicare-coverage-for-weight-loss-drugs on 4 December 2025.

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Appendix Table 1. Evidence Grading Systems of the USPSTF, ADA, and AAP

System	Description of Grades
USPSTF level of certainty	High: Multitude of well-designed, well-conducted studies in representative primary care populations Moderate: Sufficient to determine the effects of the preventive service on targeted health outcomes, but confidence in the estimate is constrained Low: Available evidence is insufficient to assess effects on health outcomes
ADA level of evidence	A: Clear or supportive, well-conducted, adequately powered RCTs B: Supportive, well-conducted cohort or case–control studies C: Poorly controlled or uncontrolled E: Expert consensus or clinical experience
AAP level of aggregate evidence quality	A: Well-designed and well-conducted trials or meta-analysis on applicable populations B: Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies C: Single or few observational studies or multiple studies with inconsistent findings or major limitations D: Expert opinion, case reports, reasoning from first principles X: Exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit or harm

AAP = American Academy of Pediatrics; ADA = American Diabetes Association; RCT = randomized controlled trial; USPSTF = U.S. Preventive Services Task Force.

Appendix Table 2. Recommendation Systems

System	Description
USPSTF recommendation grades	A: USPSTF recommends the service. There is high certainty that the net benefit is substantial. B: USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. C: USPSTF recommends selectively offering or providing the service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small. D: USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harm outweighs the benefits. I statement: USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.
ADA ratings	ADA recommendations are assigned ratings of A, B, or C depending on the quality of the evidence in support of the recommendation. Expert opinion E is a separate category for recommendations in which there is no evidence from clinical trials, clinical trials may be impractical, or there is conflicting evidence.
AAP when benefit or harm predominates	Strong recommendation with level A or B aggregate evidence quality Moderate recommendation with level B or C aggregate evidence quality Weak recommendation with level C or D aggregate evidence quality Strong or moderate recommendation based on level X aggregate evidence quality
AAP when benefit and harm are balanced	Weak recommendation with level A, B, or C aggregate evidence quality No recommendation may be made for level D

AAP = American Academy of Pediatrics; ADA = American Diabetes Association; USPSTF = U.S. Preventive Services Task Force.