

CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

Should Pharmaceuticals Be Used as Weight Loss Interventions for Adolescents Classified as Obese by BMI?

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Abstract

Ethically evaluating prescription of weight loss pharmaceuticals for adolescents classified by body mass index (BMI) as obese requires reconsideration of how medicine's overreliance on BMI as a diagnostic criterion supports a weight normative approach to health. This commentary on a case suggests that weight loss is not a safe, effective, or permanent method of health promotion. The unknown extent of pharmacotherapeutics' risks to adolescents in addition to the controvertible benefits of weight loss ethically preclude their prescription, despite scientific consensus to fight obesity by prescribing weight reduction.

Case

M is a student at Sunnyvale High School. At 16 years old, they are currently enrolled in an intensive health behavior and lifestyle treatment (IHBLT) at the local county hospital. During the pandemic, their body mass index (BMI) increased from 28 to 30, making them a candidate for liraglutide, a glucagon-like peptide 1 (GLP-1) analogue approved by the US Food and Drug Administration (FDA) in 2020 as a weight loss medication in adolescents. As M's primary care physician, Dr B recommends liraglutide as an additional means for preventing M's becoming an obese adult with comorbidities.

Commentary

Responding to the title question requires not only evaluating the risks and benefits of pharmacotherapy (particularly in adolescents), but also closely examining weight loss as a health goal. Present clinical practice is "weight normative"¹ in emphasizing weight and weight loss to define health and well-being. There is no more obvious manifestation of this practice than the continued use of BMI to define health status. BMI is based on the ratio of weight in kilograms to height in meters squared and is currently used as *the* identifying obesity indicator,^{2,3} although its value does not reflect significant considerations of the obesity disease state, including peripheral and visceral adiposity, body composition, and metabolic indices.^{2,4}

Calling attention to how questionable BMI is as a litmus test for obesity are patients classified as overweight or obese (BMI \geq 25) whose weight, when evaluated by physical

and metabolic fitness, does not necessarily pose a risk to their health.^{5,6} Research on the “obesity paradox”^{4,7} and “metabolically healthy obesity”^{8,9,10} substantiates the existence of this incongruence between the *expected* and *actual* health or risk status associated with an obesity diagnosis. Additionally, the clinical distress of obesity can exist in bodies that do not match the expected phenotype of obesity (ie, fat), which are described in literature as thin-fat phenotype, normal weight obesity, metabolic obesity, and metabolically unhealthy non-obese.¹¹

An obesity diagnosis that is defined by weight categorization (BMI \geq 30) is problematic not only because the diagnostic accuracy of BMI is debatable, but also because it arguably leaves the impression that if too much weight is the problem, then less of it is the solution. Based on data collected from 2017 to 2020, the Centers for Disease Control and Prevention (CDC) determined the obesity prevalence to be 22.2% in adolescents aged 12 to 19.^{12,13} The increasing rate of adolescents classified as obese by BMI is often cited as a public crisis on the national and global level,¹⁴ with calls to address this crisis through interventions aimed at weight loss, including IHBLT programs, pharmacotherapeutics, and **surgeries**.¹⁵ Yet a 2015 *Lancet* publication found that no country has yet resolved its obesity epidemic despite these purported weight loss solutions.¹⁶

Updated Pediatric Guidelines

The 2023 publication of the American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity¹⁷ refocused attention on pharmacotherapeutic inducement of weight loss in adolescents, with the recommendation being changed from watchful waiting to offering pharmacotherapeutics to those ages 12 years and older as an adjunct to behavioral and lifestyle obesity treatment.¹⁸

What should clinicians consider when deciding upon weight loss pharmacotherapy in obesity management? The US Food and Drug Administration (FDA) 2007 “Guidance for the Clinical Evaluation of Weight-Control Drugs” articulates these considerations:

Lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviors, is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight management product should be contemplated only after a sufficient trial of lifestyle modification has failed and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.¹⁹

Crudely summarized, lifestyle modifications must fail before clinicians consider pharmacotherapies as an adjunct. Side effects of pharmacotherapies for weight loss must be less risky than untreated excess adiposity, understood to be a risk factor for or marker of weight-related disease states. BMI stratification is utilized as a proxy for identifying excess adiposity (ie, obesity). Therefore, failure of lifestyle modifications can be understood as lack of BMI shift or, less stringently, weight reduction.

In this case, despite participation in an IHBLT, M experienced an increase in BMI, which means the program failed to inhibit or reverse weight progression. Dr B might anticipate that weight loss via pharmaceutical intervention would reduce excess adiposity and therefore resolve M’s current obesity diagnosis while reducing the likelihood of adult obesity with its associated comorbidities—benefits that would outweigh the expected risks of liraglutide. Dr B’s introduction of pharmacotherapy would be in line with

pediatric obesity treatment algorithms that recommend tiered comprehensive multidisciplinary interventions,^{20,21} including the AAP guidelines.¹⁷ These treatment approaches are rooted in the premise that, for reasons of current health and future risk, weight in excess of certain clinical parameters (ie, BMI \geq 25) is bad and that weight loss is both achievable and good for health—so much so that it merits induction by biomedical means.

The remainder of this commentary will examine the feasibility as well as the benefits of weight loss cited to justify pharmaceutical interventions, weight loss pharmaceuticals for adolescents, and the implications of weight loss encouragement as a means of achieving health with the goal of promoting greater understanding of the dialogue surrounding adolescent obesity²² and weight loss pharmacotherapeutics. (In what follows, the phrase “classified as obese” will be used in lieu of “obese adolescents” to call attention to the role of BMI in weight-related disease diagnoses and not as an endorsement of person-first language²³ in medicine’s discussion of obesity.)

Use of BMI in Pediatric Populations

Dual energy x-ray absorptiometry scans are relatively accurate measures of adiposity,¹⁷ but they are impractical on a large scale,²⁴ prompting the use of BMI as a proxy for measuring adiposity in body composition. Studies have shown that BMI has high specificity but relatively low sensitivity for detecting excess adiposity.^{25,26} In pediatric obesity studies, BMI z-score (BMIz) is often used as a standardized measurement because BMIz tends to remain the same as a child gains weight while maturing into adulthood.²⁷ However, in overweight and obese youth, BMIz is a poor predictor of relative body fat and therefore unlikely to be accurate if used to monitor adiposity changes resulting from weight management interventions.^{24,28,29}

In pediatric populations, no risk-stratified BMI cutoffs exist akin to adult BMI classifications, which the World Health Organization and National Institutes of Health developed in 1995 and 1998, respectively, based on data relating BMI to mortality risk.¹⁹ For adolescents, overweight and obesity is often defined by the 85th and 95th percentile, respectively, of the BMI-for-age in the sex-specific reference population; race/ethnicity is not taken into consideration.³⁰ These cutoff points in children, as well as the terminology of overweight and obese, lack “strong evidence for any precise” consensus,²⁷ perhaps indicating that these are nosological entities³¹ borrowed from adult medicine for their familiarity rather than their accuracy. Even if BMI/z could be used to accurately assess and longitudinally monitor adiposity composition in pediatric populations, the inflection point between adiposity being a biological necessity and a threat to health is not clearly defined, particularly in pediatric populations during development.²⁹

Realities of Weight Loss

Adolescents classified as obese generally remain so in adulthood, with a 2016 meta-analysis finding that “around 80% of obese adolescents will still be obese in adulthood.”³² The probability of attaining normal weight for people with an obesity classification is low, with one study of adults classified as overweight or obese reporting the annual probability over a maximum 9-year follow-up to be “1 in 210 for men and 1 in 124 for women [with simple obesity], increasing to 1 in 1290 for men and 1 in 677 for women with morbid obesity.”³³ Cochrane systematic reviews evaluating diet, physical activity, and surgical and pharmaceutical interventions found low-quality evidence of

their effectiveness for weight management in adolescent or childhood obesity, as well as a lack of safety data, particularly with regard to long-term effects.^{34,35,36,37,38}

For pediatric populations, there is no general consensus on what constitutes clinically meaningful weight loss (usually estimated to be 5% to 10%^{39,40} of body weight in adults) or how long the weight loss should²⁹ be sustained in order for an intervention to be considered successful (which is similarly undecided in adults³⁹). Only a few studies have tracked long-term weight loss persistence,³⁹ and even fewer have done so in pediatric populations.^{41,42} An oft-quoted 1959 study estimated that 95% of people who lose weight gain it back long term.⁴³ More recent studies confirm weight regain as being par for the course,⁴⁴ including a 2001 meta-analysis of 29 long-term studies, which found that, on average, more than 80% of lost weight was regained within 5 years.⁴⁵ Weight loss, if any, tends to be insufficient to move patients into the non-obesity BMI range: IHBLTs reduce BMI an estimated 1% to 3% in children,¹⁷ bariatric surgery reduces BMI approximately 26% to 29% long-term⁴⁶ (with a majority of adolescents having reduced bone mass and nutritional deficiencies),⁴⁷ and anti-obesity drugs in adults taken for at least 12 months induce a 2.9% to 6.8% weight reduction from baseline.⁴⁸ The Look AHEAD study found that, after 8 years of continuous intervention, only 50.3% and 35.7% of the participants in the intensive lifestyle intervention and diabetes support and education groups, respectively, lost at least 5% of their initial weight (the overall initial average BMI was 36).⁴⁹

The putative benefits of weight loss are generally positive by clinical standards,⁴⁰ but they tend to be either dependent on weight loss permanence (eg, cardiometabolic improvements^{50,51}) or relatively independent of weight loss. Lifestyle interventions can be effective in “improving obesity-related comorbidities (eg, insulin resistance, hypertension, hyperlipidemia, fatty liver disease, and exercise capacity) even in the absence of sustained weight loss.”⁵² A 2022 cohort study concluded that only 15.6% to 46.8% of the association between weight loss strategies and type 2 diabetes risk could be attributed to weight changes.⁵³ It could be concluded that perhaps it is the weight loss strategy itself, rather than the weight loss,⁵⁴ that begets the desired health outcomes.

Despite the dubious feasibility of attaining and maintaining long-term clinically significant weight loss and the indication that weight loss may not be key to addressing health concerns linked to obesity, some studies persist in recommending weight loss, suggesting that even temporary weight loss is potentially valuable.⁵⁵ However, repeated weight loss attempts^{56,57,58} with accompanying weight gain, otherwise known as weight cycling, lead to increased risk of disordered eating,⁵⁹ higher mortality due to all causes and to cardiovascular disease (CVD),⁶⁰ higher comorbidity of CVD and hypertension,⁶⁰ worse cardiometabolic and lipid measures,⁶¹ and escalated weight regain.^{62,63}

Our understanding of psychological outcomes in **weight loss-oriented treatment** is limited because existing studies rarely report mental health or well-being outcomes, and those that do show mixed results.^{64,65,66,67} Remarkably, merely perceiving failure in weight control (perhaps due to weight regain or not achieving expected weight loss in the first place) is associated with negative psychological outcomes.^{68,69} Weight treatments for adolescent are particularly ripe for concerns about disordered eating behaviors (DEBs) and eating disorders (EDs).⁷⁰ The onset of EDs is usually during adolescence,⁷⁰ with weight stigma and dieting being common precipitating factors.^{71,72} Studies have found that roughly 40% of overweight adolescent girls and 20% of

overweight adolescent boys exhibit DEBs.^{72,73} Adolescents classified as obese tend to have low self-esteem, negative self-evaluation, and high body dissatisfaction,⁷⁴ placing them at higher risk for restrictive eating escalating into a disorder.⁷⁵ The AFINOS and AVENA studies found the odds of adolescents classified as overweight developing EDs to be 2.5 to 4.9 times higher, respectively, than their peers categorized as normal weight.⁷⁶

Treatment for DEBs/EDs in adolescents classified as obese or overweight is regularly delayed by the pervasive perception of weight loss as invariably good rather than as a canary signaling clinical danger.^{77,78} Less than 6% of people with EDs are medically diagnosed as underweight,^{79,80} and the weight history of a significant portion of those presenting for ED treatment (37% to 41%) includes an overweight or obesity classification.^{73,81} As of 2022, screening tools for EDs in adolescents with obesity are still not validated,^{71,82,83} which undermines implementation of any recommendations (such as those in section IX.B.3. of the AAP guideline)¹⁷ for DEBs/EDs assessments in this targeted population prior to and during implementing weight management strategies like pharmacotherapy.

Pharmaceuticals have been described as the prescription for fat people of what is diagnosed as disordered in thin people⁸⁴—that is, the acceptable biomedicalization of the pathological: skipping meals (anorectics), diet pills (pharmacotherapeutics themselves), laxatives (orlistat), and vomiting (a common glucagon-like peptide 1-related adverse effect).^{85,86} Considering the vulnerability to and higher prevalence of DEBs/EDs in adolescents classified as overweight or obese, the explicit valuing of weight loss as a success metric in pharmaceutical obesity management is worrisome in that it aligns with a weight normative approach to health,¹ which has been shown to increase the risk for weight cycling and DEBs/EDs.^{87,88,89}

In summary, weight loss is not essential to improving comorbidities and tends to be minimal and impermanent, with repeated attempts being typical. Particularly in adolescents, making weight loss the primary aim of health interventions (including pharmaceuticals) exacerbates the likelihood of destructive outcomes such as DEBs/EDs and weight cycling.

FDA and Weight Loss Pharmaceuticals

The FDA evaluates weight loss pharmacotherapies, or anti-obesity medications, by their *mean* and *categorical* efficacy, as defined in “Guidance for Industry: Developing Products for Weight Management” (originally published in 1996 as “Guidance for the Clinical Evaluation of Weight-Control Drugs”).¹⁹ After 1 year of treatment, the difference in the mean weight loss between the active-product and placebo groups must be statistically significant and at least 5% (ie, mean efficacy). Alternatively, after 1 year of treatment, at least 35% of participants in the active-product group should lose at least 5% of their initial weight, the proportion who lose at least 5% of their initial weight “is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant” (ie, categorical efficacy). The 5% benchmark was selected because research before 1996 indicated that weight reductions of 5% to 10% improved metrics such as blood pressure, indexes of glycemia, and high-density lipoprotein cholesterol.^{90,91}

The FDA itself notes that “pediatric-specific adverse events are unlikely to be detected in development programs that are limited in size and duration” and that “long-term effects of drug treatment in children can include impacts on development, growth, and/or

maturation of organ/system function.”⁹² Additionally, the FDA evaluation does not include a period of pharmaceutical cessation, hampering our understanding of weight loss permanence and regain associated with treatment timelines.

As of February 2023, there are 4 FDA-approved weight loss drugs for adolescents older than 12 years of age: orlistat,⁹³ liraglutide,⁹⁴ semaglutide,⁹⁵ and phentermine/topiramate extended-release capsules.⁹⁶ Additionally, phentermine is permitted for individuals older than 16 years of age for 12 weeks or less (see Table).^{97,98} In the near future, the FDA is likely to approve the diabetes drug tirzepatide for adolescent weight loss.⁹⁹ Practitioners also use other medications off-label, including bupropion/naltrexone, topiramate, lisdexamfetamine, and (most commonly) metformin.^{100,101}

Table. US Food and Drug Administration-Approved Weight Loss/Anti-obesity Medications for Adolescents

| Name | Class of drug | Year approved for adults | Year approved for adolescents |
|---------------------------|--------------------------------|--------------------------|-------------------------------|
| Phentermine | Anorectic | 1959 | 2015 |
| Orlistat | Lipase inhibitors ^a | 1999 | 2003 |
| Liraglutide | GLP-1 agonist ^b | 2014 | 2020 |
| Phentermine/topiramate ER | Anorectic, anticonvulsant | 2012 | 2022 |
| Semaglutide | GLP-1 agonist ^b | 2021 | 2022 |

Abbreviations: ER, extended release; GLP, glucagon-like peptide.

^a Prevents some of the fat in foods eaten from being absorbed in the intestines. The unabsorbed fat is then removed from the body in the stool.

^b Mimics glucagon-like peptide 1, a gastrointestinal hormone that helps regulate glucose.

The history of weight loss/anti-obesity medications is littered with recalls,¹⁰² including of fenfluramine, dexfenfluramine, sibutramine¹⁰³ and, most recently, lorcaserin,¹⁰⁴ due to postmarket phase discovery of risks ranging from primary pulmonary hypertension^{91,105} to cardiac valvulopathy¹⁰⁶ to cancer.¹⁰⁴ The more recently approved medications, such as liraglutide and semaglutide, should arguably be safer given the availability of safety information on their active compounds, which have been used for years in other formulations.¹⁰⁷ However, the application of weight loss/anti-obesity pharmacotherapies to adolescents is still relatively new and therefore the risk profile is relatively undetermined.

Weight Loss Medications for Adolescents

Weight loss medications specifically approved for adolescents are relatively new, with off-label prescriptions being the norm.¹⁰⁸ Currently, pharmaceuticals are intended as an adjunct rather than as monotherapy¹⁷ after lifestyle and behavioral medications, such as IHBLTs, fail to produce weight loss.¹⁹

IHBLTs are intended to serve as a first-line approach to reduce the frequency of pharmaceutical prescription, thereby avoiding unnecessary exposure to harm.¹⁰⁹ However, numerous studies document that IHBLT and other similar interventions do not result in weight loss for the majority of adult^{49,110,111} and adolescent^{112,113} participants long-term, with the result that, for most, the lifestyle intervention will be deemed a failure, prompting clinicians to recommend pharmaceutical intervention.^{17,19} IHBLT

programs vary in their characteristics¹¹⁴ while similarly suffering high patient attrition,^{112,113, 115} possibly because the intense time and resource investment required negatively impact participation.¹⁷ Without uniform quality standards for IHBLTs, it is difficult to determine whether weight loss failure is due to treatment resistance or nonadherence or to poor intervention quality. With IHBLTs tending toward failure and pharmaceuticals being relatively undemanding to implement, weight loss pharmacotherapeutics may rapidly become the dominant treatment modality for adolescent obesity.

In its 2023 practice guidelines, the AAP concedes that evidence on using pharmaceuticals to aid weight/BMI reduction is currently insufficient.¹⁷ There are a relatively small number of completed clinical trials, which tend to collect limited information¹¹⁶ and be inadequately powered due to small sample sizes.¹¹⁷ Available data indicate that average weight loss is typically minimal: 1.5% BMI reduction from baseline after 12 months' treatment with orlistat,¹¹⁸ 4.1% BMI reduction from baseline after 6 months' treatment with phentermine,⁵² 4.29% BMI reduction from baseline after treatment with liraglutide for 56 weeks,⁵⁵ and 16.1% BMI reduction from baseline after treatment with semaglutide for 68 weeks.¹¹⁹ Common side effects (eg, nausea, vomiting, gastrointestinal distress)¹²⁰ cause a noteworthy number of participant treatment discontinuations during clinical trials: 17.1% for orlistat vs 11.7% for the placebo group,¹²¹ 13.8% for liraglutide vs 6.8% for the placebo group,⁵⁵ and 14.8% for semaglutide vs 4.3% for the placebo group.¹¹⁹

The history of weight loss medications indicates that adverse drug reactions (including those resulting in a box warning or withdrawal) are not fully understood until the postmarket phase.^{122,123,124} Studies assessing FDA approval of new drugs^{125,126} find that approval is increasingly based on “fewer, smaller, or less rigorous pivotal trials,”¹²⁷ thereby shifting the burden of evidence of adverse effects to the post-approval period.¹²⁸ A study of all drugs approved by the FDA between 2001 and 2010 found that more than a third were affected by a postmarket safety event (withdrawals, boxed warnings, safety communications).¹²⁴ With regard to weight loss drugs specifically, there is a dearth of long-term studies of the effects of weight loss pharmaceuticals in adolescents,¹²⁹ and, as a result, our knowledge of their risks is lacking. Extrapolating potential side effects in adolescents from studies with adults¹³⁰ is insufficient because, as the AAP notes, adolescents are undergoing growth and pubertal development, which can “alter the kinetics, end-organ responses, and toxicities” of the pharmaceutical in question.¹³¹ Health care practitioners will need to consider that early adoption of weight loss medications means that significant side effects—particularly long-term or developmental ones—will likely be identified in their patients during postmarket surveillance. This possibility is ethically troubling, given that many adolescents who will initially qualify for pharmaceutical intervention due to BMI belong to minoritized or under-resourced populations,¹⁷ raising concerns about the justness of these adolescents bearing the brunt of side effect discovery during the postmarket phase without more significant investment to discover these issues during the clinical trial phase.

Research on weight regain in adolescents after pharmaceutical discontinuation is scarce, but the emerging evidence is consistent with the pattern found in adults.^{51,55} Weight regain and loss of “attendant health benefits”^{17,51} after pharmaceutical cessation are mentioned as reasons to switch framing obesity from an acute¹²¹ to a “chronic relapsing progressive disease process”¹³² requiring continuous treatment. This push to extend treatment timelines indefinitely should spark concerns not only about

our limited understanding of long-term side effects of weight loss medications in adolescents, but also about the potential impact of out-of-pocket cost on medication adherence.¹³³ Medication adherence is low in adolescents to begin with, and even lower for those with long-term conditions.^{134,135} Many private insurers follow the lead of Medicare, which, outside of Advantage plans, does not cover anti-obesity medications, leaving patients to pay hundreds of dollars a month out of pocket or risk weight regain.^{136,137} Inconsistent use could result from these access challenges, inadvertently exposing adolescents to the dangers of weight cycling.

The nonprofit Obesity Action Coalition (OAC) is currently pushing for the passage of the Treat and Reduce Obesity Act of 2021, which would expand Medicare benefits for IHBLT-type programs and expand coverage for FDA-approved chronic weight management medications.^{138,139} Top corporate partners of the OAC are Novo Nordisk® (semaglutide) and Eli Lilly (tirzepatide),¹⁴⁰ both of which stand to make a fortune with the prescription of weight loss and anti-obesity pharmaceuticals for obesity diagnosed by what could be considered an indiscriminate standard—BMI.

In summary, the threshold for initial prescription of weight loss medications is low, given how failure is defined for lifestyle modifications. Pharmaceutical interventions induce modest weight loss at best (frequently with side effects) that requires persistent usage to maintain. Long-term side effects of such interventions in adolescents—especially on development—have arguably not been sufficiently established for adequate risk assessment. What few studies there are examining pharmaceutical safety and efficacy in adolescents tend to be small and inadequately powered.

Conclusion

Should pharmaceuticals be used as a weight loss intervention for adolescents classified as obese? There is no disputing that pharmaceuticals are an essential part of clinical practice, but as a result of sparse investigation and overvaluing of weight loss, physicians might be inaccurately assessing the benefits as outweighing the risks in prescribing pharmaceuticals to induce weight loss. There is no general consensus for what constitutes a healthy BMI or clinically significant weight loss in adolescents. What weight loss that does occur is typically transient, not enough to shift BMI categorization, and not necessary to produce desired health outcomes. The pursuit of weight control,¹⁴¹ a tactic of **weight-normative health promotion**, is likely to result in—but is not limited to—weight dissatisfaction^{142,143,144} and stigma,¹⁴⁵ DEBs/EDs, and weight cycling. All of these consequences are linked to worse health outcomes and further weight gain—the very opposite of the intended effect. The risks of continuous pharmaceutical treatment in adolescents in order to potentially stabilize weight loss are not yet known. The unknown extent of pharmacotherapeutics' risks to adolescents for the controvertible benefits of weight loss ethically precludes their prescription, despite the scientific consensus to fight obesity by prescribing weight reduction.¹⁴⁶

BMI and weight as defining clinical metrics distort our conception of what is required for health, justifying a dogged commitment to the erasure of fatness as health promotion rather than the interrogation of the biological, social, environmental, and economic factors impacting bodies.¹⁴⁷ Pharmacological interventions might eventually become a key, safe, and effective component of the comprehensive care of patients navigating obesity. However, the justification of risks—particularly for adolescents—will depend on the congruence of the intended outcome with health reconceptualized as more than just anti-fatness. This reconceptualization will require scientific and ethical examination of

the evidence, narratives,¹⁴⁸ and assumptions influencing how medicine understands and deems desirable goals of health.¹⁴⁹ Weight-neutral and weight-inclusive approaches^{1,87,88,150,151,152,153} provide insight into actualizing a clinical practice in which weight status—rather than being the definitive standard—is just one factor informing our understanding and pursuit of health.

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