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Working Toward Precision Medicine Approaches to Treat Severe Obesity in Adolescents: Report of an NIH Workshop

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Abstract

Adolescent severe obesity is a prevalent, chronic, and serious disease with few effective and safe treatment options. To address this issue, a National Institutes of Health-sponsored workshop entitled “Developing Precision Medicine Approaches to the Treatment of Severe Obesity in Adolescents,” was convened, bringing together a multidisciplinary group of experts to review the current state of the science and identify 1) what is known regarding the epidemiology and biopsychosocial determinants of severe obesity in adolescents, 2) what is known regarding effectiveness of treatments for severe obesity in adolescents and predictors of response, and 3) gaps and opportunities for future research to develop more effective and targeted treatments for adolescents with severe obesity. Major topical areas discussed at the workshop included: appropriate BMI metrics, valid measures of phenotypes and predictors, mechanisms associated with the development of severe obesity, novel treatments informed by biologically- and psychosocially-plausible mechanisms, biopsychosocial phenotypes predicting treatment response, standardization of outcome measures and results reporting in research, and improving clinical care. Substantial gaps in knowledge were identified regarding the basic behavioral, psychosocial, and biological mechanisms driving the development of severe obesity and the influence of these factors on treatment response. Additional exploratory and observational studies are needed to better understand the heterogeneous etiology of severe obesity and explain the high degree of variability observed with interventions. Tailored treatment strategies that may be developed by achieving a better understanding of individual differences in genetic endowment, clinical, metabolic, psychological, and behavioral phenotypes, and response to environmental exposures need to be tested. It is anticipated that these recommendations for future research, including

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strategies to enhance methodological rigor, will advance precision medicine approaches to treat severe obesity in adolescents more effectively.

Introduction

Pediatric obesity remains a global medical and public health threat as rates continue to rise and accumulating evidence has led to the acknowledgement of its status as a disease leading to numerous health problems and comorbidities.(1) Obesity among children and adolescents is prevalent and continues to trend upward with almost 19 percent of United States (U.S.) youth at or above the 95th percentile BMI for their age and sex.(2–5) Most concerning is the high prevalence and rate of increase of severe obesity in adolescents and its associated medical and psychological co-morbidities. Severe obesity in U.S. adolescents, defined as BMI \geq 120% of the 95th percentile,(6) has approximately tripled since 1988–1994, increasing from 2.6% to 7.7% in 2015–2016, and disproportionately affects certain racial and ethnic minority groups and families with low socioeconomic status.(2;5;7) Adolescents with severe obesity are at elevated risk for multiple medical comorbidities, including hypertension, dyslipidemia, insulin resistance and type 2 diabetes, non-alcoholic fatty liver disease, and orthopedic disorders.(6;8;9) Moreover, this group is also more likely to suffer from a wide range of psychosocial co-morbid conditions including depression, anxiety, binge- and loss-of-control eating, and poorer psychological well-being.(10) Unfortunately, most youth with severe obesity retain their excess weight throughout childhood/adolescence and into adulthood.(11;12)

Adolescent severe obesity is an intractable disease; even with current state-of-the-art treatment, the majority of those affected will not achieve and maintain a healthy weight. Behavioral and lifestyle interventions performed in Europe and the U.S. have demonstrated relatively small improvements in mean BMI that are not sustained,(13–15) and the limited pharmacotherapy options available also show modest efficacy.(16;17) Cohorts from Europe and the U.S. have demonstrated that bariatric surgery leads to the greatest and most durable weight loss; however, response is variable and surgical approaches, even in the most recent studies, can be associated with short- and long-term health risks.(18–20) Furthermore, despite surgical intervention, a substantial proportion of adolescents continue to have a BMI within the obese range.(19;20) Few treatments lead to meaningful and sustained weight loss in adolescents with severe obesity and little is known about how to tailor treatments to maximize efficacy.

A workshop led by the National Institute of Diabetes and Digestive and Kidney Diseases and in cooperation with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Heart, Lung, and Blood Institute, National Institutes of Health (NIH) Office of Behavioral and Social Sciences Research, and NIH Office of Disease Prevention, entitled “Developing Precision Medicine Approaches to the Treatment of Severe Obesity in Adolescents,” was convened in September 2017 with the goal of bringing together scientists with expertise in pediatric obesity, endocrinology, epidemiology, psychology, physiology, genetics, behavioral medicine, adolescent medicine, and bariatric surgery to address this important and urgent medical and public health issue. The purpose of

this workshop was to explore the current state of the science and identify 1) what is known regarding the epidemiology and biopsychosocial determinants of severe obesity in adolescents, 2) what is known regarding effectiveness of treatments for severe obesity in adolescents and predictors of response, and 3) gaps and opportunities for future research to develop more effective and targeted treatments for adolescents with severe obesity. The workshop specifically targeted adolescents because outcomes in this group have been especially poor and this developmental period is associated with unique challenges in terms of behavior and adherence, including executive function and emerging autonomy.

Presentations by experts were organized around four topic areas 1) the scope of the problem as it relates to the epidemiology of severe obesity in adolescence and characterization of adolescent neurocognitive development, 2) biopsychosocial and behavioral factors that are associated with the development of severe obesity in adolescents, 3) treatment approaches for severe obesity in adolescents, and 4) biomarkers and phenotypes that predict response to treatment in adolescents with severe obesity. Speakers, discussants, and participants were then asked to synthesize the information presented at the workshop and draw from their knowledge of the literature to make recommendations on gaps and opportunities to accelerate research that will identify which treatment approaches will be most beneficial for specific patients based on a better understanding of individual differences in genetic endowment, clinical, metabolic, psychological, and behavioral phenotypes, and response to environmental exposures. This article summarizes the state of the science and provides recommendations for future research to advance precision medicine approaches to treat severe obesity in adolescents, as well as to enhance methodological rigor in pediatric obesity research.

General State of the Evidence for Weight Management Interventions in Adolescents with Severe Obesity

Lifestyle Modification Therapy

Lifestyle modification programs that incorporate evidence-based behavioral strategies to promote changes in eating and diet-related behaviors and physical activity are generally considered fundamental in the management of pediatric obesity. The United States Preventive Services Task Force (USPSTF) has recommended that all children over the age of six years be screened for obesity and offered comprehensive, intensive (at least 26 hours of contact) behavioral interventions to improve weight status.(21) The USPSTF recommendation, which was offered at a moderate level of certainty, is consistent with recommendations from other relevant groups,(22;23) and consensus statements from international organizations.(1;24) Family-based pediatric lifestyle modification programs are reliably associated with modest decreases in BMI and improvements in cardiometabolic risks that can persist long-term.(21;25;26) Nevertheless, lifestyle interventions appear to be less effective for older children and those with more severe obesity,(13;15;27) raising the question of their use as a stand-alone therapy in the management of adolescents with severe obesity given the cost and complexity of such programs.

Available research has shown that lifestyle interventions targeting adolescents with severe obesity are associated, on average, with minimal to modest decreases in weight-related parameters.(6;15) However, at least one randomized, controlled trial has found significant effects of an intensive lifestyle intervention for youth with severe obesity. Lifestyle modification was associated with minimal changes in BMI in the intervention group over a 2-year period of observation, but adolescents randomized to usual care demonstrated significant increases in BMI.(28;29) Further, youth in the intervention group experienced improvements in body composition and insulin resistance relative to those who did not receive treatment. In this context, lifestyle intervention may benefit adolescents by reducing ongoing weight gain and increases in associated comorbidity. Further, it should be noted that response to treatment can be highly variable - some youth with severe obesity achieve clinically meaningful reductions in adiposity,(13–15;27–29) suggesting the possibility that there may be patient characteristics that could be used to select those adolescents who might respond considerably better to lifestyle intervention. Finally, there is some evidence that even in the absence of changes in BMI, lifestyle modification therapy for adolescents with severe obesity may be associated with improvements in quality of life and select cardiometabolic risk factors.(30)

Although there are few adolescent data directly testing the importance of lifestyle modification therapy in programs that involve other modalities such as pharmacotherapy or surgery, extant adult research leads to an expectation that lifestyle modification is a crucial and indispensable component of any comprehensive treatment approach to severe obesity. (31) Additional research is needed to optimize how to select adolescents that will benefit most from lifestyle intervention or the combination of lifestyle modification with other modalities, and evaluate how to stage interventions in the context of chronic care.(32)

Pharmacotherapy

Historically, medications have not been widely used to treat pediatric obesity due to lack of availability of effective agents and concerns about safety, particularly related to growth and development. However, a recent increase in the number of new medications approved for use in adults has generated a renewed interest in pharmacotherapy as a treatment option for select youth with obesity. Relatively few medications have been evaluated in the pediatric population and most of the clinical trials performed have been small. The reader is referred to recent reviews and meta-analyses detailing the safety and efficacy of currently-available medications used both on- and off-label in pediatric populations, including orlistat, metformin, exenatide, topiramate, and phentermine.(16;17;33;34) In summary, these medications offer modest weight loss efficacy ranging on average from approximately 3 to 5% placebo-subtracted BMI reduction. Adverse events vary by agent but, in general, these medications appear to have acceptable short-term safety profiles based on the somewhat limited scope of the data.(16;17;33;34) Additional research is needed to evaluate the safety and efficacy of long-term medication use since there have been few clinical trials of treatment greater than 6 months in the pediatric population. For young people with 70 or more years of future life, methods to predict which individuals will continue to benefit from pharmacotherapy into adulthood remain insufficiently explored.

Looking forward, the pediatric pipeline includes four new medications that have recently been approved for adult use but have yet to be evaluated in pediatric trials: lorcaserin (selective serotonin receptor agonist) producing placebo-subtracted weight loss of approximately 3–4% in adults;(35;36) phentermine (norepinephrine reuptake inhibitor) plus extended-release topiramate (gamma-aminobutyric acid modulation) producing placebo-subtracted weight loss of approximately 7–9% (depending on dose) in adults;(37) naltrexone extended-release (opioid receptor antagonist) plus bupropion extended-release (dopamine/norepinephrine reuptake inhibitor) producing placebo-subtracted weight loss of approximately 5% in adults;(38;39) and high dose (3 mg) liraglutide (glucagon-like peptide-1 receptor agonist) producing placebo-subtracted weight loss of approximately 5% in adults.(40) An even more extensive pipeline of obesity medications are currently in phase II and III development in adults, suggesting that a host of treatments may be available for evaluation in the pediatric population in the coming years. Other medications targeting specific genetic forms of obesity are also in development. In terms of precision medicine, one relevant example owing to its well-characterized mechanism of action is the melanocortin receptor agonist setmelanotide, which appears remarkably efficacious for patients with genetic defects affecting the proximal leptin signaling pathway.(41) As additional medications are brought to the market targeting a host of pathways of the energy regulatory system, it will be important to identify predictors of response to tailor treatment with a goal of maximizing effectiveness while minimizing risk of side effects.

Device Therapy

A number of devices, each targeting different aspects of energy balance, have been recently approved for the treatment of adult obesity including the intra-gastric balloon, vagal blockade, and aspiration therapy (the use of percutaneous gastrostomy to evacuate stomach contents). All but one of these devices (intra-gastric balloon) remains to be tested in the pediatric population. Adult trials of the intra-gastric balloon have demonstrated relatively modest mean weight reduction (approximately 4%) with adverse events including flatulence, abdominal fullness, abdominal pain, abdominal discomfort, and gastric ulcer.(42) Such results might reduce enthusiasm for using this approach in adolescents. A number of relatively small uncontrolled, observational pilot studies of intra-gastric balloon treatment in adolescents with obesity have demonstrated mean weight losses ranging from 0–16% with treatment for 3–6 months with the most commonly-reported adverse events being gastric pain/cramping.(43–46) Before obesity devices are considered for clinical use in the pediatric population, it will be necessary to perform rigorous evaluation in randomized controlled trials with long-term follow-up to assess safety and efficacy (including weight loss maintenance) as well as identify predictors of response to inform patient selection.

Bariatric Surgery

Bariatric surgery is widely acknowledged as the most effective weight loss intervention in adolescents with severe obesity. Recent prospective studies of Roux-en-Y gastric bypass (RYGB) and the vertical sleeve gastrectomy (VSG) have demonstrated BMI reductions of approximately 30% or more at follow-up time-points ranging from 1–8 years after surgery. (19;20;47) In addition to producing meaningful and sustained weight loss, bariatric surgery appears to improve obesity-associated co-morbidities such as type 2 diabetes, hypertension,

dyslipidemia, and musculoskeletal pain, as well as reduce levels of inflammation and oxidative stress.(19;48;49) Potential barriers to bariatric surgery include limited access to specialized programs, the life-altering nature and irreversibility of some procedures, and long-term risks such as micronutrient deficiencies (which may vary by procedure type) and the possibility of alcohol use disorders and suicidality that have been observed in adult bariatric surgery patients.

Like all other obesity treatments, bariatric surgery outcomes are variable – most adolescents lose a significant amount of weight while some experience much more modest weight reduction or none at all.(19;50) Future work should prioritize the identification of factors predictive of suboptimal vs. superior weight loss and co-morbidity resolution. Also, research efforts should focus on methods for early identification of suboptimal responders so that adjunctive treatments that can be initiated after bariatric surgery can be evaluated for their ability to enhance weight loss and maintenance in these individuals.

Gaps and Opportunities

The Workshop identified significant knowledge gaps and therefore opportunities for future research in seven domains, which are summarized in the following sections.

Valid and Clinically-Meaningful BMI Metrics for Severe Obesity

The best metric(s) to assess body weight/adiposity among those with severe obesity remains unclear. Fully-validated standardized scores (BMIz) are available for U.S. children only within the 3rd to 97th percentiles.(51) Extending the range beyond these percentiles using the LMS estimation method employed by the U.S. growth charts uncovers nonlinearities such that high BMIz does not track well either with adiposity(52) or with change in BMI.(53–55) For longitudinal studies, some researchers have suggested that individual changes in raw BMI may be most meaningful.(56;57) More recently, given the limitations of BMI z-scores and percentiles in children with very high BMI's,(52) investigators have suggested calculating percentages relative to the 95th percentile (%BMIp95) and defining severe obesity as BMI \geq 120% of the 95th percentile.(58) Change in %BMIp95 as a continuous measure has also been proposed for tracking and to assess obesity treatment outcome.(6;59) We are only beginning to understand how %BMIp95 relates to the medical and psychosocial comorbidities of obesity,(8) and there are insufficient data regarding how changes in any of the aforementioned metrics to measure treatment efficacy relate to improvements in comorbid conditions in adolescents with severe obesity. There are also known issues regarding how BMI relates to adiposity, particularly when children with race/ethnicity other than Non-Hispanic White are studied,(60) suggesting the possibility that metrics based on measuring fat mass might be valuable. For adolescents with severe obesity, there are very limited data regarding how much change in BMI, BMIz, or fat mass is required to improve health as measured by reductions in comorbid conditions.(23) Studies are needed to:

- Determine the utility of BMI charts that express BMI as a percent above the 95th percentile to predict co-morbidities (medical and psychosocial) for those with severe obesity; examine whether there are differences by sex, race, or ethnicity.

- Examine how changes in BMI percent above the 95th percentile translate into changes in co-morbidities (medical and psychosocial risk) for those with severe obesity. These studies should establish the degree of reduction that is considered clinically meaningful, determine what amount of BMI reduction or weight loss needs to be sustained (and what is the needed length of time for which it needs to be sustained) to maintain initial co-morbidity/risk factor improvements, and ascertain if there are important differences by sex, race, and ethnicity or as a result of BMI change or weight loss before or after the completion of puberty.
- Evaluate the performance and utility of alternative anthropometric indices such as the tri-ponderal index.(61)
- Establish if determinations of regional (e.g. visceral or hepatic) fat mass or total fat mass by criterion methods like dual-energy x-ray absorptiometry or by other more clinically-practical methods such as bioelectrical impedance offer important advantages over BMI-based metrics for prediction of improvements in health among adolescents with severe obesity.

Valid and Developmentally-Appropriate Measures of Phenotypes and Predictors

There has been insufficient investigation into how best to measure the key factors that promote weight gain and impede weight loss in adolescents with severe obesity. One important issue is how to determine the energy intakes of free-living children and adolescents accurately before and during treatment. Food records and food frequency questionnaires have been shown to be problematic because of underreporting that is greater in adolescents with, versus without, obesity.(62–64) Similarly, because many proposed neuropsychological phenotypes are determined via questionnaires, there are continued questions about their validity and a desire to relate them to physiological measurements(65) or to replace subjective responses with more objective biomarkers. For total daily energy expenditure, which in the absence of weight change is presumed to be equivalent to intake, satisfactory approaches such as use of doubly-labeled water(66) exist but are not widely employed because of cost. In terms of assessing treatment outcomes, quality of life (QOL), which is inherently subjective, is potentially an important metric because regulatory agencies like the FDA may accept improvements in QOL as evidence of treatment efficacy. (67) Some data suggest adolescents with severe obesity have health-related QOL comparable to that of adolescents with cancer.(68) However, the extant questionnaires require additional validation in pediatric populations. Furthermore, because children and adolescents have evolving neurocognitive abilities, a developmental perspective is essential, and the validity of questionnaire approaches that are found satisfactory at one age cannot be assumed to be equally appropriate for older (or younger) adolescents. Studies are needed to:

- Develop reliable and valid objective measurements or biomarkers to complement self-report measures or questionnaires where possible. This is particularly needed for measures of dietary intake.
- Validate questionnaires against biological measures where possible.
- Develop and validate novel measures of neurocognitive function.

- Develop and validate measures of obesity-related QOL.

Mechanisms and Biopsychosocial Predictors of Developing Severe Obesity

Although successful treatments need not necessarily reverse the underlying cause of a disease, it is logical to expect that a greater understanding of the reasons why some adolescents develop severe obesity could lead to better outcomes from a more personalized approach to treatment.(69) Important differences in environmental, psychosocial, cultural, and economic factors, epigenetic events, and other factors, including gene-environment interactions appear involved in determining who develops severe obesity.(70) There is a relative dearth of data from longitudinal (as opposed to cross-sectional) observational studies that could shed light on how severe adolescent obesity develops. Elaboration of comprehensive models could supply novel targets for prevention or intervention efforts and suggest how most effectively to combine interventions focused on disparate targets. Studies are needed to:

- Characterize the longitudinal growth trajectories, beginning from infancy to childhood and adolescence to determine the various patterns defined by timing of onset of severe obesity and its persistence.
- Determine how pubertal maturation relates to developing severe obesity.
- Understand the qualitative similarities and differences between severe obesity and moderate obesity or overweight.
- Develop an integrated, interdisciplinary and comprehensive conceptual model of biopsychosocial factors that affect the development of severe obesity. This includes but is not limited to a variety of domains including environmental conditions, genetics, dietary intake, physical activity, brain and executive functioning, eating behaviors (including disordered eating behaviors such as binge eating), food or taste preferences and choices, mood and other mental health disorders, medications and sleep.
- Advance and organize conceptual models of eating and activity behavior phenotypes.
- Define subtypes of severe obesity using a comprehensive set of biopsychosocial factors, genotypes, epigenetic modifications, metabolomic changes, and other phenotypes.
- Characterize dyads or families with clustering of severe obesity and conduct family phenotyping as well as youth phenotyping regarding their roles, communication, and interpersonal skills. This would include characterizing how family relationships and dynamics vary by the age of the child and the sociocultural environment and over time, as these factors may not be static.
- Examine the differences in phenotypes and biomarkers between siblings divergent in obesity status.
- Conduct extensive evaluation of lean individuals to better understand differences from severe obesity.

- Attempt to disaggregate and identify the independent effects of race/ethnicity and SES where possible.
- Leverage brain maturation studies to understand developmental processes that may be related to developing severe obesity to generate hypotheses for future studies.

Novel and Developmentally-Appropriate Treatments, Driven by Biologically- and Psychosocially-Plausible Mechanisms

Evidence points to the fact that most individuals with obesity have multiple genetic and environmental risk variants (each with relatively small effects) that may impact body weight. At present, there are no approaches other than bariatric surgery that appear effective for most adolescents with severe obesity. As noted earlier, even intensive behavioral obesity treatment has been found to be less efficacious among adolescents than younger children. Further, many trials of obesity therapies in adults and adolescents exclude the most severely affected individuals. As a result, there is a lack of published data on non-surgical approaches among adolescents with severe obesity. Given the heterogeneity expected in the etiologic factors contributing to the development of obesity, many different approaches need to be studied more intensively. Studies are needed to:

- Examine the safety and efficacy of various medications, devices, or surgical approaches that either have already been tested in adults, or are novel therapies for subtypes identified in youth. These studies should also address the biology or mechanisms of various treatment approaches.
- Examine the efficacy based on phenotype and genotype of specific dietary approaches on body weight trajectories and their impact on relevant obesity biomarkers, metabolic risk factors, microbiome endpoints, etc.
- Optimize medication dosing to metabolism or develop precision pharmacological treatments using pharmacogenomics approaches.
- Identify the optimal timing for various treatment interventions approaches in youth with severe obesity. These studies should determine the social, behavioral and developmental considerations and the periods of plasticity, where one can alter the trajectory of severe obesity and if there are important differences in how the sequence in which therapies are offered impacts outcome.
- Identify the optimal intensity of weight management lifestyle intervention in terms of hours of intervention and setting as well as health benefits and costs for various subgroups of adolescents with severe obesity. In particular, elucidate the processes of behavior change and/or use of adjunct technologies such as mobile health applications that may promote adherence to lifestyle intervention.
- Examine if there are useful predictors for determining when interventions involving parents will help or hinder treatments for adolescents with severe obesity.

- Determine the optimal culturally-sensitive messaging about health risks associated with obesity to promote positive behavior change in various racial and ethnic subgroups with severe obesity as well as approaches to address strong environmental influences in these subgroups such as poverty and stress.
- Examine the efficacy of innovative study designs for treatments including adaptive designs, matching the treatment to the underlying hypothesized mechanisms in study participants, to improve response to treatment.
- Examine the efficacy of combination or stepwise therapies.

Biopsychosocial Phenotypes that Predict Treatment Response

Given the poor response of adolescents with severe obesity to available non-surgical interventions, it is critical to characterize subgroups that may respond differentially to treatment. Biopsychosocial phenotypes (observable traits resulting from the influence of genes and environment) that are associated with weight gain or obesity treatment outcome have been identified across multiple domains. These include basic brain-behavior associations such as those related to response inhibition,(71;72) gut microbiome enterotypes, (73) eating behaviors such as eating in the absence of hunger or binge eating,(74–77) and relative reinforcing value of, or affective response to, physical activity.(78) Relatively little of the research on obesity phenotypes has focused on youth with severe obesity, and there is a need to characterize and examine potential phenotypes in prospective studies of different interventions. Studies are needed to:

- Examine the results of treatment studies in secondary data analyses to identify responders and determine whether there are biomarkers or biopsychosocial characteristics that could be used to predict response and identify those most likely to discontinue or choose not to comply with treatment. Results could generate hypotheses for future studies that may be designed to tailor interventions more precisely.
- Perform interventional weight management trials that prospectively evaluate which biopsychosocial factors or phenotypes predict initial treatment success and longer-term maintenance. Trials should be designed to conduct baseline phenotyping with serial assessment during the trial (and potentially after withdrawal of treatment) to examine changes in these factors over time.
- Examine relationships between multiple phenotypes (e.g., metabolomic and psychosocial) and their potential effects on outcomes of different interventions.
- Examine changes in obesity-related hormones and substrates relevant to the energy regulatory system (e.g., metabolomics) that occur with various treatments and how they predict response.

Standardization of Research Outcome Measures and Reporting of Results

One of the most pertinent issues for studies of any treatment is how best to define the most important primary and secondary outcomes. For approaches to treat adolescent severe obesity, this question has not been definitively answered. It is clear that a reduction in

adiposity is the primary goal, but the degree of reduction needed for improved health has not been established. Further, there is no agreed-upon essential list of obesity-associated conditions and laboratory abnormalities that should be reported for all adolescent trials.(16) Establishing a *lingua franca*, a widely-accepted set of common outcome measures for treatment success to be reported for every trial, will allow investigators to conduct meta-analyses and comparisons among treatments that cannot currently be done. It is also clear that there is substantial heterogeneity in outcomes from different approaches to treat severe adolescent obesity. Understanding if the response heterogeneity may indicate sub-types of adolescents who may be successfully treated by more personalized, precision approaches(69) will require characterization of the heterogeneity of response in publications. Efforts in the adult obesity research community are already underway to develop an integrated model for how various factors may influence obesity treatment responses and for establishing a core set of measures that can be used consistently across trials. Indeed, the “Accumulating Data to Optimally Predict Obesity Treatment (ADOPT)” core measures project(79) may serve as a future roadmap for similar work in the pediatric obesity arena. In the interim, studies are needed to:

- Develop consensus recommendations on appropriate BMI/adiposity metrics, comorbid condition definitions, outcome measures, and other common data elements to be used and reported in clinical trials.
- Determine what non-BMI/adiposity-based health outcomes should be utilized for weight management interventions in adolescents with severe obesity, including the possibility of health composite or QOL measures.
- Develop reliable, valid, and developmentally-appropriate common exposure and outcome measures for obesity studies in youth. This would help to harmonize or even standardize assessments/phenotyping in research as well as clinical settings allowing for valid comparisons across studies and for subsequent pooling of data.
- Report the heterogeneity in response to interventions, expressed as the distribution of changes in weight or BMI metrics in the results of trials. Such reporting would further our understanding of the most appropriate types of interventions for various genotypes/phenotypes or groups of adolescents in future trials.
- Improve access to various measures being used in studies to promote the use of common measures and resource sharing across studies and allow for pooling of research data.

Establishing a Clinical Context for the Development and Delivery of Precision Care

Advances in novel evidence-based precision medicine approaches will surely lead to enhanced clinical care and better outcomes for adolescents with severe obesity. Given the scope and treatment-resistant nature of adolescent severe obesity, research is needed to identify if there are individuals who can be effectively managed in primary care settings and to determine if personalized management strategies offered in a tertiary care specialty weight management program offering comprehensive services (individualized lifestyle modification therapy including dietary and physical activity interventions, family-based and

psychosocial, interventions, pharmacotherapy, and bariatric surgery) produce better outcomes. Research to improve early identification and timely referral of adolescents on a trajectory toward, or newly-entering, the category of severe obesity may also be important, as data suggest that most youth seeking medical weight management already have severe obesity.(80;81) Notable limitations of clinical obesity care and priority areas in need of improvement include accessibility and cost (not all regions have a tertiary care program), patient retention, and variability in how these programs are funded and how care is delivered (e.g., resources available, services provided, medical subspecialties/staffing models utilized, and frequency of follow-up offered).(81) As new treatments with better efficacy yet potentially higher risk are approved for pediatric use (e.g., medications, devices, etc.) and become clinically-available in the coming years, it will be important to identify and implement strategies to ensure there are a sufficient number of appropriately-trained medical providers knowledgeable and experienced in their use. Equally important is the need to equip these providers with practical guidance regarding which treatments should be selected for specific patients to maximize health outcomes and minimize side effects. Studies are needed to:

- Evaluate methods for and barriers to early identification of youth on a path to severe obesity (including stigma and bias) in order to improve referral and access to specialty clinical care.
- Develop and test the use of a chronic care model for treating severe obesity, potentially using other diseases with “medical homes” such as type 1 diabetes, sickle cell anemia, and ulcerative colitis as a model.
- Evaluate the effects, including health outcomes, of existing clinical care models for obesity. This may help to develop a toolbox of successful intervention approaches that could be offered to a care team factoring in age, development, family factors, and social-cultural factors as well as other relevant factors.
- Determine the meaningful health outcome(s) (including psychosocial improvements) for weight management interventions in youth with severe obesity for patients, families, providers, and insurance payers.

Conclusion

Given the growing prevalence of severe obesity in adolescents and the burden of its medical and psychosocial co-morbidities on patients and families, it will be critically important to accelerate efforts to develop and test novel and individually-tailored behavioral, pharmacological, device-based, and surgical interventions (and beyond) that promote clinically-meaningful and sustained weight loss. However, it is evident that there are substantial gaps in knowledge regarding the basic behavioral, psychosocial, and biological mechanisms driving the development and response to treatment of severe obesity in adolescence. More research is therefore also needed through both exploratory and observational studies to better understand the heterogeneous etiology of severe obesity and the variability in response to treatment that has been observed. Multi-disciplinary approaches with expertise from basic, behavioral, and clinical sciences are likely needed to address this in a comprehensive and scientifically thoughtful way. The recommendations in

this report are intended to stimulate research that can advance our understanding of underlying mechanisms for developing severe obesity and guide the development and testing of targeted, evidence-based, safe, and effective treatments aimed at improving the outlook for young people suffering from this chronic and debilitating disease.

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