*NIH Sponsored Workshop*

# Developing
# Precision Medicine Approaches to the
# Treatment of Severe Obesity in Adolescents

## September 18-19, 2017

**5635 Fishers Lane**
**Rockville, MD**

National Institutes of Health
*Turning Discovery Into Health*

Fishers Lane Conference Center, 5635 Fisher Lane, Rooms 508/509, Rockville, MD
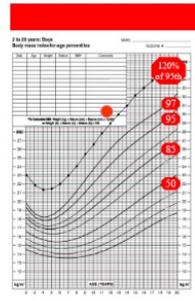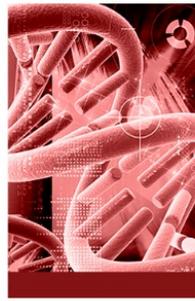
*Workshop on*
# Developing Precision Medicine Approaches to the Treatment of Severe Obesity in Adolescents

September 18-19, 2017

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## BACKGROUND

Severe obesity in adolescents is a growing and serious concern and is associated with significant physical and psychological co-morbidities. Response to behavioral and lifestyle interventions generally show relatively small improvements in BMI that are not sustained, and the limited pharmacotherapy options available also show modest efficacy. Bariatric surgery leads to the greatest and most sustained weight loss; however, it can be associated with considerable short and long-term health risks, and despite surgical intervention, many adolescents continue to have severe obesity. Little is known regarding which treatment approaches will promote meaningful and sustained weight loss in adolescents with severe obesity or how to target such treatments to maximize efficacy.

## MEETING OBJECTIVES

This workshop will bring together scientists with expertise in genetics, pediatric obesity, endocrinology, epidemiology, psychology, behavioral medicine, adolescent medicine, bariatric surgery, and other disciplines to discuss 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 goal of this trans-NIH workshop is 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.

## WORKSHOP CO-CHAIRS

*Aaron S. Kelly, Ph.D.*
Associate Professor of Pediatrics and Medicine
Co-Director, Center for Pediatric Obesity Medicine
University of Minnesota Medical School
University of Minnesota Masonic Children's Hospital

*Marsha D. Marcus, Ph.D.*
Professor of Psychiatry and Psychology
University of Pittsburgh School of Medicine
Western Psychiatric Institute and Clinic

*Jack A. Yanovski, M.D. Ph.D.*
Chief of the Section on Growth and Obesity
Program on Developmental Endocrinology and Genetics
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health

## NIH ORGANIZING COMMITTEE MEMBERS

*National Institutes of Diabetes and Digestive and Kidney Diseases*

Voula Osganian, M.D., Sc.D., M.P.H. (Chair)
Andrew Bremer, M.D.
Mary Evans, Ph.D.
Robert Kuczmarski, Dr.P.H.
Barbara Linder, M.D., Ph.D.
Pamela Thornton, Ph.D.
Susan Yanovski, M.D.

*Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health*

Layla Esposito, Ph.D., M.A.

*National Heart, Lung, and Blood Institute*

Charlotte Pratt, Ph.D., R.D.

*Office of Behavioral and Social Sciences Research*

Christine Hunter, Ph.D., ABPP
Deborah Young-Hyman, Ph.D.

*Office of Disease Prevention*

Rachel Ballad, M.D., M.P.H.

# AGENDA

**Day 1: Monday, September 18, 2017 8:15 AM - 5:30 PM**

8:15 a.m.   Welcoming Remarks
*Griffin P. Rodgers, MD, MACP, National Institute of Diabetes and Digestive and Kidney Diseases*

8:20 a.m.   Introduction and Workshop Goals

*Voula Osganian, MD, ScD, National Institute of Diabetes and Digestive and Kidney Diseases*

**Session 1:  Scope of the Problem: Severe Obesity and the Adolescent**

Moderator: *Robert Kuczmarski, DrPH, National Institute of Diabetes and Digestive and Kidney Diseases*

8:30 a.m.   Epidemiology of Severe Obesity in Adolescents

*Cynthia Ogden, PhD, Centers for Disease Control and Prevention*

8:50 a.m.   Adolescent Development
*Meg Zeller, PhD, Cincinnati Children's Hospital Medical Center*

9:10 a.m.   Question and Answer Panel

| **9:40 a.m.** | **MORNING BREAK** |
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**Session 2:  Biopsychosocial and Behavioral Factors that are Associated with the Development of Severe Obesity in Adolescents**

Moderator*: Deborah Hyman-Young, PhD, Office of Behavioral and Social Sciences Research Office of the Director*

10:10 a.m.   Psychosocial, Behavioral and Environmental Risk Factors

*Elissa Jelalian, PhD, Alpert Medical School of Brown University*

10:35 a.m.   Genetics and Epigenetics
*Sadaf Farooqi, MBChB, PhD, University of Cambridge*

11:00 a.m.   Hedonic Eating, Food Reward, and Appetite
*Ania Jastreboff, MD, PhD, Yale University School of Medicine*

11:25 a.m.   Question and Answer Panel

| **11:55 a.m.** | **LUNCH BREAK** |
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**Session 3:  Treatment Approaches for Severe Obesity in Adolescents**

Moderator: *Charlotte Pratt, PhD,* National Heart, Lung, and Blood Institute

12:45 a.m.    Lifestyle and Behavioral Interventions

*Marsha Marcus, PhD*, University of Pittsburgh School of Medicine

1:05 p.m.    POWER Clinical Registry- Clinical Experience and Health Outcomes
*Shelley Kirk, PhD, RD, LD, Cincinnati Children's Hospital Medical Center*

1:25 p.m.    Pharmacologic Interventions
*Aaron Kelly, PhD, University of Minnesota Medical School*

1:45 p.m.    Surgical Interventions
*Thomas Inge, MD, PhD, Children's Hospital Colorado*

2:05 p.m.    Emerging Therapies
*Lee Kaplan, MD, PhD, Harvard Medical School*

2:25 p.m.    Developing and testing a Chronic Care Model for the adolescent with severe obesity
*Stephen Cook, MD, MPH, University of Rochester Medical Center*

2:45 p.m.    Question and Answer Panel


| 3:15 p.m. | **AFTERNOON BREAK** |
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**Session 4: Biomarkers and Phenotypes that Predict Response to Treatment in Adolescents with Severe Obesity**

Moderator: *Susan Yanovski, MD*, *National Institute of Diabetes and Digestive and Kidney Diseases*

3:45 p.m.    Eating Behaviors and Psychological Phenotypes/Factors
*Kerri Boutelle, PhD, University of California, San Diego School of Medicine*

4:05 p.m.    Physical Activity Phenotypes/Factors
*Molly Bray, PhD, RD, LD, The University of Texas at Austin*

4:25 p.m.    Biomarkers
*Charles Burant, MD, PhD, University of Michigan*

4:45 p.m.    Question and Answer Panel

5:15 p.m.    Closing Remarks Day 1 from Co-Chairs

8:00 a.m.     Opening Remarks and Goals for Day 2

*Voula Osganian, MD, ScD, National Institute of Diabetes and Digestive and Kidney Diseases*

**8:15 a.m.       Breakout Sessions**

*Working Groups to discuss and report on summary of research gaps and needs from each topic area*

1. *Epidemiology and Subgroups at Risk including Disparities and Special Populations*
   *Leader: Cynthia Ogden, PhD, Centers for Disease Control and Prevention*
   *Facilitator: Pamela Thornton, PhD, National Institute of Diabetes and Digestive and Kidney Diseases*
   *Discussants:*
      *Linda Bandini, PhD, University of Massachusetts Medical School*
      *Brook Belay, MD, MPH, MSc, Centers for Disease Control and Prevention*
      *Ihuoma Eneli, MD, MS, Nationwide Children's Hospital Center*
      *Aviva Must, PhD, Tufts University School of Medicine*

2. **Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity**
   Leader: *Elissa Jelalian, PhD, Alpert Medical School of Brown University*
   Facilitator: *Mary Evans, PhD, National Institute of Diabetes and Digestive and Kidney Diseases*
   Discussants*:*
      *Christoph U Correll, MD, Hofstra Northwell School of Medicine*
      *Sadaf Farooqi, MBChB, PhD, University of Cambridge*
      *Ania Jastreboff, MD, PhD, Yale University School of Medicine*
      *Chantelle Hart, PhD, Temple University*
      *Julie Mennella, PhD, Monell Chemical Senses Center*
      *Marsha Marcus, PhD, University of Pittsburgh School of Medicine*
      *Elsie Taveras, MD, MPH, Harvard Medical School, Massachusetts General Hospital*
      *Meg Zeller, PhD, Cincinnati Children's Hospital Medical Center*

3. **Treatment Approaches for Severe Obesity in Adolescents**
   Leader: *Stephen Cook, MD,* MPH, *University of Rochester Medical Center*
   Facilitator*: Robert Kuczmarski, DrPH, National Institute of Diabetes and Digestive and Kidney Diseases*
   Discussants:
      *Thomas Inge, MD, PhD, Children's Hospital Colorado*
      *Lee Kaplan, MD, PhD, Harvard Medical School, Massachusetts General Hospital*
      *Aaron Kelly, PhD, University of Minnesota Medical School*
      *Shelley Kirk, PhD, RD, LD, Cincinnati Children's Hospital Medical Center*

4. **Biomarkers and Phenotypes that Predict Response to Treatment**
    Leader: *Charles Burant, MD, PhD, University of Michigan*
    Facilitator: *Susan Yanovski, MD, National Institute of Diabetes and Digestive and Kidney Diseases*
    Discussants:
    *Kerri Boutelle, PhD, University of California, San Diego School of Medicine*
    *Molly Bray, PhD, RD, LD, The University of Texas at Austin*
    *Anita Courcoulas, MD, MPH, University of Pittsburgh Medical Center*
    *Claudia Fox MD, MPH, University of Minnesota*
    *Tom Robinson, MD, MPH, Stanford University, Lucile Packard Children's Hospital Stanford*
    *Marian Tanofsky-Kraff, PhD, USUHS*
    *Jack Yanovski, MD, PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development*

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| **9:30 a.m.** | **MORNING BREAK** |

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| **9:45 a.m.   Subgroup Presentations and Full Panel Discussion** |
| *Breakout session presentations and discussion followed by summary and recommendations for future research needs to develop precision medicine approaches for* the treatment of severe obesity in adolescents |

   9:45 a.m.    Breakout Session Subgroup Presentations by Leaders with Open Discussion led by Co-chairs (25 min per Subgroup)

   11:35 a.m.    Workshop Summary and Recommendations with Concluding Remarks from Co-Chairs

   12:05 p.m.                                                                                                Wrap up and Adjournment
                    *Voula Osganian, MD, ScD, National Institute of Diabetes and Digestive and Kidney Diseases*

*Roles and Responsibilities

**Session Moderator**: Responsibilities will be to (a) introduce the speakers and talks for the session, b) keep the session and question and answer panel discussion on track timewise, and c) facilitate the orderly presentation of questions from the audience as well as clarifications of questions where needed during the question and answer panel discussion.

**Break Out Session Leader**: In addition to participating in the discussion, responsibilities will be to (a) facilitate the discussion, (b) keep the group focused and on topic, (c) engage all members of the group in the discussion, (d) build consensus, and (e) report the small group's findings during the full panel discussion.

**Break Out Session Facilitator:** In addition to participating in the discussion, responsibilities will be to (a) assist the Leader, (b) take notes for the Leader to present during the full panel discussion, and (c) keep the group on track timewise.

# ABSTRACTS OF PRESENTATIONS

(*in order of meeting presentation*)

## SESSION 1: *Scope of the Problem*: *Severe Obesity and the Adolescent*

### Epidemiology of severe obesity in US adolescents
### Cynthia L Ogden, PhD

In the United States, severe obesity among youth aged 2-19 years is often defined as 120% of the 95th percentile on the sex-specific 2000 CDC BMI-for-age growth charts. Some researchers had used the 99th percentile to define severe obesity but the CDC growth charts do not extend beyond the 97th percentile. Consequently, a percentage of the 95th percentile (the definition of obesity) was recommended for monitoring growth in youth with very high BMIs. Recently, cut points reflective of 120%, 130%, 140% and 150% of the 95th percentile of BMI-for-age have been proposed to be added to clinical growth charts. These charts will be announced in the Federal Register in the Fall of 2017. Following the Federal Register Notice, the charts, along with a detailed report, will be posted on the CDC growth charts website.

There are differences in body fat by race/Hispanic origin within BMI categories. Non-Hispanic black youth have less body fat than non-Hispanic white and Hispanic youth. Research indicates that health risk for Asian adults begins at lower BMI values than the traditional adult cut points of 25 and 30. In fact, in Taiwan, obesity for adults is defined at 27 instead of 30. Additional research may be needed on defining severe obesity in Asian American youth.

Estimates of severe obesity from the National Health and Nutrition Examination Survey (NHANES) indicate that in 2013-2014, 9.1% of US adolescents aged 12-19 years had severe obesity, triple the prevalence in 1988-1994. Obesity prevalence doubled among adolescents over the same time period from about 10 to 20%. Disparities in prevalence of severe obesity exist. Based on data from 2011-2014, the prevalence of severe obesity was 11.6% among non-Hispanic black, 8.8% among Hispanic, 6.7% among non-Hispanic white and 2% among non-Hispanic Asian adolescents 12-19 years of age. Unlike in adults the prevalence of severe obesity was higher for non-Hispanic black compared to non-Hispanic white adolescents for both males and females.

### Adolescent Development
### Meg Zeller, PhD

Developmental science provides a framework where adolescence is uniquely characterized as a period of rapid change in physical, emotional, interpersonal, social, and cognitive domains. Adolescence is also a period distinguished by an increase in behaviors considered to be risky and/or harmful and of high public health concern. Some teens navigate this period relatively unscathed, while others are launched on a trajectory of increasing burden and risk in young adulthood. Within this context, the provision of health care and the management of chronic

health conditions, specifically, can be uniquely challenged. Adolescence is a known period of higher non-adherence to self-management regimens and treatment session non-attendance, with known contributors ranging from aspects of the developing brain (i.e., executive functioning, reward-seeking, impulse control), their navigating increased independence from caregivers, or alternately, aspects of emotional well-being or social support. Our empirical understanding of the adolescent with severe obesity and effective treatments have not grown at the pace of the epidemic.  Nonetheless, there are important extant data from the broader literature as well as emerging data which highlight areas of vulnerability (versus normative adolescent risk) for this obesity sub-population that can inform the design and execution of effective treatments to improve weight, health, and psychosocial outcomes.

## SESSION 2*: Biopsychosocial and Behavioral Factors that are Associated with the Development of Severe Obesity in Adolescents*

### Psychosocial, Behavioral, and Environmental Risk Factors
### Elissa Jelalian, PhD

Retrospective and longitudinal studies provide evidence that growth trajectories of adolescents with severe obesity may be identified with some degree of accuracy from a fairly young age. For example, there is work to suggest that children with severe obesity at 6 years of age may be distinguished from those who are healthy weight by as early as 4 months, and that severe obesity during school age has a high probability of persisting into adolescence. While these trajectories have been identified, relatively little work has been conducted to determine the environmental, behavioral, and psychosocial factors that serve to promote or mitigate the risk of remaining on such a pathway. Research supports the importance of lifestyle behaviors such as dining out, consumption of sugar sweetened beverages, reduced sleep, and sedentary behavior, as well as socioedemographic and psychological factors, in the development of obesity in children and adolescents; however, virtually none of this work focuses on risk for *severe obesity* and few studies even identify severe obesity as a distinct outcome. Research is needed to understand whether severe obesity during adolescence results from incremental cumulative risk among these better examined factors or constitutes a qualitatively different trajectory with a unique set of risk factors.

There is an emerging body of evidence examining behavioral and psychosocial correlates of severe adolescent obesity, focused primarily on teens seeking weight loss surgery. While this work provides important information regarding potential risk factors for the development and maintenance of severe obesity, the cross-sectional nature of the research limits its predictive value.  There is a clear need for longitudinal studies to identify sociodemographic, behavioral, and psychosocial influences that place children at risk for severe obesity from an early age, with specific attention to the interaction between these characteristics and genetic and epigenetic factors. Further, conceptual models derived from this work should be developmental, such that risks and opportunities may be identified at multiple points in development.

## Hedonic Eating/Food Reward and Appetite Regulation
## and the Development of Severe Obesity in Adolescents
## Ania Jastreboff, MD, PhD

The role of the brain is critical in controlling eating and a complex interplay exists within neural networks implicated in reward-motivation (striatum), hunger-satiety (hypothalamus), and decision-making (prefrontal cortex) to control food consumption. Notably, the prefrontal cortex is not fully developed in adolescents, continuing to develop through adolescence into early adulthood. Brain maturation and strengthening of connectivity between the prefrontal cortex and hedonic and homeostatic brain regions and networks occurs through changes in neural branches and synapses so as to achieve higher order executive regulatory capacity over impulse control, choices, and decision-making. An important aspect of the prefrontal cortical brain maturation process is that it strengthens regulation of and connectivity with hypothalamic and striatal (reward-motivation) regions of the brain, including the nucleus accumbens part of the striatum which has been implicated in processes that lead to addiction. Indeed, adolescence is a time of increased risk-taking behavior and as is evident in addiction literature, adolescents may be particularly vulnerable to the effects of rewarding substances and potentially rewarding highly palatable foods, such as those containing sugar. This appears to be related to immature functional development of the prefrontal cortex in the setting of relatively more mature striatal-limbic regions. Thus, adolescents are potentially more vulnerable to excessive intake of highly palatable rewarding foods (e.g. high in sugar) which promote weight gain and obesity. Additionally, pubertal changes, which occur during adolescence, involving metabolic changes (e.g. insulin, leptin, etc.), may also impact neural responses and affect eating behavior and food consumption. There is evidence that these developing brain networks in adolescents are altered in the setting of obesity, particularly in response to rewarding food cues and consumption of sugar (glucose). It is not known whether metabolic changes due to weight gain and severe obesity alter the normal developmental process of these neural networks and the neuro-metabolic processes that support healthy food intake throughout childhood and adolescence. There is clearly a need for better understanding of the impact of pubertal (physiologic) and adolescent (bio-psycho-social) development on weight-related metabolic changes and obesity and its impact on brain development and resulting behavioral implications. Additionally, there is a need for mechanistic (translational) and longitudinal cohort studies of children and adolescents with and without obesity to assess the effects of weight gain and obesity on metabolism, cognition, and obesity-related diseases throughout the lifespan.

## SESSION 3: *Treatment Approaches for the Adolescent with Severe Obesity*

### Lifestyle and Behavioral Interventions
### Marsha D. Marcus, PhD

Intensive lifestyle interventions for school-aged children with moderate obesity are efficacious and associated with improvements in health-related parameters, which has led to recommendations that children and adolescents with obesity be offered or referred for intensive behavioral weight loss interventions (US Preventive Services Task Force, 2017). Nevertheless, accumulating evidence has documented that lifestyle interventions are less effective for adolescents and those with severe obesity. Few randomized trials have focused on lifestyle interventions for youth with severe obesity, but available data have shown that weight losses are modest, at best, and are not sustained over time. Despite these findings, future research to enhance the impact of lifestyle interventions is crucial. Adolescents with severe obesity are likely to remain so and suffer an increasing health risk burden over time. Importantly, even very modest weight losses have been shown to be associated with positive effects on cardiometabolic risk factors over a two-year period, and thus successful intervention may serve to mitigate health risk over time.

In an age of precision medicine, it is important to consider whether any sub-group of adolescents with severe obesity respond differentially to lifestyle intervention. The search for robust socio-demographic predictors of positive response has been disappointing, but there is consistent evidence that session attendance defined as $\geq$ 75% of planned sessions, which has served as a proxy for intervention adherence, is positively associated with weight loss outcomes. Available data also show that adherence to self-monitoring, a key component of behavioral interventions, is unsatisfactory. Thus, future research to identify strategies to improve adherence to lifestyle interventions is indicated. Additional work to identify individuals (e.g., those with psychiatric comorbidity) who may benefit from alternative or additional intervention components is warranted. Finally, it is imperative to examine how to combine and sequence lifestyle interventions with other treatment modalities in the service of developing chronic-care interventions for these high-risk adolescents.

### POWER Clinical Registry- Clinical Experience and Health Outcomes
### Shelley Kirk, PhD, RD, LD

The Pediatric Obesity Weight Evaluation Registry (POWER) was established in 2013 and is comprised of 31 multi-component pediatric weight management programs, serving youth with obesity ages 18 and younger. The goal of POWER is to identify and promote effective intervention strategies for pediatric obesity. Data from the registry were used to investigate improvement in weight status and its association with patient characteristics and program exposure features. We will present results from our analyses of treatment-seeking adolescents with obesity (ages 12-18; N=2,999) and discuss important research needs going forward.

## Pharmacologic Interventions
### Aaron S. Kelly, PhD

Numerous medications have been evaluated for the treatment of adolescent obesity. Unfortunately, the benefit/risk profile of pharmacotherapy is questionable owing to the relatively modest efficacy of the individual medications investigated to date. The burgeoning pipeline of obesity medications currently in development for adults offers hope that safe and effective agents will be available for pediatric use within the next 5-10 years. As the field of pediatric obesity medicine continues to mature, identifying predictors of response and implementing adaptive clinical protocols will maximize benefit while minimizing risks of pharmacotherapy.

## Surgical Interventions
### Thomas Inge, MD, PhD

This presentation will discuss how precision medicine relates to precision surgery, and emphasize that as currently practiced, weight loss surgery is not a "precision" intervention. Meaning, there is little information available to aid surgeons in use of the "right operation for the right patient." We will review what is known regarding the effectiveness of surgical treatment for severe obesity in adolescents based on two sizable cohort studies from Sweden and the USA. In addition, the "hidden" heterogeneity in the weight/BMI change response will be highlighted and discussed. This heterogeneity in BMI response of adolescents to surgical treatment will be compared to that of adults to note similarities and differences. The possible existence of individual subpopulations with differential BMI response to surgery will also be noted, as defined statistically using latent class growth modeling of Teen-LABS data for those adolescents treated by roux en Y gastric bypass and vertical sleeve gastrectomy. With these findings, the presentation will hopefully drive a robust discussion of the potential factors predictive of membership in the latent classes of response in an effort to accelerate future research that will consider 1) how more detailed preoperative phenotyping (eg., genetic background, clinical, metabolic, psychological, and behavioral phenotypes) may be used to improve patient selection criteria, and 2) how to better understand latent factors that portend poorer surgical response might lead to early and successful use of adjunctive behavioral, pharmacologic, or other therapies to maximize treatment responses.

## Emerging Therapies
### Lee Kaplan, MD, PhD

Regardless of the proximal contributors – environmental, behavioral, developmental and/or genetic – disrupted regulation of energy balance and defended energy stores (fat mass) is the final common pathway in the pathophysiology of obesity. Because maintenance of an appropriate and stable fat mass in the face of widely varying nutrient sources and energy demands is critical to normal human biology, numerous genes, signaling pathways and biochemical mechanisms contribute to metabolic homeostasis. Disruption in any one or more of these mechanisms has the potential to cause or exacerbate obesity, generating a panoply of different clinically relevant subtypes of obesity, each with its own phenotypic characteristics. The heterogeneity of these multiple obesity subtypes underlies the profound patient-to-patient variation observed in response to all anti-obesity therapies, whether based in lifestyle change,

pharmacology or bariatric surgery.  The wide variability in obesity subtype and individual patient response limits the effectiveness and applicability of any single anti-obesity therapy, necessitating development and use of multiple treatments with distinct, and complementary, mechanisms of action.  With our growing understanding of the biological underpinnings of obesity, multiple new therapies are currently being developed.  They include (1) novel lifestyle-based treatments targeting environmental contributors other than diet and physical activity, (2) novel pharmacological therapies that influence relevant, newly-discovered biochemical and signaling pathways, and (3) novel endoscopic, vascular and neurostimulatory therapies aiming to exploit our growing understanding of the physiological mechanisms underlying the effectiveness of bariatric and metabolic surgery.  Because these therapies target distinct and complementary mechanisms, their concurrent use in different combinations hold the promise of additive or synergistic benefits.  Growing clinical experience with such combination therapy has provided important support for this approach, but controlled studies in different populations are required to determine the most effective of the many combinatorial possibilities.  Ultimately, as with other complex, chronic and heterogeneous diseases, optimal treatment will likely result from matching each patient with the treatment or treatments most effective for him or her.  Achieving this goal will benefit from more accurate predictors of therapeutic and potential adverse outcomes of each treatment modality.  Many current studies are aimed at identifying demographic, clinical, biomarker and genetic predictors of response to each anti-obesity therapy that are powerful enough to guide clinical decision-making.  Looking to the future, it is likely that our effectiveness in treating obesity will be most strongly enhanced by (1) our growing recognition and appreciation of the heterogeneity of obesity, (2) greater understanding of the biological basis of effective treatment, (3) the accelerating emergence of new therapies, (4) the increasing embrace of combination therapy, and (5) a greater focus on identifying and applying predictors of clinically relevant therapeutic response.

### Developing and testing a Chronic Care Model for the adolescent with severe obesity
### Stephen Cook, MD, MPH

 The Chronic Care Model focuses on improving patient self-management, but it has been tested and applied from the Quality Improvement science/methodology side or as part of a clinical focused strategy. The CCM incorporates health system level changes within the context of community policies to support practices/providers as well as patients toward change. The CCM focuses on 3 main goals 1) creating informed/activated patients; 2) created informed/activated providers; and 3) improve patient self-management for improved health outcomes. Improving a patient's ability to self-manage a disease has used Behavior Economic approaches or external rewards or punishments with minimal effect on long term change. Strategies aimed at improving patient and provider autonomy are lacking and Self-Determination Theory represents a behavioral approach that is uniquely for application within precision medicine research. Lastly, obesity is the most stigmatized and biased condition in America and this must be examined both from the provider standpoint and the patient (teen) and parent standpoint. There are a number of child focused research networks that could serve as real-world laboratories to test treatment interventions for teens with severe obesity.

## SESSION 4: *Biomarkers and Phenotypes that Predict Response to Treatment in Adolescents with Severe Obesity*

### Eating Behaviors and Psychological Phenotypes/Factors
### Kerri Boutelle, PhD

The prevalence of severe obesity in youth is increasing and affects between 4% and 6% of the population. Despite the serious immediate and long-term comorbidities, current treatments are limited in effectiveness. Data with children, adolescents and adults shows that not all individuals who participate in weight loss programs lose a clinically significant amount of weight, and of those who lose weight, many do not retain the weight loss. Recently, the field is beginning to understand that individuals with overweight and obesity are a heterogeneous group and that individual differences may contribute to both overeating and weight gain, and responsiveness to weight loss programs. Although many research studies evaluate and control for individual factors, these strategies cannot address multiple factors acting in concert. This presentation will review the psychological and eating behaviors that contribute to eating beyond nutritional needs and weight gain. The literature regarding the psychological and eating phenotypes in children, adolescent and adults will be reviewed, as well as some of our own emerging data on food and satiety responsiveness. Finally, I will review the strengths and weaknesses of analyses used to evaluate phenotypes, and next steps for the field. It is important that this knowledge is used to determine specific psychological and eating phenotypes among adolescents with severe obesity, to ultimately develop targeted and effective treatment programs.

### Physical Activity Phenotypes/Factors in Adolescent Obesity
### Molly S. Bray, PhD

An imbalance between energy intake and energy expenditure is at the heart of the development of obesity – a person cannot become obese without consuming more energy than he/she is expending. Nevertheless, the processes that control the physiological partitioning of both energy intake and expenditure are more complex than merely those related to eating and exercise. It is often assumed that adolescents with severe obesity are not capable of being physically active; however, many studies have reported successfully engaging severely obese children and teens in physical activity. In fact, adolescents with severe obesity are often very strong, as the act of simply moving a large body through space can strengthen skeletal muscle. Unfortunately, muscular strength is often accompanied by low fitness and musculoskeletal joint pain in adolescents with severe obesity, due in part, to excessive stress on potentially still-developing bones. Thus, exercise programs designed for adolescents with severe obesity should include activities that take advantage of the child's strength, while considering potential joint or fitness limitations (e.g., rope swing, tire pull, swimming). While the "output" or physical activity side of the energy balance equation generally has less impact on weight gain and loss than dietary intake, it may play a critical role in the prevention of obesity-related co-morbidities; thus, encouraging physical activity and exercise in adolescents with severe obesity is important. Regrettably, behavioral/lifestyle interventions that include physical activity and/or dietary modification are associated with limited long-term success, particularly in children with severe

obesity.  Poor adherence is often a key factor in the lack of response to behavioral interventions, and understanding how to prevent program dropout is a critical component of improving intervention efficacy.  For adolescents who voluntarily enrolled in a 15-week aerobic exercise regimen, physiological factors that predicted exercise dropout included obesity severity, low fitness, depression, age, anxiety, waist circumference, and percent body fat.  In addition, exercise adherence and exercise tolerance had a substantial genetic component. SNPs in 10 genes exceeded a genome-wide significance of $p<10^{-4.5}$ for exercise dose, including FN3KRP, FAM148A, CUX2, RIPK2, ABCB11, B3GNTL1, BRE, BDNF, ZHX3, IDE, and TBCD. Pathways contributing to lipid metabolism, neural signaling, muscle contraction, and adiposity were significantly represented by SNPs with a nominal $p<0.0001$. The brain-derived neurotropic factor (BDNF) signaling pathway emerged as a central factor linking multiple other pathways, highlighting neural signaling as a target for exercise tolerance.  As with other phenotypes associated with severe obesity, the complex interaction of both genetic and non-genetic factors combine to influence both physical activity behavior and response to exercise interventions in adolescents.  More research is needed to examine how exercise can promote weight loss, and in turn, how physical activity patterns change as adolescents with severe obesity begin to lose weight.

## Biomarkers
## Genetic and epigenetic programming of altered metabolism and its association with oxidative capacity and the development and maintenance of obesity
## Charles Burant, MD, PhD

The incidence of obesity has risen markedly and studies have provided a genetic framework for understanding obesity. More recently, the contribution of epigenetic programming and its potential role in the regulation of gene expression. Observational studies in humans and experimental animal studies have shown that altered nutrient exposures in utero can result in transgenerational alterations in weight trajectories and affect the risk of metabolic diseases, including type 2 diabetes and cardiovascular disease.  High intrinsic oxidative capacity ($VO_2max$) is positively related to human lifespan and negatively related risks of obesity, diabetes and cardiovascular disease regardless of age, sex, race, and other risk factors.  Multiple studies have shown that intrinsic (genetically driven) oxidative capacity, rather than exercise-associated increases in VO2max is the primary determinant of an individual's cardiometabolic health.  I will show that genetic selection for oxidative capacity in an animal model affects mitochondrial fatty acid and amino acid fuel utilization and provide evidence that in humans, similar alterations in metabolism related to oxidative capacity can be identified.  I will also provide data that signals of altered nutrient utilization can be found in adolescents by plasma metabolomics profiling. Finally, I will present preliminary evidence that intrauterine nutrient exposures can affect fetal growth and generate a reflection of altered fuel metabolism in fetal cord blood.  I will present a model that will suggest that genetic and epigenetic mechanisms work in concert to affect metabolism that may predispose to life-long obesity risks.

# PROFILES AND PERSPECTIVES

## Co-Chairs, Speakers, and Discussants
*(in alphabetical order)*

### *Linda Bandini PhD, RD*
Associate Professor in Pediatrics
Eunice Kennedy Shriver Center, UMASS Medical School
Clinical Professor
Boston University, Sargent College, Department of Health Sciences

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**Biosketch**

Dr. Bandini is an Associate Professor in Pediatrics at the University of Massachusetts Medical School and Clinical Professor in the Department of Health Sciences at Boston University. Her research has focused on energy expenditure in obese and non-obese adolescents and children with developmental disabilities. She has also conducted studies to understand risk factors associated with obesity in both typically developing children and children with developmental disabilities and weight loss interventions in adolescents with intellectual disabilities. She is the PI and Co-Director of the MCHB-funded Healthy Weight Research Network for Children with Autism and Developmental Disabilities. She is the Director of Nutrition for the UMMS-Shriver LEND program where she is responsible for overseeing the development of health promotion materials for adolescents and young adults with intellectual disabilities and supervision of nutrition graduate students in experiential learning with individuals with intellectual and developmental disabilities in both research and education.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Our research group conducted several cross-sectional and longitudinal studies to determine whether reduced energy expenditure is related to obesity in adolescents. We found that energy expenditure did not differ between obese and non-obese adolescents. We looked at the effects of overfeeding on both energy expenditure and weight gain and found no differences among obese and non-obese adolescents. In a subsequent 10-year longitudinal study of 197 non-obese girls we examined whether a lower energy expenditure at baseline would contribute to excess weight gain during the adolescent period. Our findings did not support the hypothesis that low energy expenditure is a risk factor for obesity. Overall our studies on energy expenditure in adolescents contributed to the literature that reduced energy expenditure does not appear to be a risk factor for development or maintenance of obesity in adolescents.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the risk factors associated with severe obesity that could be used to identify and treat those overweight and obese children likely to become severely obese?
- What are the factors that would indicate which children would benefit from an intensive lifestyle, medication, or surgical approach to treat obesity?
- What dose of a lifestyle intervention (e.g. length of intervention, physical activity time, caloric restriction behavioral intervention,) would be needed to treat severely obese adolescents effectively?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

My recent research has focused on obesity in youth with intellectual and developmental disabilities (IDD). Adolescents with IDD and severe obesity may not be motivated to lose weight. Thus, finding ways to motivate them to change their eating habits and limit preferred foods which are often high in caloric content is difficult. This is made even more difficult as food is often used as a reward in school and behavioral programming.

In this population of vulnerable youth, there are often many caretakers including parents, aides, teachers, and residential staff who have influence on both dietary intake and physical activity opportunities. Effectively targeting adolescents with IDD and severe obesity requires working with the adolescent and these caretakers and service providers.

**Publications from your own work that are most applicable to the workshop objectives:**

- Bandini LG, Schoeller DA, Edwards J, Young VR, Oh SH, and Dietz WH. Energy expenditure during carbohydrate overfeeding in obese and non-obese adolescents. Am J Physiol. 1989;256:E357-E367.
- Bandini LG, Schoeller DA, and Dietz WH. Energy expenditure in obese and non-Obese adolescents. Pediatric Research. 1990;27:198-203.
- Curtin C, Bandini LG, Must A, Gleason J, Lividini K, Phillips S, Eliasziw M, Maslin M, and Fleming RK. Parent support improves weight loss in adolescents and young adults with Down syndrome. J Pediatr. 2013;163(5):1402-8.

**Publications from others that are most applicable to the workshop objectives:**

- Freedman DS, Mei Z, Srinivasan SR, Berenson GS, Dietz WH. Cardiovascular risk factors and excess adiposity among overweight children and adolescents: the Bogalusa Heart Study. J Pediatr. 2007;150(1):12-17.

### *Brook Belay, MD, MPH, MSc*
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**Biosketch**

Dr. Belay is a senior medical officer at the Center for Disease Control (CDC) and Prevention's Division of Nutrition, Physical Activity, and Obesity (DNPAO). Dr. Belay's background is in pediatrics and public health. He is responsible for obesity control efforts the health care setting and works on a variety of initiatives that focus on identifying and promoting innovative strategies in the health care setting. These include linking the health care setting and community-based strategies, leveraging electronic health records to support obesity surveillance by public health, and promoting systems-level strategies to best address obesity in the health care setting. Dr. Belay received his undergraduate training at Harvard University, completed his medical and public health schooling at Columbia University College of Physicians & Surgeons, and trained in pediatrics and nephrology at Montefiore Medical Center in New York City.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

In most weight management programs, adolescents with severe obesity may not be clearly identified to allow for specific strategies to address severe obesity. Furthermore, because they are not specifically identified, follow-up on the impact of the intervention for this particular group may be insufficient.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the most appropriate strategies to address severe obesity that involve a combination of intensive counseling, nutrition therapy and drug therapy?
- What clinical protocols can be readily developed to assist primary care in assisting these adolescents and their families in conjunction with specialized centers of care and weight management programs?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

There is a lack of standardized definitions of severe obesity. Where there is agreement, it is unclear if there should be stratifications of severe obesity as sub-classifications. The graded approach to managing severe obesity based on the degree of severity and presence of comorbidities and involving nutrition therapy and drug and/or surgical therapy is not agreed upon. These difficulties are compounded by inconsistent support and coverage of services by third party payors.

**Publications from your own work that are most applicable to the workshop objectives:**

The following are publications of that include (but not limited to) colleagues of mine from my office at CDC:

- Freedman DS, Butte NF, Taveras EM, Goodman AB, Ogden CL, Blanck HM. The Limitations of Transforming Very High Body Mass Indexes into z-Scores among 8.7 Million 2- to 4-Year-Old Children. J Pediatr. 2017 Apr 19. pii: S0022-3476(17)30451-1. doi: 10.1016/j.jpeds.2017.03.039. [Epub ahead of print]
- Freedman DS, Butte NF, Taveras EM, Lundeen EA, Blanck HM, Goodman AB, Ogden CL. BMI z-Scores are a poor indicator of adiposity among 2- to 19-year-olds with very high BMIs, NHANES 1999-2000 to 2013-2014. Obesity (Silver Spring). 2017;25(4):739-746.

**Publications from others that are most applicable to the workshop objectives:**

- Kelly A, Daniels S. Rethinking the Use of Body Mass Index z-Score in Children and Adolescents with Severe Obesity: Time to Kick It to the Curb? J Pediatr. 2017 Jun 7. pii: S0022-3476(17)30619-4. doi: 10.1016/j.jpeds.2017.05.003. [Epub ahead of print]

## *Kerri Boutelle, Ph.D.*

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**Biosketch:**

Dr. Boutelle is a Professor in the Departments of Pediatrics, Family Medicine and Public Health, and Psychiatry and the Director of the Center for Healthy Eating and Activity Research at University of California, San Diego. She has over 20 years of experience conducting clinical trials and epidemiological studies with children, adolescents and adults who are overweight and obese and who have eating disorders. The goals of her research are 1) to work toward optimizing currently available approaches for treatment of obesity and overeating, and to create translatable versions of these treatments for the clinic and other populations, and 2) to identify highly novel targets for the treatment of people who are obese, who overeat or who binge eat, based on findings from basic behavioral sciences and on neuroscience, to work toward developing the next generation of treatment models. Dr. Boutelle has evaluated both a parent-only treatment for childhood obesity as well as a guided-self-help treatment for childhood obesity, to allow for greater dissemination and access to obesity treatment for more patients. Dr. Boutelle has also pioneered treatments based on extinction theory for overeating in children and adults, as well as cognitive interventions as ancillary targets to reduce overeating and obesity. Dr. Boutelle has been continually funded by NIH since 2002. Dr. Boutelle is a Fellow of the Obesity Society and a Board Member of the Society for the Study of Ingestive Behavior.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Cognitive mechanisms are understudied factors that represent how the brain interacts with the current environment.  Resisting eating highly palatable, calorically-dense foods requires a high degree of both attentional and behavioral inhibition. Research demonstrates that individuals with overweight and obesity have high reward (have high food cue responsivity) and have impaired inhibitory resources. We have tested a number of cognitive interventions that are designed to reduce food cue reactivity and build inhibitory resources.  For example, in two small studies, we have shown that training attention away from food impacts eating behavior in children and is associated with decreased weight in adults with binge eating.  We have also developed and tested a cue-exposure treatment for overeating, based on extinction theory, with children, adolescents and adults. Our research shows that the cue-exposure treatment decreases physiological food cue reactivity and cravings.   Furthermore, we have developed a novel model, called Regulation of Cues (ROC), which focuses on improving satiety responsiveness and decreasing food cue responsivity to decrease overeating and weight.  This model shows promise with children and in pilot studies with adults.

Not all individuals (children, adolescents, or adults) respond to state of the art behavioral weight loss programs.  We published the first study that shows that satiety responsiveness and food cue responsiveness may drive behavioral phenotypes of obesity in children. Whether these cognitive variables impact weight loss in adolescents with severe obesity is yet to be explored. More recently, we developed a program that targets emotional eating in adolescents with overweight and obesity, to improve current treatments for weight loss in this population.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What behavioral and cognitive phenotypes exist among adolescents with severe obesity, are they similar to adolescents with overweight or obesity, and do they predict weight loss in treatment?
- Are there novel cognitive targets for adolescents specifically, and can these targets improve weight loss outcomes?
- How and to what extent should parents be involved in the treatment of adolescents with severe obesity?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Although behavioral weight loss programs, which target physical activity and energy intake, work for some, they do not work for all individuals.  Adolescents, in particular, have variable outcomes.  Current research programs focus on providing the same program to all individuals.  It is possible that unstudied characteristics or factors, or the combination of these, influence responsivity to these interventions.  Clearly more research is needed to identify the behavioral, cognitive, neural and biological phenotypes that could predict responsivity to current programs, and to contribute to the development of novel interventions based on underlying mechanisms.

Another barrier to the development of more effective treatments for adolescents with severe obesity is the lack of creative ideas regarding interventions.  It is critical that we foster and reward creativity in researchers, and allow them to think outside of the box.  Funding is needed for these high-risk ideas, however, many times the applications are reviewed with conservative criteria.  Novel and creative ideas could ultimately identify mechanisms that will contribute to successful prevention or weight-loss programs.

**Publications from your own work that are most applicable to the workshop objectives:**

- Boutelle KN, Peterson CB, Crosby R, Rydell SA, Zucker N, Harnack LJ. Overeating Phenotypes in Overweight and Obese Children. Appetite. 2014;76:95-100.
- Boutelle, KN, Bouton ME. Implications of learning theory for developing programs to decrease overeating. Appetite, Special Issue on Childhood Obesity and Cognition. 2015;93:62-74.
- Boutelle KN, Rhee KE, Liang J, Braden A, Douglas J, Strong D, Rock C, Wilfley D, Epstein LH, Crow S. Effect of attendance of the child on body weight, energy intake, and physical activity in childhood obesity treatment: A randomized controlled trial. JAMA Pediatr. 2017;171(7):622-628.

**Publications from others that are most applicable to the workshop objectives:**

- Field AE, Camargo CA JR, Ogino S. The merits of subtyping obesity: One size does not fit all. JAMA. 2013;310:2147-8.
- Martin A, Davidson T. Human cognitive function and the obesogenic environment Physiol Behav. 2014;136:185–193.
- Jansen A, Houben K, Roefs A. A Cognitive Profile of Obesity and Its Translation into New Interventions. Front Psychol. 2015;*6:*1807.

## *Molly Bray, PhD*
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**Biosketch**

Dr. Bray holds the Susan T. Jastrow Endowed Chair in the Department of Nutritional Sciences at the University of Texas at Austin, with a master's degree in Exercise Physiology and a PhD in Human and Molecular Genetics. Dr. Bray's research focuses on the relationship between genetic variation, energy balance, and lifestyle factors such as exercise, nutrition, and circadian patterns of behavior. Work in her laboratory is designed to identify the mechanisms by which timing and quality of energy intake affects weight gain and metabolic health, in particular through intestinal absorption and the gut microbiome. Dr. Bray also currently leads one of the largest genetic studies of exercise adherence established to date, the Training Interventions and Genetics of Exercise Response (TIGER) study, with a total cohort of more than 3,500 individuals. Dr. Bray's research has included investigations of aerobic fitness and resting and exercise energy expenditure in children and adolescents and clinical studies of morbidly obese adolescents undergoing bariatric surgery.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Since 2003, we have amassed extensive data on almost 4,000 adolescents and emerging adults, in which a well-controlled, 15-week exercise trial has been conducted, resulting in more than 200,000 recorded exercise sessions. We have identified differences in body composition by race/ethnicity that are driven by genetic variation, as well as the genetic underpinnings of response to exercise and exercise adherence. Work from our lab has established a genetic basis for both body weight/adiposity and weight change in adolescents and young adults. Interestingly, the FTO pathway, which has been identified in numerous studies as predisposing individuals to obesity and diabetes, is also predictive of both baseline and change in body weight post-exercise training in our study. Pathways related to lipid and glucose metabolism are also important in weight change following exercise, with differential effects observed between males and females. Interestingly, the FTO gene is also strongly predictive of exercise adherence in our cohort, potentially suggesting that FTO may influence regulation of energy balance through both neural and metabolic pathways.

In animals, we have shown that the timing of macronutrient intake is very important in influencing metabolic outcomes, with fat and protein intake upon waking, combined with carbohydrate intake prior to sleeping resulting in the most optimal metabolic outcomes. We have also shown very clearly that all kilocalories are not created equally, and even restricting caloric intake can be detrimental if the quality of kilocalories is not considered. Currently, generic recommendations to "eat less and move more" don't consider the many ways in which individuals are unique, both biologically and behaviorally. Our work is targeted on identifying which factors are most important in influencing individual responses to obesity interventions.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What biological factors influence a child's natural patterns of eating and activity?
- Are there naturalistic ways to intervene on diet or physical activity, such as focusing on timing, that may increase efficacy as well as adherence?
- Can modifying breakfast quality have an impact on adolescent physiology and mental health?
- We need to understand how food additives are affecting children's brain development and function.
- We need to better understand the role of sleep in childhood/adolescent obesity.

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

- Severe obesity in childhood/adolescence is strongly influenced by genes but a barrier to capitalizing on this observation is the frequent assumption that either genes can't be measured or that we can't understand their effect.
- We need better, more integrative approaches and statistics for assessing individuals wholistically.
- We need better tools for measuring dietary intake – both quality and quantity.

**Publications from your own work that are most applicable to the workshop objectives:**

Our most important papers right now are in preparation or review:

- Vazquez AI, Hwasoon K, Dong F, Rubio YLB, Fernandez J, Bray MS (In preparation) Pleiotropic effects between body composition and obesity traits after an intensive exercise intervention. *Nature Genet.*
- Herring MP, Vazquez AI, Hwasoon K, Dong F, Fernandez J, Bray MS (In preparation) Genetic predictors of adherence to a controlled aerobic exercise intervention. *Am J Hum Genet.*
- Bray MS, Tsai J-Y, Villegas-Montoya C, Boland BB, Blasier Z, Egbejimi O, Kueht M & Young ME. Time-of-Day-Dependent Dietary Fat Consumption Influences Multiple Cardiometabolic Syndrome Parameters in Mice. Int J Obes (Lond.). 2010;34(11):1589-98.

**Publications from others that are most applicable to the workshop objectives:**

- Pihl AF1, Fonvig CE1,2, Stjernholm T1, Hansen T2,3, Pedersen O2, Holm JC. The Role of the Gut Microbiota in Childhood Obesity. Child Obes. 2016;12(4):292-9.
- Mannan M, Mamun A, Doi S, Clavarino A. Prospective Associations between Depression and Obesity for Adolescent Males and Females- A Systematic Review and Meta-Analysis of Longitudinal Studies. PLoS One. 2016;11(6):e0157240.
- Howe LD, Firestone R, Tilling K, Lawlor DA. Trajectories and Transitions in Childhood and Adolescent Obesity. In: Burton-Jeangros C1, Cullati S2, Sacker A3, Blane D3, editors. A Life Course Perspective on Health Trajectories and Transitions [Internet]. Cham (CH): Springer; 2015, Chapter 2.

## *Charles Burant, MD, PhD*
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**Biosketch**

Dr. Burant is a clinical adult endocrinologist and director of the NIH-funded University of Michigan Nutrition Obesity Research Center and the Regional Comprehensive Metabolomics Resource Core. His personal research program centers on the interaction between genetics and environmental factors, especially nutrients in the development of insulin resistance, obesity and β-cell failure in both man and in animal models. He has a specific interest in intermediary metabolism and his laboratory combines metabolomics, lipidomics and gene expression profiling to understand the development of cellular dysfunction. Together with his colleague Amy Rothberg, they established the University of Michigan Weight Management Program, which overlays a systematic clinical, psychological and molecular phenotyping of subjects recruited from an insurance-paid weight loss clinical program. Investigators can access the patients, collected data and biospecimens from the program for use in their research programs.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Our research program is trying to understand the relationships between intrinsic cardiorespiratory fitness (CRF) and its relationship to the development of obesity and type 2 diabetes. Genetically inherited CRF, usually measured as oxygen consumption during a graded exercise test, is a significant predictive factor for the development of metabolic diseases, including obesity, diabetes, and cardiovascular disease as well as longevity. Our work in animal models, and more recently humans, has shown that intrinsic differences in the capacity of mitochondrial fuel utilization may underlie the differences in CRF and may also reflect differences in behavioral and metabolic responses to diet. Our results also suggest that the accumulating biomarker evidence for alterations in fatty acid and branched chain amino acid levels that predict onset of type 2 diabetes and other metabolic diseases reflect an intrinsic alteration in mitochondrial metabolism. Finally, we are investigating to what extent intrauterine epigenetic programming may modulate genetic susceptibility to altered mitochondrial metabolism.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the relative contributions of genetics and epigenetics vs. environment in determining risk of severe obesity?
- What is the mechanism(s) by which bariatric surgery works so much better than other interventions in the treatment of severe obesity and what are the biological difference between success and failure to maintain weight loss following bariatric surgery?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

- Poor animal models for human obesity and bariatric surgery.
- Inaccessibility to important target tissues, such as hypothalamic and other brain areas to assess variation in human cellular function in lean, obese and severely obese humans.
- A path may be the use of iPSC from individuals to create surrogates for inaccessible tissues types.

**Publications from your own work that are most applicable to the workshop objectives:**

- Overmyer KA, Evans CR, Qi N, Minogue CE, Carson JJ, Chemside-Scabbo CJ, Koch LG, Britton SL, Pagliarini DJ, Coon JJ, Burant CF. Maximal oxidative capacity during exercise is associated with skeletal muscle fuel selection and dynamic changes in mitochondrial protein acetylation. Cell Metabolism. 2015;21:468-478.
- Marchlewicz E, Dolinoy D, Tang L, Milewski S, Jones T, Goodrich J, Tanu Son Ti, Domino S, Song P, Burant CF, Vasantha Padmanabhan V. Lipid metabolism is associated with developmental epigenetic programming. Nature Sci Reports. 2016;6:34857.
- Biwer C, Rothberg AR, IglayReger H, Derksen H, Burant CF. Najarian K. Windowed Persistent Homology: A Novel Signal Processing Algorithm Applied to Analyze Clinical Obesity Data. 2017;PLOS One 12(5):e0177696.

**Publications from others that are most applicable to the workshop objectives:**

- Oktay AA, Lavie CJ, Kokkinos PF, Parto P, Pandey A, Ventura HO. The Interaction of Cardiorespiratory Fitness With Obesity and the Obesity Paradox in Cardiovascular Disease. Prog Cardiovasc Dis. 2017 Jun - Jul;60(1):30-44. Review.

## *Stephen Cook, MD, MPH*

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**Biosketch**

Dr. Cook is an Associate Professor of Pediatrics with combined training in Internal Medicine and Pediatrics. He is fellowship trained at University of Rochester, with research defining metabolic syndrome in adolescents, along with co-morbid risk factor & environmental influences of tobacco (K-23). He also conducts research on practice based implementation/interventions to adopt guidelines and practice change, using IHI/MFI. Dr. Cook directs studies for childhood obesity for the division of General Pediatrics at URMC; through the UR CTSI PRN and state-wide networks. The work of his group includes regional epidemiology studies and clinical training collaboratives for practice/system improvement. This work has involved training practices on obesity guidelines, improving access for youth with epilepsy, incorporating RDs into pediatric primary care practices, improving policies, systems and environments for supporting breastfeeding at practices, childcare centers & worksites. He is site-PI for a Multi-site U-01 grant from NHLBI to implement a family-therapy based child weight loss intervention into primary care practices that is co-directed by Denise Wilfley and Len Epstein. He serves as Associate Director for the Institute for Healthy Childhood Weight at the AAP. He has directed a pilot study embedding RDs into pediatric practices to test feasibility of a shared care delivery approach in North Carolina and Pennsylvania. He was Co-Investigator for an AHRQ funded national conference grant R13HS02281601: "Evidence-based childhood obesity treatment: Improving access and systems of care", and is PI for the AAP on a survey of a national sample of pediatricians tracking their practices around obesity screening and nutrition/exercise counseling and referral.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

The Chronic Care Model focuses on improving patient self-management and has been applied from the Quality Improvement science/methodology side. The CCM helps clinical teams to make practice changes as well as help patients make individual change. Three of the main goals of the CCM are; 1) creating informed/activated patients; 2) created informed/activated providers; and 3) improve patient self-management for improved health outcomes. Improving self-management should focus on patient autonomy (Self-Determination Theory) as opposed to external motivators (Behavior Economics) to drive and maintain behavior change. The Healthcare system is shifting from Fee-for-service to more global/shared risk models of payment, yet insurers continue to try to use external motivators to improve patient self-management. The implications for this approach to the management of any chronic disease have shown minimal benefit to long term or sustained patient behavior change.

Obesity is the most stigmatized and biased condition people experience and this must be examined both from the provider, the patient (teen) and the parent standpoint. Adolescence is a time when youth struggle to achieve independence and identify. SDT focuses on individual autonomy to drive and maintain behavior change. It therefore represents an ideal behavioral approach to use within precision medicine research. Large pediatric networks have been developed and represent

opportunities to test multiple interventions, include individual behavior, family behavior, pharmacotherapy, surgery, and community level changes. The PEDSnet (CTSI), the PROS Network (AAP), CORNET (APA), PRIS (CHCA/APA/SHM/AAP) and the POWER network represent unique clinical laboratories to apply precision medicine to adolescent obesity, as well as study the obesity of parents and siblings. There is also the recently emerging Trial Innovation Network, from NCATs' CTSA program includes Trial Innovation Centers, Recruitment Innovation Centers, and CTSA Program Hubs.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- Testing the application of SDT on **adolescents** for their individual autonomy, along with the application of SDT on **parents**, for their own autonomy over lifestyle change, and the possible mediating effect on the autonomy of the adolescent or other siblings.
- Testing the application of SDT on PROVIDERS will improve their autonomy for delivering effective counseling
- Assessing the role or level of individual stigma patients w/ obesity experience, as well as the level of weight bias (implicit or explicit) provider have on their ability to implement evidence based interventions.
- Testing multi-layer models be tested at the individual level, family level, practice/health system level and the community level?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity (1-2 paragraphs)?**

All research of adolescents and children represent studies of vulnerable populations. In order to pilot, recruit, implement and track any clinical research involving these subjects requires significantly more precautions, time, regulations and safety constraints, than any equivalent studies of adults. Therefore, any studies of pediatric populations must be accompanied with significantly more financial resource dollars, as well as added training for current and new investigators conducting research in pediatric populations, along with added training for IRB or regulatory staff that work at our academic and research institutions. Studies on the use of Behavior Economics are showing minimal to no-effect on changing patient behaviors or self-management of chronic diseases. The lack of support for research to examine the role of Self-Determination Theory on both patient and provider behavior change represents a barrier to overcome.

**Publications from your own work that are most applicable to the workshop objectives:**

- Cook S, Belay B, Rogers V, Hassink S, O'Connor Baker A, Lindros, J. Understanding Pediatricians' Care Practices for Childhood Obesity: Results from National Surveys, 2006-2017 of the AAP. (In Press)
- Pont S, Puhl R, Cook S, Slusser W. The Stigma Experienced by Children and Adolescents With Obesity: Policy Statement of American Academy of Pediatrics. (In press).
- Wilfley DE, Staiano AE, Altman M, Lindros J, Lima A, Hassink SG, Dietz WH, Cook S. Improving Access and Systems of Care for Evidence-based Childhood Obesity Treatment Conference Workgroup. Improving access and systems of care for evidence-based childhood obesity treatment: Conference key findings and next steps. *Obesity.* 2017;25(1):16-29.
- Hadjiyannakis S, Buchholz A, Chanoine JP, Jetha MM, Gaboury L, Hamilton J, Birken C, Morrison KM, Legault L, Bridger T, Cook SR, Lyons J, Sharma AM, Ball GDC. The Edmonton Obesity Staging System for Pediatrics (EOSS-P): A proposed clinical staging system for pediatric obesity. Paediatr Child Health. Jan/Feb, 2016; 21(1):21-26.

**Publications from others that are most applicable to the workshop objectives:**

- Ng JY, Ntoumanis N, Thøgersen-Ntoumani C, Deci EL, Ryan RM, Duda JL, Williams GC. Self-Determination Theory Applied to Health Contexts: A Meta-Analysis. Perspect Psychol Sci. 2012;7(4):325-40.
- Dietz WH, Solomon LS, Pronk N, Ziegenhorn SK, Standish M, Longjohn MM, Fukuzawa DD, Eneli IU, Loy L, Muth ND, Sanchez EJ, Bogard J, Bradley DW. An Integrated Framework For The Prevention And Treatment Of Obesity And Its Related Chronic Diseases. Health Aff (Millwood). 2015;34(9):1456-63. Review.
- Taveras EM, Marshall R, Sharifi M, Avalon E, Fiechtner L, Horan C, Gerber MW, Orav EJ, Price SN, Sequist T, Slater D. Comparative Effectiveness of Clinical-Community Childhood Obesity Interventions: A Randomized Clinical Trial. *JAMA Pediatr.* 2017;171(8):e171325.
- Rhodes ET, Boles RE, Chin K, Christison A, Testa EG, Guion K, Hawkins MJ, Petty CR, Sallinen Gaffka B, Santos M, Shaffer L, Tucker J, Hampl SE. Expectations for Treatment in Pediatric Weight Management and Relationship to Attrition. Child Obes. 2017;13(2):120-127.

## *Christoph U Correll, MD*

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**Biosketch**

Dr Correll is Professor of Psychiatry at Hofstra Northwell School of Medicine, and Medical Director of the Recognition and Prevention program at the Zucker Hillside Hospital, both in New York. He is both a board-certified general psychiatrist, and child and adolescent psychiatrist.

Professor Correll's research and clinical work focus on the identification, characterisation, and treatment of adults and youth with severe psychiatric disorders, including psychotic and mood disorders, as well as the interface between mental and physical illness, especially cardiometabolic conditions and adverse effects of psychotropic drugs.

Professor Correll has authored over 450 journal articles and has received over 30 awards and fellowships for his work. Since 2014, the year of inception of this metric, he has been listed each year by Thomson Reuters in as one of "the most influential scientific minds" and "top 1% cited scientists in the area of psychiatry".

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

We have been investigating the cardiometabolic status in psychiatrically ill youth and adults as well its determinants. We identified in first episode and never-treated youth and young adults that cardiometabolic risk factors, including overweight, obesity and metabolic abnormalities, both precede psychotropic medication treatment, and are severely and lastingly aggravated by psychotropic medications, especially antipsychotics. Furthermore, longer lasting psychiatric illness, not only psychosis, was significantly associated with higher BMI, more so than short-term antipsychotic exposure, whereas metabolic abnormalities were mostly driven by antipsychotic treatment duration.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- How can engagement in and adherence to effective treatments for pediatric obesity be optimized?
- What are predictors of favorable and unfavorable outcomes and how can treatments be individualized or stepped (up or down) in each subgroup?
- How much and in whom should psychiatric antecedents (e.g., trauma), symptoms and comorbidities be identified and addressed to optimize outcomes?

**What are the barriers to and creative ideas for advancing research in order to develop effective and targeted treatments for adolescents with severe obesity?**

- Lack of appreciation of the urgency of the problem of pediatric obesity
- Adult societal norms and behaviors that promote or condone unhealthy lifestyle, overweight and obesity
- Target physical exercise and diet behaviors in schools
- Outreach, teaching and programs for parents

**Publications from your own work that are most applicable to the workshop objectives:**

- Maayan L, Vakhrusheva J, Correll CU. Effectiveness of Medications Used to Reduce Antipsychotic-Related Weight Gain and Metabolic Abnormalities: A Systematic Review and Meta-analysis. Neuropsychopharmacology. 2010;35(7):1520-30.
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**Publications from others that are most applicable to the workshop objectives:**
- Mannan M, Mamun A, Doi S, Clavarino A. Prospective Associations between Depression and Obesity for Adolescent Males and Females- A Systematic Review and Meta-Analysis of Longitudinal Studies. PLoS One. 2016;11(6):e0157240.
- Kelly, KP, & Kirschenbaum, DS. Immersion treatment of childhood and adolescent obesity: The first review of a promising intervention. Obesity Reviews. 2011;12, 37–49.
- Danielsson P, Kowalski J, Ekblom Ö, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med. 2012 Dec;166(12):1103-8.

## *Anita P. Courcoulas, MD, MPH*

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**Biosketch**

Dr. Courcoulas directs a clinical service and surgical research group at one of the oldest and largest academic bariatric surgery programs in the country. Her groups focuses on surgical outcomes research, clinical trials, and emerging technologies in bariatric surgery. She has been the Principal Investigator for several NIH-funded studies; the Longitudinal Assessment of Bariatric Surgery (LABS) Study, Adolescent Bariatrics: Assessing Health Benefits and Risks (Teen-LABS) Study, and A Randomized Trial to Compare Surgical and Medical Treatments for Type 2 Diabetes (The Triabetes and ARMMS Studies). She has also more recently developed a translational research focus with the Intestinal Metabolic Reprogramming as a Key Mechanism of Gastric Bypass in Humans study.

She is also the founder and co-director of the University of Pittsburgh's Surgical Outcomes Research Center and am also the Program Director for the Fellowship Training Program in Advanced Laparoscopic and Bariatric Surgery. Her interests are in the treatment of severe obesity and the study of outcomes, predictors, and mechanisms of bariatric surgery in target populations, including adolescents.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

- The variability in the trajectories of weight loss following bariatric surgery in adults may inform approaches to adolescent treatments.
- The lack of robust predictors of response to bariatric surgery treatment demonstrated in adult studies may also inform adolescent studies.
- The results of surgical versus medical treatments for type 2 diabetes in the setting of obesity (BMI 30-40) in adults may have implications for the adolescent population, as well.
- The recognition of the increase in alcohol, substance use, and risk-taking behaviors after bariatric surgery has important implications for the younger population at risk.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

Identifying predictors of response to various treatments, understanding the variability of response and identifying more relevant obesity subtypes. Understanding more fully the basic mechanisms of action of bariatric surgical procedures for both weight loss and metabolic effects. A complete understanding of long-term (5-10 years and longer) risks and complications versus long-term durability of effect following bariatric surgical procedures.

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

<u>Barriers:</u>

- Longer-term follow up of individuals undergoing surgery to completely assess risks versus benefits.
- Promoting and utilizing common measures between obesity treatment studies, so study results can be compared and / or pooled.

<u>Ideas:</u>

- Create a mandatory dynamic registry for data collection related to all bariatric surgery in younger patients including key outcomes not routinely collected in the medical record, such as mental health outcomes.
- Create a serum and tissue bank with specimens more easily obtained during bariatric surgical cases to link clinical data (baseline factors and clinical outcomes) to metabolomic, genetic, and other factors.

**Publications from your own work that are most applicable to the workshop objectives:**

- Courcoulas AP, Yanovski SZ, Bonds D, Eggerman TL, Horlick M, Staten MA, Arterburn DE. Long-term outcomes of bariatric surgery: a National Institutes of Health symposium. JAMA Surg. 2014;149(12):1323-9. Review.
- Courcoulas AP, Christian NJ, Belle SH, Berk PD, Flum DR, Garcia L, Horlick M, Kalarchian MA, King WC, Mitchell JE, Patterson EJ, Pender JR, Pomp A, Pories WJ, Thirlby RC, Yanovski SZ, Wolfe BM; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Weight change and health outcomes at 3 years after bariatric surgery among individuals with severe obesity. JAMA. 2013 Dec 11;310(22):2416-25.
- Courcoulas AP, Christian NJ, O'Rourke RW, Dakin G, Patchen Dellinger E, Flum DR, Melissa Kalarchian PD, Mitchell JE, Patterson E, Pomp A, Pories WJ, Spaniolas K, Steffen K, Wolfe BM, Belle SH. Preoperative factors and 3-year weight change in the Longitudinal Assessment of Bariatric Surgery (LABS) consortium. Surg Obes Relat Dis. 2015;11(5):1109-18.
- Courcoulas AP, Belle SH, Neiberg RH, Pierson SK, Eagleton JK, Kalarchian MA, DeLany JP, Lang W, Jakicic JM. Three-Year Outcomes of Bariatric Surgery vs Lifestyle Intervention for Type 2 Diabetes Mellitus Treatment: A Randomized Clinical Trial. JAMA Surg. 2015 Oct;150(10):931-40.

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- Field AE, Camargo CA JR, Ogino S. The merits of subtyping obesity: One size does not fit all. JAMA. 2013;310:2147-8.
- Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick M, Buncher CR; Teen-LABS Consortium. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. N Engl J Med. 2016;374(2):113-23.
- Inge TH, Jenkins TM, Xanthakos SA, Dixon JB, Daniels SR, Zeller MH, Helmrath MA. Long-term outcomes of bariatric surgery in adolescents with severe obesity (FABS-5+): a prospective follow-up analysis. Lancet Diabetes Endocrinol. 2017;5(3):165-173.
- Olbers T, Beamish AJ, Gronowitz E, Flodmark CE, Dahlgren J, Bruze G, Ekbom K, Friberg P, Göthberg G, Järvholm K, Karlsson J, Mårild S, Neovius M, Peltonen M, Marcus C.

Laparoscopic Roux-en-Y gastric bypass in adolescents with severe obesity (AMOS): a prospective, 5-year, Swedish nationwide study. Lancet Diabetes Endocrinol. 2017;5(3):174-183.

# *Ihuoma Eneli, MD, MS*
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**Biosketch**

Dr Eneli is Director, Nationwide Children's Hospital Center for Healthy Weight and Nutrition (CHWN), Columbus Ohio. She is a board certified general pediatrician and Professor of Clinical Pediatrics at The Ohio State University College of Medicine, Columbus, Ohio. Dr Eneli oversees a comprehensive pediatric obesity center with activities that include advocacy, prevention, medical weight management and adolescent bariatric surgery. Dr Eneli also directs the Primary Care Obesity Network (PCON) which provides obesity-related training, resources and community integration for 25 primary care practices in Central Ohio. She has particular interest in intervention research for pediatric obesity for which she has received funding. These include a feeding dynamic intervention for young children, Protein sparing modified fast for severe obesity, a multicenter study on family behavioral therapy for pediatric obesity in the primary care practices and statistical phenotyping for type 2 diabetes in children. Dr Eneli received her medical degree from the University of Nigeria, completed her pediatric training and Masters of Science degree in Epidemiology from Michigan State University.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Characterizing the population of children with severe obesity can be the first step to unraveling appropriate treatment options. In doing so, we can expect an emergence of subtypes or phenotypes that can serve as a basis for research. For instance, in a nationally representative database, children aged 2-5 years with severe obesity have even greater disparities in social determinants of health (ethnicity, maternal smoking, SES), have significantly more screen time than their overweight and obese peers; but energy intake and Healthy Eating Index (HEI) were not significantly different (Tester et al. *in review*). The process for subtyping used in conditions like schizophrenia, epilepsy, chronic pelvic pain syndromes can serve as a guide.

Traditional obesity treatment programs generally involve restrictive and controlling caregiver feeding practices. Paradoxically, these types of feeding practices can counterproductively reduce the child's ability to self-regulate energy intake and have been linked to future increases in body weight. The effect of eating behaviors, caregivers' excessive controlling feeding practices and the

feeding dynamic in early childhood on a child's self-regulation of energy intake is not well understood. Investigating how we can apply the pathophysiology of appetite regulation for childhood obesity interventions especially for severe obesity that begins in early childhood will be important.

The gap between lifestyle intervention and bariatric surgery as treatment options for adolescents with severe obesity is another area for further research. Structured dietary interventions like the protein sparing modified fast either an adjunct to lifestyle intervention, medication or bariatric surgery can be a viable treatment options for adolescent with severe obesity and comorbidities.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- How can we define heterogeneity within populations with obesity, is there an opportunity for phenotyping or genotyping? Will the results help target treatment in a meaningful way?
- Is there a combination or permutation of risk factors (biological, social, psychological) that increase or decrease rate of weight gain?
- How do we define success? Are the improvements in cardiometabolic outcomes sustained even in the presence of weight regain?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

There is significant practice variation across providers, programs and geographic regions. Thus it is often challenging to evaluate interventions unless through a research framework such an RCT. However, these research studies are expensive, time consuming and may not reflect outcomes that will be seen in clinical practice. Supporting pragmatic programs or evaluation studies of existing interventions/protocols in clinical settings is needed.

Severe obesity needs a public messaging campaign that pulls together all stakeholders and redefines how the public think about the condition and treatment. There are several conditions (Autism, Cystic fibrosis) with much lower prevalence than severe obesity that have robust advocacy campaigns. At this time, industry has taken the lead. How the child, parent, and public perceive the reason for their weight gain or likelihood of success for a particular intervention ultimately affects the outcome. Building or supporting a positive educational campaign around severe obesity with diverse stakeholders can reframe the conversation at several levels. This approach can also help address the stigma and bias associated with obesity.

**Publications from your own work that are most applicable to the workshop objectives:**

- Watowicz, R.P., Tindall, A., Eneli, I. (2015). Implementation of an inpatient protein-sparing modified fast for severely obese adolescents. ICAN: Infant, Child & Adolescent Nutrition. 7(5), 233-241.
- Watowicz RP, Taylor CA, Eneli IU. Lifestyle behaviors of obese children following parental weight loss surgery. Obes Surg. 2013;23(2):173-8.
- Baughcum AE, Gramling K, Eneli I. Severely obese preschoolers in a tertiary care obesity program: characteristics and management. Clin Pediatr (Phila). 2015;54(4):346-52.
- Eneli, I.U., Woolford, S.J., Hassink, S. (2015). Advancing the care of children and adolescents with severe obesity: A Reason for clinical subtyping. Institute of Medicine (IOM), **http://nam.edu/wp-content/uploads/2015/06/ObesitySubTyping1.pdf**

**Publications from others that are most applicable to the workshop objectives:**

- Miller JL, Goldstone AP, Couch JA, Shuster J, He G, Driscoll DJ, Liu Y, Schmalfuss IM. Pituitary abnormalities in Prader-Willi syndrome and early onset morbid obesity. Am J Med Genet A. 2008;146A(5):570-7.
- Lohrmann D., YoussefAgha A., Jayawardene W. 2014. Trends in body mass index and prevalence of extreme high obesity among Pennsylvania children and adolescents, 2007-2011: promising but cautionary. *American Journal of Public Health* 104(4):e62-8.
- Taylor SJA, Rennie K, Jon C. Clinical outcomes of an inpatient pediatric obesity treatment program in the USA. Int J Adolesc Med Health. 2017 Jun 9. pii:/j/ijamh.ahead-of-print/ijamh-2016-0141/ijamh-2016-0141.xml. doi:10.1515/ijamh-2016-0141. [Epub ahead of print]
- Zeller MH, Hunsaker S, Mikhail C, Reiter-Purtill J, McCullough MB, Garland B, Austin H, Washington G, Baughcum A, Rofey D, Smith K; TeenView Study Group and in collaboration with the Teen-LABS Consortium. Family factors that characterize adolescents with severe obesity and their role in weight loss surgery outcomes. Obesity (Silver Spring). 2016;24(12):2562-2569.

## *Sadaf Farooqi, MBChB, PhD*
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**Biosketch**

Dr. Farooqi is Professor of Metabolism and Medicine at the University of Cambridge. Prof. Farooqi is also an Honorary Consultant in Diabetes and Endocrinology at Addenbrooke's Hospital in Cambridge, U.K.

Her research team studies the molecular and physiological pathways involved in the regulation of human appetite and body weight and their disruption in obesity. Using a candidate gene approach in patients with severe, early onset obesity recruited to the Genetics Of Obesity Study (GOOS), her team has identified patients with mutations in genes encoding leptin, the leptin receptor and targets of leptin action (including the melanocortin 4 receptor, MC4R). They have demonstrated that the central leptin-melanocortin axis plays a critical role in the regulation of human food intake. They are currently using neuroimaging particularly functional MRI to study the brain response to hunger and satiety in defined subsets of patients with molecularly defined causes for their obesity.

**Publications from your own work that are most applicable to the workshop objectives:**

- van der Klaauw A, Keogh J, Henning E, Stephenson C, Trowse VM, Fletcher P, Farooqi S. Role of melanocortin signalling in the preference for dietary macronutrients in human beings. Lancet. 2015;385 Suppl 1:S12.
- van der Klaauw AA1, Farooqi IS. The hunger genes: pathways to obesity. **Cell**. 2015;161(1):119-32.

- Ramachandrappa S, Raimondo A, Cali AM, Keogh JM, Henning E, Saeed S, Thompson A, Garg S, Bochukova EG, Brage S, Trowse V, Wheeler E, Sullivan AE, Dattani M, Clayton PE, Datta V, Bruning JB, Wareham NJ, O'Rahilly S, Peet DJ, Barroso I, Whitelaw ML, Farooqi IS. Rare variants in single-minded 1 (SIM1) are associated with severe obesity. J Clin Invest. 2013;123(7):3042-50.
- Farooqi S. Insights from the genetics of severe childhood obesity. Horm Res. 2007;68 Suppl 5:5-7.

# *Claudia Fox, MD, MPH*

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**Biosketch**

Dr. Fox is an Assistant Professor of Pediatrics and Co-Director of the Center for Pediatric Obesity Medicine at the University of Minnesota.  Board certified by the American Board of Obesity Medicine, she specializes in the care of children and adolescents with severe complicated obesity. She leads a multidisciplinary, comprehensive weight management clinic which includes the University of Minnesota Teen Weight Loss Surgery Program.   Dr. Fox is active in developing clinical protocols for the safe and effective use of pharmacotherapy for pediatric obesity.  Her research portfolio has focused on pharmacological approaches to managing severe pediatric obesity.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Our group conducted several retrospective chart reviews of our clinical outcomes using pharmacotherapy for severe pediatric obesity.  We demonstrated that the use of phentermine and topiramate were associated with a 4% and 6% reduction in BMI, respectively.

Our group also conducted several randomized controlled clinical trials examining the safety and efficacy of pharmacological approaches to the management of severe obesity in adolescents.  Two pilot RCTs found that exenatide, a GLP-1 receptor agonist, resulted in approximately 3% decrease in BMI.  A larger NIH-funded study of exenatide is underway.  We also conducted a pilot RCT which examined the effect of topiramate following an induction phase with meal-replacements.  This study also had only modest results.

Notable among all of these studies is the considerable variability in response.  While the mean BMI reduction was on the order of 3-5%, some individuals experienced 9-10% BMI reduction while others experienced an increase in BMI.  Predicting responsiveness must be a key area of investigation.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the predictors of response to various therapies, whether single pharmacological agents vs combination pharmacology vs surgery vs device vs behavioral therapies vs combination of any of these? What tools can we use in the clinical setting that will measure these predictors of response?
- When is the optimal time to intervene with more advanced therapies for pediatric obesity?
- What is the appropriate target outcome of interventions for severe obesity in adolescents? How much BMI reduction is optimal for patients who don't yet have frank cardiometabolic disease?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

A significant barrier to advancing research is the belief by many health care providers that severe obesity in youth is not a disease that warrants aggressive management. The reality is that the psychological cost of obesity in youth exceeds that of pediatric cancer. Further, although the medical costs of severe obesity in youth are prominent, the full ramifications are not experienced until adulthood. We cannot "pass the buck" to our adult medical providers to take care of the problem that is emerging in childhood. It is too late. (It is even too late to reverse the course of many, if not most adolescents, with severe obesity.) Does this justify intervening with pharmacotherapy for a 6-year old with a BMI at the 99th percentile, for example?

**Publications from your own work that are most applicable to the workshop objectives:**

- Fox CK, Kaizer AM, Rudser KD, Nathan BM, Gross AC, Sunni M, Abuzzahab MJ, Schwartz BL, Kumar S, Petryk A, Billington CJ, Ryder JR, Kelly AS. Meal-replacements followed by topiramate for the treatment of adolescent severe obesity: A pilot randomized controlled trial. Obesity. 2016;24(12):2553-2561
- Ryder JR, Kaizer AM, Rudser KD, Gross AC, Kelly AS, Fox CK. Effect of phentermine on weight reduction in a pediatric weight management clinic. Int J Obes. 2017;41(1):90-93.

**Publications from others that are most applicable to the workshop objectives:**
- Seymour KE, Reinblatt SP, Benson L, Carnell S. Overlapping neurobehavioral circuits in ADHD, obesity, and binge eating: evidence from neuroimaging research. CNS Spectr. 2015;20(4):401-11.
- McElroy SL, Hudson JI, Capece JA, Beyers K, Fisher AC, Rosenthal NR; Topiramate Binge Eating Disorder Research Group. Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study. Biol Psychiatry. 2007;61(9):1039-48.

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## Biosketch

Dr. Hart is an Associate Professor in the Department of Social and Behavioral Sciences and a Research Scientist at the Center for Obesity Research and Education within the College of Public Health at Temple University. She holds a graduate degree in clinical psychology from Case Western Reserve University and completed internship and fellowship training in pediatric obesity at the Alpert Medical School of Brown University. Dr. Hart's research focuses on novel behavioral approaches for prevention and treatment of pediatric obesity and cardiovascular disease risk reduction, including identification of effective approaches to decrease health disparities in pediatric populations. Dr. Hart has two primary lines of research: understanding the role of enhancing children's sleep to decrease risk of obesity and cardiometabolic disturbance, and the effect of early life risk factors on children's obesity risk.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Extant findings, including our own research, suggest that sleep may be an important yet understudied behavior that may affect weight regulation in children and adolescents. Specifically, we have found that when school-aged children's sleep is enhanced (experimentally or via behavioral intervention) there are a number of benefits, including improvements in reported self-control behaviors, decreased motivation for a food reward, decreased reported caloric intake (particularly in the evening hours), decreased reported television viewing, and increased daytime activity. Importantly, the net result of enhancing sleep across our studies seems to be a modest benefit in weight status over the short term. Whether findings extend to adolescents with severe obesity is unclear-although extant evidence suggests that, for some adolescents with extreme obesity, improving sleep may be a novel adjunct target that could enhance treatment outcomes.

In addition, work conducted with colleagues suggests that behavioral lifestyle intervention for adolescents with obesity produces high variability in treatment response. A number of factors, including behavioral factors that can be identified early in treatment, are predictive of both attrition and BMI change. These findings are consistent with other studies, and speak to the potential for identifying subgroups that may benefit from tailored or novel approaches to enhance engagement and treatment response.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

Given modest and variable impact of behavioral lifestyle interventions for adolescents with severe obesity, can we identify underlying behavioral, psychosocial, environmental and genetic phenotypes to enhance early identification of those who will be more/less responsive to treatment and thus may benefit from tailored or novel approaches?

Given increasing prevalence of adolescents with severe obesity, associated comorbidities, and limitations associated with extant treatment approaches, can we identify those children at risk of developing severe obesity earlier in life to enable targeted preventive treatment approaches?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Advancing research on enhanced treatment approaches for adolescents with severe obesity warrants an interdisciplinary approach that involves consideration of multimodal treatment strategies. This necessitates the allocation of appropriate resources to convene individuals from varied backgrounds with expertise in areas such as epidemiology, genetics/epigenetics, behavioral approaches, pharmacotherapy, and bariatric surgery. Resources to stimulate collaboration and encourage exploration of novel approaches for treatment of severe obesity will be important.

**Publications from your own work that are most applicable to the workshop objectives:**

- Hart CN, Carskadon MA, Considine R, Fava JL, Lawton J, Raynor HA, Jelalian E, Owens JA, Wing RR. Changes in children's sleep duration on food intake, weight, and leptin. *Pediatrics.* 2013;132 (6) e1473-80.
- Hart CN, Jelalian E, Raynor H, Mehlenbeck R, Lloyd-Richardson E, Kaplan J, Flynn-O'Brien, K. Early patterns of food intake as predictors of BMI change in an adolescent weight loss trial. *Eating Behaviors.* 2010;11:217-222.

**Publications from others that are most applicable to the workshop objectives:**

- Kelly AS, Barlow SE, Rao G, Inge T, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels R. on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: Identification, associated health risks, and treatment approaches: A scientific statement from the American Heart Association. Circulation. 2013;128:1689-1712
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# Tom Inge, MD, PhD
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**Biosketch**

Dr. Inge is a pediatric surgeon who currently directs a large department of pediatric surgery at the Children's Hospital of Colorado, one of the nation's top children's hospitals.   During the last 15 years of academic practice at Cincinnati Children's Hospital, he surgically treated more than 300 adolescents with severe obesity and comorbidities.  He is the PI of the NIDDK funded Teen LABS study, the largest (n=242 participants) and longest term (now in year 12) prospective outcome study of adolescents undergoing bariatric surgery.  In addition, his team has completed the FABS-5 study, providing long term (8 year) estimates of outcome for adolescents who underwent roux en Y gastric bypass surgery from 2001-2007.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

The finding that adolescents undergoing bariatric operations have similar weight loss outcomes to adults over 3 years suggests that both of these procedures could be durable over the longer term.

The finding that gastric bypass and sleeve gastrectomy procedures result in similar weight loss in adolescents suggests that both of these procedures could be of value to an even broader pediatric age group, particularly those at lower ages who are currently considered too young for these interventions.

Variability in weight loss outcome suggests the possibility that obesity subgroups exist in these cohorts, some of which respond very well and others which respond less well to surgical intervention.  Elucidation of the factors that define such subgroups could be valuable for patient selection.  Elucidation of factors portending poor weight loss outcomes may lead to more individually tailored treatment regimens, including multimodal management.

Following bariatric surgery in adolescence, remission of multiple comorbid conditions has been documented.  Response of comorbid conditions may well be greater than that response seen when these operations are used in adults.  Better understanding of optimal timing of use of surgery during the progression of comorbid disease then re-frames the indications for surgery as a way to prevent development of such comorbidities.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

The study of the influence of genetic variants on obesity development has yielded important insights in recent years, however limited information is available regarding how genetic and epigenetic factors influence response to surgery.  This should be a high priority area, especially

given the existence of rigorously studied surgical populations (LABS and Teen-LABS for example) and the availability of DNA samples from these cohorts.

What is the role of surgical therapy in the treatment of clinically important obesity-related comorbid conditions (eg., type 2 diabetes and obstructive sleep apnea) in pediatric age groups? Can predictors of progression from pre-diabetes to frank T2DM be elucidated which will guide the thoughtful application of surgical intervention to prevent the progression to T2DM and/or prevent the development of the medical complications of T2DM (eg., renal, retinal, cardiovascular)?

There is a need to intensify efforts to study effective surgical interventions in important demographic subpopulations which have been historically poorly represented, but for whom obesity takes a considerable toll on health. In particular, those with lower socioeconomic status; Blacks, Hispanics, and pre-adolescents require dedicated study.

Other special populations exist which bear the burden of early onset severe obesity including those with syndromic conditions (eg, Prader Willi) and those who have sustained a hypothalamic insults (eg., craniopharyngioma). What is the role of surgery in treatment of such conditions?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Investigators with expertise in 1) examining latent predictors of outcome of clinical treatment, and 2) defining mechanisms by which surgical procedures result in durable long-term weight loss are not well networked with clinicians who have access to important pediatric patient populations (willing research participants). Sponsorship to develop or expand research networks that promote collaboration should be a high priority.

**Publications from your own work that are most applicable to the workshop objectives:**
- Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick M, Buncher CR; Teen-LABS Consortium. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. N Engl J Med. 2016;374(2):113-23.
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**Publications from others that are most applicable to the workshop objectives:**

- Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM. Heritability of the weight loss response to gastric bypass surgery. J Clin Endocrinol Metab. 2011;96(10):E1630-3.
- Butler AA, O'Rourke RW. Bariatric surgery in the era of personalized medicine. Gastroenterology. 2013 Mar;144(3):497-500.
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**Biosketch**

Dr. Jelalian is Professor of Psychiatry & Human Behavior and Pediatrics at the Alpert Medical School of Brown University and Director of the interdisciplinary hospital-based weight control program. The continuous thread in her research is the development, implementation, and testing of novel interventions for adolescents with obesity. Her work has examined interventions focused on combining standard behavioral weight control strategies with peer enhancement, physical activity, and parental involvement to improve outcomes for adolescents.  Collectively, this research has demonstrated that behavioral interventions can be effective in supporting modest weight loss in adolescents with overweight and obesity, with maintenance of effects up to 24 months. Programmatic development of this line of research includes examining models for intervention dissemination and application to groups with mental health comorbidities. Specifically, they recently published findings from a study that included providing mood and weight control intervention for adolescents with comorbid obesity and depression, the majority of whom met criteria for severe obesity. Dissemination to community settings includes a development study testing a weight control intervention for adolescents delivered through area YMCAs.  She is committed to translating evidence-based interventions into clinical practice.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Historically, some adolescents meeting criteria for severe obesity have been excluded from lifestyle weight control interventions, including those conducted by our research team. The rationale for such exclusions is that behavioral interventions that include weekly contact are not of adequate intensity to address severe obesity. In recent work targeting adolescents with mood disorders, we did not exclude on the basis of weight severity and the majority of our participants met criteria for severe obesity (mean baseline BMI=37.0, SD=7.0). In this small RCT, participants who received an intervention to address mood, without attention to weight control, demonstrated a nearly one-unit increase in BMI during 6-months of treatment, despite the fact that they showed significant improvements in mood. In contrast, adolescents who received a combined treatment addressing both mood and weight, showed modest decrease in BMI as well as significant improvements in mood.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

Adolescents are an understudied population in general and provide unique challenges with regard to physical and emotional maturation and intervention.  A very general question is whether we can develop effective non-surgical intensive interventions with this population. To date, very few

controlled studies have been conducted to examine the effectiveness of behavioral interventions that are of high intensity, such as partial hospitalization or home-based treatment models.

It is important to continue to identify early risk factors and trajectories of rapid weight gain during infancy and early childhood such that the course of excess weight gain can potentially be curtailed at a more malleable point in development. Specific questions include whether there are "critical periods", defined through either psychosocial or biological parameters, which provide key opportunities for intervention, and how such periods can be identified.

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

One of the barriers to conducting research in this area is the challenge of obtaining funding to examine the effectiveness of novel and more intensive treatment paradigms. These interventions may be more costly, but are potentially cost effective if they prevent the onset of, or lead to remission of, obesity-related comorbidities. Opportunities to examine promising high intensity interventions in fully powered trials would be beneficial.

Another challenge is identifying "optimal" opportunities and targets for intervention. Large data sets using electronic medical records could potentially be utilized to understand a host of factors related to trajectories of accelerated weight gain, leading to severe obesity, as well as deceleration, leading to reversal of obesity. Using "big data" to identify unique trajectories and the variables that predict them could lay the foundation for development of intervention targets.

**Publications from your own work that are most applicable to the workshop objectives:**

- Jelalian E, Jandasek B, Wolff JC, Seaboyer LM, Jones RN, Spirito A. Cognitive-Behavioral Therapy Plus Healthy Lifestyle Enhancement for Depressed, Overweight/Obese Adolescents: Results of a Pilot Trial. J Clin Child Adolesc Psychol. 2016 Jun 16:1-10.

**Publications from others that are most applicable to the workshop objectives:**

The following study reflects works on identification of early trajectories of severe obesity:

- Smego A, Woo JG, Klein J, Suh C, Bansal D, Bliss S, Daniels SR, Bolling C, Crimmins NA. High Body Mass Index in Infancy May Predict Severe Obesity in Early Childhood. J Pediatr. 2017;183:87-93.

The following two papers are representative of potential intensive treatment approaches that may warrant further inquiry with this population:

- Berkowitz RI, Wadden TA, Gehrman CA, Bishop-Gilyard CT, Moore RH, Womble LG, Cronquist JL, Trumpikas NL, Levitt Katz LE, Xanthopoulos MS. Meal replacements in the treatment of adolescent obesity: a randomized controlled trial. Obesity(Silver Spring). 2011;19(6):1193-9.
- Kelly KP, Kirschenbaum DS. Immersion treatment of childhood and adolescent obesity: the first review of a promising intervention. Obes Rev. 2011;12(1):37-49.

# *Ania M. Jastreboff, MD, PhD*
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**Biosketch**

Dr. Jastreboff is an Assistant Professor in Medicine (Endocrinology & Metabolism) and Pediatrics (Pediatric Endocrinology) at Yale University School of Medicine and is board certified in Obesity Medicine, Endocrinology & Metabolism, Pediatric Endocrinology, Internal Medicine, and Pediatrics. After completing a combined Internal Medicine and Pediatrics residency program, Dr. Jastreboff completed both an adult and a pediatric Endocrinology fellowship at Yale, during which she also earned a PhD. In 2013, she received an American Society of Clinical Investigation (ASCI) Young Physician-Scientist Award, a prestigious early investigator recognition award, and her work has been funded by a NIDDK K23 Mentored Patient-Oriented Research Career Development Award.

As a neurobehavioral endocrinologist, the goal of Dr. Jastreboff's research is to better understand how the brain controls eating behaviors in children and adults. Dr. Jastreboff utilizes functional magnetic resonance imaging (fMRI) to examine neural responses in reward-motivation, decision-making, and homeostatic brain regions to various food-related cues (such as food images, oral glucose and fructose ingestion, and intravenous insulin administration via euglycemic-hyperinsulinemic clamp technique) and relate the observed neural responses to food-related behaviors (such as food craving and food intake).

Dr. Jastreboff's clinical expertise is caring for patients with obesity, prediabetes, metabolic syndrome, and diabetes. Recently, Dr. Jastreboff served on the expert panel for developing the 2016 AACE/ACE (American Association of Clinical Endocrinologists and America College of Endocrinology) *Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity*. Through her clinical work and research, ultimately, Dr. Jastreboff aims to impact public health and public policy by providing evidence for effective interventions to address the obesity epidemic; thus, optimizing health and well-being of children and adults with obesity.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

**Understanding the impact of metabolic adaptations of increased adiposity on the neurobiology of obesity:**

The most significant findings from our research have been that well-known weight-related metabolic adaptations in insulin sensitivity, insulin, glucose, leptin and ghrelin levels alter brain response in reward and motivation neuro-circuitry to influence food motivation and intake of highly-palatable foods. We have found that in individuals with obesity (but not normal weight), food craving, insulin levels, and measures of insulin resistance correlate positively with neural activity in corticolimbic-striatal brain regions during favorite-food and stress cues. Additionally, the relationship between insulin resistance and food craving in individuals with obesity is mediated by activity in motivation-reward regions including the striatum. This suggests that targeting insulin sensitivity may affect food

craving and eating behavior. In children, we found that brain responses to high-calorie food relative to non-food images are increased in adolescents with obesity (compared to normal weight) in striatal-limbic regions, involved in motivation-reward and emotion processing. In adolescents, higher endogenous leptin levels correlated with increased neural activation to high-calorie food images. This significant association between higher circulating leptin and hyper-responsiveness of brain motivation-reward regions to high-calorie food images suggests that dysfunctional leptin signaling may contribute to the risk of overconsumption of these foods, thus further predisposing adolescents to the development of obesity. We have also assessed brain perfusion responses to drinking glucose and fructose in adolescents and found that adolescents with obesity exhibited decreases in brain perfusion in executive function brain regions (prefrontal cortex) and increases in hypothalamic perfusion in response to sugar ingestion. Obesity-induced homeostatic (hypothalamic) region changes were found to be associated with attenuated suppression of the hunger hormone, acyl-ghrelin, and increased insulin levels. Our data demonstrate that adolescents with obesity may have impaired prefrontal executive control responses to drinking sugars, while their homeostatic and reward response appears to be heightened. Notably, these obesity-related brain adaptations in adolescents may promote excessive and prolonged consumption of sugar, thereby promoting further weight gain.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

How do we gain a better understanding of the impact of pubertal/adolescent development on weight-related metabolic changes and its impact on the brain development? There are virtually no studies in this area but with rise in childhood and adolescent obesity, it is critical to understand how these changes affect the developing brain. How do we design, structure, and support both mechanistic and longitudinal cohort studies of children and adolescents to assess the effects of obesity/weight gain on metabolism, cognition, and obesity-related diseases throughout the lifespan?

How do we design, structure, and support well-designed, multi-center, randomized control trials (RCT) to assess safety and efficacy of anti-obesity medications and other weight loss/maintenance interventions in adolescents with severe obesity? How do we support adolescent weight management programs to create the setting for such multi-center, randomized control trials to take place?

How do we effectively influence public policy change to prevent and attenuate adolescent obesity through targeted research to create a healthier food environment by: 1) reducing sugar-sweetened beverage availability/consumption, 2) creating healthier school food (default) choices, 3) improving the built environment to increase safe and accessible playgrounds, parks, and sidewalks, and 4) providing support for parents/families to enable healthy food choices, daily physical activity, and consistent sleep for the family?

How do we design, structure, and support long-term prospective epidemiologic studies to best understand and address the contributing factors to adolescent obesity, including but not limited to: the food environment, built environment, eating behavior, physical activity, sleep, social determinants of eating behavior, and genetic factors contributing to obesity?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Several **barriers** for advancing research include: 1) concern for safely and long-term (side) effects of anti-obesity medications, bariatric surgery, and other weight loss/maintenance treatments for adolescents with obesity resulting in lack of efficacy data and long-term safety data of these treatments; 2) lack of infrastructure and support to do large multi-center, RCT in adolescents with obesity and difficulty in the financial sustainability of pediatric/adolescent obesity treatment centers

(due in part due to reimbursement from insurance payers) where such multi-center, RCT could be carried out; 3) lack of insurance reimbursement and FDA approval for various treatments (anti-obesity medications etc.) making it more challenging to do prospective observational studies of weight loss/maintenance treatments; and 4) lack of focus on the importance of childhood/adolescents development and brain development in the scientific agenda of obesity (which this workshop is helping to address!).

Several **creative ideas** for advancing research include: 1) incorporating the use of technology-based interventions utilizing Smartphones in this adolescent cohort who grew up in the Smartphone/internet era; 2) developing monitored gamification of Smartphone Apps for healthy food choices and physical activity by making it a peer-to-peer positive (peer pressure) social challenge (i.e. as is done with Fitbit etc.); and 3) creating a nation-wide (and global) multi-center database of children/adolescents with obesity - tracking the development of obesity-related comorbidities and longitudinally follow the cohort throughout their lifespan to assess various contributing factor to the development/exacerbation of obesity and obesity-related diseases, as well as assessing treatment outcomes for various anti-obesity/weight loss/maintenance interventions.

**Publications from your own work that are most applicable to the workshop objectives:**

- Jastreboff AM, Sinha R, Arora J, Giannini C, Kubat J, Malik S, Van Name MA, Santoro N, Savoye M, Duran EJ, Pierpont B, Cline G, Constable RT, Sherwin RS, Caprio S. Altered Brain Response to Drinking Glucose and Fructose in Obese Adolescents. Diabetes. 2016;65(7):1929-39.
- Jastreboff AM, Lacadie C, Seo D, Kubat J, Van Name MA, Giannini C, Savoye M, Constable RT, Sherwin RS, Caprio S, Sinha R. Leptin is associated with exaggerated brain reward and emotion responses to food images in adolescent obesity. *Diabetes Care.* 2014 Nov; 37(11):3061-8.
- Jastreboff AM, Sinha R, Lacadie C, Small D, Sherwin RS, Potenza MN. Neural correlates of stress- and food-cue–induced food craving in obesity: association with insulin levels. *Diabetes Care.* 2013; 36(2):394-402.
- Sinha R, Jastreboff AM. Stress as a common risk factor for obesity and addiction. Biol Psychiatry. 2013;73(9):827-35.

**Publications from others that are most applicable to the workshop objectives:**

- Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, Yanovski JA. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(3):709-757.
- Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689-712.
- Spear BA, Barlow SE, Ervin C, Ludwig DS, Saelens BE, Schetzina KE, Taveras EM. Recommendations for treatment of child and adolescent overweight and obesity. Pediatrics. 2007;120 Suppl 4:S254-88. Review.

### *Lee M. Kaplan, MD, PhD*
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**Biosketch**

Dr. Kaplan is the director of the Obesity, Metabolism and Nutrition Institute and founding director of the Weight Center at the Massachusetts General Hospital (MGH), and associate professor of medicine at Harvard Medical School (HMS).  His research focuses on the role of the GI tract in the regulation of energy balance and metabolic function, including the mechanism of action of bariatric and metabolic surgery.

Dr. Kaplan graduated from Harvard University and received an M.D. and a Ph.D. in molecular biology from the Albert Einstein College of Medicine.  He completed an internship and residency in internal medicine and a fellowship in gastroenterology at the Massachusetts General Hospital and Harvard Medical School and a fellowship in genetics at the Brigham and Women's Hospital. He is the author of more than 200 scientific and medical papers in leading journals.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

- Demonstration of wide patient-to-patient variability in response to all types of anti-obesity treatment
- Identification of clinical and genetic predictors of weight loss response to bariatric surgery, and demonstration of the substantial added utility of genetic predictors
- Demonstration of additive or synergistic utility of combination anti-obesity therapies
- Demonstration of efficacy of endoscopic anti-obesity therapies

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What is the relative effectiveness of currently available therapies in pediatric subgroups, divided by: age or developmental stage; race, ethnicity and other subpopulations; or known obesity subtypes?
- Which of the available therapies currently available for adults are safe and effective in adolescents?
- How can we identify clinically relevant obesity subtypes and/or reliable predictors of response to different anti-obesity treatments?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Barriers:

- Inadequate appreciation of obesity as a disease state among providers, patients and the public
- Inadequate appreciation of the pathophysiological basis of obesity
- Inadequate appreciation of the substantial heterogeneity of obesity and wide variation in response to all anti-obesity therapies
- Inadequate understanding of the biological basis and phenotypic differentiation among clinically relevant obesity subtypes
- Inadequate means of predicting response to therapy in individual patients
- Insufficient evaluation of the efficacy and safety of available anti-obesity therapies in adolescents
- Insufficient information about the efficacy, safety and clinical utility of combination anti-obesity therapies

Opportunities:
- Clinical testing of available and emerging pharmacological and medical device anti-obesity therapies in adolescent population
- Development and implementation of improved clinical phenotyping strategies
- Broad implementation of registries, biobanks and data repositories to generate and analyze clinical, demographic, genetic, and biomarker data for their ability to predict therapeutic outcomes in individual patients
- Identification of mechanism of action of lifestyle-based anti-obesity therapies, including how they alter physiological regulation of energy balance
- Identification of the physiological programs underlying clinically effective anti-obesity therapies

**Publications from your own work that are most applicable to the workshop objectives:**

- Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM.  Heritability of the response to gastric bypass surgery.  J Clin Endocrinol Metab. 2011; 96(10):E1630-3.
- Hatoum IJ, Greenawalt DM, Cotsapas C, Daly MJ, Reitman ML, Kaplan LM. Weight loss after gastric bypass is associated with a variant at 15q26.1. Am J HumGenet. 2013 May 2;92(5):827-34.
- Carmody JS, Ahmad NN, Machineni S, Lajoie S, Kaplan LM. Weight Loss After RYGB Is Independent of and Complementary to Serotonin 2C Receptor Signaling in Male Mice. Endocrinology. 2015 Sep;156(9):3183-91.
- Klebanoff MJ, Chhatwal J, Nudel JD, Corey KE, Kaplan LM, Hur C.  Cost-effectiveness of bariatric surgery in adolescents with obesity.  JAMA Surg. 2017;152:136-141.

**Publications from others that are most applicable to the workshop objectives:**

*Papers on effectiveness of endoscopic treatments of obesity*

- Jain D, Bhandari BS, Arora A, Singhal S. Endoscopic Sleeve Gastroplasty – A New Tool to Manage Obesity. Clin Endosc. 2017 Jun 13. doi: 10.5946/ce.2017.032. [Epub ahead of print] PubMed PMID: 28607328.
- Tate CM, Geliebter A. Intragastric Balloon Treatment for Obesity: Review of Recent Studies. Adv Ther. 2017 Jul 13. doi: 10.1007/s12325-017-0562-3. [Epub ahead of print] Review.
- Kumar N, Sullivan S, Thompson CC. The role of endoscopic therapy in obesity management: intragastric balloons and aspiration therapy. Diabetes Metab Syndr Obes. 2017;10:311-316.

*Papers from Teen LABS*

- Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick M, Buncher CR; Teen-LABS Consortium. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. N Engl J Med. 2016;14;374(2):113-23.
- Sarwer DB, Dilks RJ, Spitzer JC, Berkowitz RI, Wadden TA, Moore RH, Chittams JL, Brandt ML, Chen MK, Courcoulas AP, Harmon CM, Helmrath MA, Michalsky MP, Xanthakos SA, Zeller MH, Jenkins TM, Inge TH. Changes in Dietary Intake and Eating Behavior in Adolescents After Bariatric Surgery: an Ancillary Study to the Teen-LABS Consortium. Obes Surg. 2017 Jun 17. doi: 10.1007/s11695-017-2764-9. [Epub ahead of print] PubMed PMID: 28625002.

## *Aaron S. Kelly, PhD*

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### Biosketch

Dr. Kelly is an Associate Professor of Pediatrics and Medicine and Co-Director of the Center for Pediatric Obesity Medicine at the University of Minnesota. His research focuses on the clinical aspects of pediatric severe obesity with an emphasis on pharmacotherapy. Dr. Kelly's research portfolio includes NIH-funded studies assessing the vascular status of children and adolescents with severe obesity, evaluating outcomes following bariatric surgery in teens, and clinical trials investigating the combination of lifestyle modification and pharmacotherapy in adolescents with severe obesity. He is a Fellow of The Obesity Society and American Heart Association and has served in various leadership roles for these organizations and is the chair of the Minnesota Pediatric Obesity Consortium.

### What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?

My colleagues and I are actively investigating various medications for the treatment of adolescent severe obesity. We have conducted 2 pilot clinical trials evaluating the safety and efficacy of glucagon-like peptide-1 (GLP-1) receptor agonist treatment in adolescents with severe obesity and are currently performing a large NIH-funded clinical trial assessing the effectiveness of GLP-1 treatment in enhancing weight loss maintenance following meal replacement therapy. In addition, we serve as a site for an international multicenter clinical trial of high-dose liraglutide (GLP-1 receptor agonist) for the treatment of adolescent obesity. We recently completed a pilot clinical trial investigating the safety and efficacy of topiramate as a weight loss medication in adolescents with severe obesity and have reported on the clinical outcomes with phentermine treatment in this population. While the respective safety profiles of these medications appear to be acceptable, BMI

reduction has so far been relatively modest (3-5% reduction). We believe combination pharmacotherapy will ultimately provide more favorable safety and efficacy but these studies will have to wait until the monotherapies have been sufficiently vetted. Finally, we are beginning to identify potential predictors of response to specific medications and plan to accelerate our efforts in the area of precision medicine.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the sources of variability (biological, psycho-social, genetic, etc.) in response to various treatments?
- What are the unique features/characteristics of adolescents (biological, developmental, psycho-social, etc.) that help explain the poorer weight loss outcomes (compared to younger children and adults)?
- What are the most appropriate pairings/combinations of treatments (lifestyle/behavioral, pharmacotherapy, device therapy, bariatric surgery, etc.) to achieve the best outcomes?
- What is the ideal timing for deploying various interventions with respect to a potential age/development-related window of opportunity for achieving the best outcomes and how long to wait before intensifying treatment (i.e., is a staged/stepped approach appropriate or are we simply wasting precious time by initiating treatment with conservative strategies)?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

- We need to break down the barriers that tend to separate researchers/experts into silos (i.e. the "lifestyle/behavioral" folks, the "drug" folks, the "surgery/device" folks) - we too often talk around each other and fail to fully acknowledge that a multifactorial treatment approach is necessary
- We need to reduce the time from when adult obesity medications, devices, and other treatments are approved and the initiation of the adolescent safety/efficacy clinical trials. Revising the Best Pharmaceuticals for Children Act legislation regarding timeline expectations could help address this issue.
- The pediatric obesity research community needs to be bolder and more innovative in its approaches. We do not have the luxury of time; incremental advances will not suffice. We cannot continue to reevaluate the same (or materially similar) interventions that have previously been shown to be ineffective.

**Publications from your own work that are most applicable to the workshop objectives:**

- Fox CK, Kaizer AM, Rudser KD, Nathan BM, Gross AC, Sunni M, Jennifer Abuzzahab M, Schwartz BL, Kumar S, Petryk A, Billington CJ, Ryder JR, Kelly AS. Meal replacements followed by topiramate for the treatment of adolescent severe obesity: A pilot randomized controlled trial. Obesity (Silver Spring). 2016;24(12):2553-2561. *This study addressed the concept of using pharmacotherapy to target weight regain
- Kelly AS, Fox CK, Rudser KD, Gross AC, Ryder JR. Pediatric obesity pharmacotherapy: current state of the field, review of the literature and clinical trial considerations. Int J Obes (Lond). 2016;40(7):1043-50. Review *This article provided a review of the literature of pediatric obesity pharmacotherapy and offered insights in the design and conduct of future clinical trials
- Nathan BM, Rudser KD, Abuzzahab MJ, Fox CK, Coombes BJ, Bomberg EM, Kelly AS. Predictors of weight-loss response with glucagon-like peptide-1 receptor agonist treatment

among adolescents with severe obesity. Clin Obes. 2016 Feb;6(1):73-8.*This study identified predictors of response to GLP-1 treatment for obesity

**Publications from others that are most applicable to the workshop objectives:**

- Danielsson P, Kowalski J, Ekblom Ö, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med. 2012;166(12):1103-8. *This study shows us exactly what we are up against in the real-world clinical setting
- Inge TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmrath MA, Brandt ML, Harmon CM, Zeller MH, Chen MK, Xanthakos SA, Horlick M, Buncher CR; Teen-LABS Consortium. Weight Loss and Health Status 3 Years after Bariatric Surgery in Adolescents. N Engl J Med. 2016;374(2):113-23. *This study demonstrates the superior effectiveness and acceptable safety of bariatric surgery in adolescents with severe obesity – no other treatment comes close to reducing BMI and improving co-morbidities to the degree of bariatric surgery
- De Peppo F, Caccamo R, Adorisio O, Ceriati E, Marchetti P, Contursi A, Alterio A, Della Corte C, Manco M, Nobili V. The Obalon swallowable intragastric balloon in pediatric and adolescent morbid obesity. Endosc Int Open. 2017;5(1):E59-E63. *This study evaluated the novel intra-gastric balloon device in adolescents with severe obesity

## *Shelley Kirk, PhD, RD, LD*
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**Bio-sketch**

Dr. Kirk is Associate Professor of Clinical Pediatrics at the University of Cincinnati College of Medicine and Director of HealthWorks!, a family-based, multi-component pediatric weight management program at Cincinnati Children's Hospital Medical Center. She has worked as a clinical dietitian in the field of pediatric obesity for over 30 years and Director of HealthWorks! the pediatric medical weight management program in the Center for Better Health and Nutrition at Cincinnati Children's Hospital Medical Center (CCHMC) for the past 18 years. In addition, I served as Lead Dietitian for the bariatric surgery program for adolescents with severe obesity at CCHMC for 8 years (2001-2008). She has a PhD in Epidemiology and Biostatistics from the University of Cincinnati, with a focus on nutritional epidemiology. Her thesis research involved the design and administration of a randomized clinical trial, which prepared her to serve as PI of the first published long-term randomized clinical trial on the safety and efficacy of carbohydrate-modified diets in obese children (Funding source: Thrasher Research Foundation).  During her tenure at CCHMC, her primary goal as a researcher and clinician has been to develop more effective clinical interventions for the

management of childhood and adolescent obesity. The multi-disciplinary HealthWorks! program offers pediatric weight management services using standardized clinical protocols to over 900 new patients a year.  In addition, she serves as PI for the Pediatric Obesity Weight Evaluation Registry (POWER). POWER is a centralized, data repository for the on-going collection and maintenance of demographic and clinical data from hospital-based pediatric weight management programs across the country. She also serves as co-investigator for the R01 - NIH/NIDDK clinical trial, "Bariatric Surgery vs. Comprehensive Lifestyle Intervention for NASH", and provides direct clinical services for the comprehensive lifestyle arm of the study.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Here is a summary of the most significant findings to date from research conducted with POWER (Pediatric Obesity Weight Evaluation Registry).  The goals of POWER are to describe health outcomes in youth with obesity (age 18 and younger) and to identify patient characteristics and program exposure features associated with favorable outcomes. Participating pediatric weight management programs in POWER meet criteria for providing multi-component interventions (medical, nutrition, physical activity and behavioral strategies), however there is considerable variation in program format (duration and intensity), program provider types, patient assessments and treatment strategies.

The vast majority (73%) of children and adolescents (ages 2 to 18) presenting for treatment in tertiary-care pediatric weight management programs from 2014-2016 (31 POWER sites; 5,953 enrolled patients) have severe obesity (>120% of the 95th percentile for BMI), and obesity-related co-morbidities. Since national guidelines recommend youth be referred for weight management services when at the 95th percentile for BMI, our findings with POWER indicate a disproportionate number of youth with severe obesity are receiving multi-component weight management services later than advised. In regard to patient outcomes, those with more severe obesity and Hispanic ethnicity were associated with greater improvement in weight status, based on change in the percent of the 95th percentile for BMI. However overall, outcomes with regard to change in weight status are modest.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- Identify a "favorable outcome" value for change in weight status for adolescents with severe obesity based on the recommended BMI-metric ($\Delta BMI_{p95}$; $\%BMI_{p95}$) that is associated with clinically-relevant improvement in identified co-morbidities. This is needed in order to determine the effectiveness of targeted treatments for adolescents with severe obesity.

- Ways to utilize the POWER aggregate database in order to identify patient characteristics and program exposure features that are associated with this "favorable outcome". These findings can then help develop innovative hypotheses for treatments that can be tested in multi-site clinical trials.

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

**Barrier:**

POWER's funding model may prevent the registry from realizing its full potential to help contribute in developing more effective and targeted treatments for adolescents with severe obesity. The

current source of funding for POWER are the enrollment fees from participating sites [Cycle 1 (2014-2016): $5,000; Cycle 2 (2016-2018): $6,000]. These fees support the POWER Data Coordinating Center and associated administrative costs. Though POWER has been successful in securing sufficient funds to date, the registry would be more representative of existing multi-component pediatric weight management programs if funding was secured to help stabilize and broaden site participation, while supporting POWER's sustainability.

**Creative idea:**

POWER is uniquely positioned to identify a sub-set of the treatment-seeking adolescents with severe obesity who have a "favorable" outcome and then determine their association with programmatic features and patient-level exposures. This can help contribute to the development of targeted interventions for adolescents with severe obesity based on a nationally-representative patient population.

**Publications from your own work that are most applicable to the workshop objectives:**

- Kirk S, King EC, Trapp CM, Grow HM, Tucker JM, Joseph MM, Liu LL, and Stratbucker W on behalf of the POWER Work Group. Establishment of the Pediatric Obesity Weight Evaluation Registry (POWER): A National Research Collaborative for Identifying the Optimal Assessment and Treatment of Pediatric Obesity. Childhood Obes. 2017;13(1):9-17.
- Jasik, CB, King EC, Rhodes E, Sweeney B, Mietus-Snyder M, Grow HM, Harris JM, Lostocco L. Estrada E, Boyle K, Tucker JM, Eneli IU, Woolford SJ, Datto G, Stratbucker W, and Kirk S. Characteristics of Youth Presenting for Weight Management: Retrospective National Data from the POWER Study Group. Childhood Obes. 2015;11(5):630-7.
- Kirk S, Brehm B, Saelens BE, Woo JG, Kissel E, D'Alessio D, Bolling C, Daniels SR. Role of carbohydrate modification in weight management among obese children: A randomized clinical trial. J Pediatr. 2012;161(2):320-327.

**Publications from others that are most applicable to the workshop objectives:**

- Freedman DS, Butte NF, Taveras EM et al. BMI *z*-Scores are a Poor Indicator of Adiposity Among 2- to 19-Year-Olds with Very High BMIs, NHANES 1999-2000 to 2013-2014. *Obesity.* 2017; 25:739-746.
- Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689-712.
- Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of weight management interventions in children: a targeted systematic review for the USPSTF. Pediatrics. 2010 Feb;125(2):e396-418. Review.

# *Marsha D. Marcus, PhD*
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**Biosketch**

Dr. Marcus is Professor of Psychiatry and Psychology at the University of Pittsburgh School of Medicine. Dr. Marcus served as the Chief of the Eating Disorders Program at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center from 1998-2014 and is Director Emerita of the Western Psychiatric Institute and Clinical Psychology Internship Program. Her research program has focused on the assessment and treatment of eating disorders, and pediatric and adult obesity, and she has been the Principal Investigator of numerous research projects funded by the National Institutes of Health. Dr. Marcus is a past president of the Academy for Eating Disorders and the Eating Disorders Research Society. She serves on the Editorial Board of the International Journal of Eating Disorders, and was a member of the Eating Disorders Work Group of the DSM-5 Taskforce. In 2017 Dr. Marcus was the recipient of Academy for Eating Disorders Lifetime Achievement Award. Dr. Marcus is the author of more than 225 publications.


**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Findings from our research group documented that a comprehensive family-based behavioral lifestyle program for school-aged children (M age = 10.2 years) with severe obesity (average BMI percentile = 99.2 percentile for age and sex) was associated with modest weight losses when compared with a waiting list control group. Between group differences in weight change were not sustained after the 6-month intervention, but improvements in waist circumference, systolic blood pressure and total body fat were sustained over a 1-year follow-up. Given the health risks associated with severe obesity, we concluded there was a compelling need to develop and evaluate chronic-care interventions for these high-risk children.

Subsequent work with students participating a multi-site school-based diabetes prevention intervention (HEALTHY Study) confirmed that the start of middle school youth (M age = 11.3 years) with severe obesity (defined as BMI $\geq$ 99th percentile for age and sex; average BMI = 35.2) exhibited significantly higher levels of cardiometabolic risk factors when compared with those with less severe obesity (defined as BMI $\geq$ 95th - < 99th percentile for age and sex) and were more likely to be of Black or Latino race/ethnicity. Longitudinal data indicated that severe obesity was more likely to endure over the course of middle school than was moderate obesity and was associated with significantly higher levels of cardiometabolic risk throughout the study period.

Finally, as an investigator on the TODAY clinical trial, which was designed to examine the impact of metformin, metformin plus rosiglitazone and metformin plus lifestyle intervention in the management a pediatric type 2 diabetes, I participated in the development, implementation and

evaluation of the comprehensive lifestyle intervention component of the study. At the start of the study the youth averaged 14 years of age and 78.9% overweight. The addition of lifestyle intervention to metformin was not associated with durable metabolic control, but adolescents who received the lifestyle intervention showed greater decreases in percent overweight during the period of most intensive lifestyle intervention (approximately 6 months) when compared with those in the other intervention conditions. Differences in changes in percent overweight between metformin and metformin plus lifestyle groups did not persist at follow-up assessments despite ongoing, but less intensive intervention.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are critical behavioral strategies of lifestyle interventions and how can they be enhanced to increase the effectiveness of lifestyle interventions?
- Are there behavioral phenotypes that are associated with response to lifestyle interventions?
- How can lifestyle interventions for severe obesity be combined/sequenced with other treatments over time to optimize treatment outcomes?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

One major barrier is a lack of funding to address the complex issues associated with obesity across multiple levels of analysis, i.e., the full gamut of translational work. Basic work to identify mechanisms and treatment targets, research to elucidate the behavioral processes involved in obesity and other chronic health problems that require ongoing self-management, efficacy trials for combination treatments and adaptive and pragmatic clinical trials to deliver interventions in community settings all are imperative.

Health disparities as a function of race, ethnicity and social class in the US are widespread, and remain despite increased efforts to address them. Severe obesity in youth is differentially associated with minority race/ethnicity and often affects families with multiple socioeconomic and health challenges. Prevalent severe obesity during adolescence reflects broader health disparities, but may pose an additional challenge because of pervasive stigmatization that may influence the willingness of health care providers and policy makers to address the issue.

Publications from your own work that are most applicable to the workshop objectives (up to 3 papers):

- Kalarchian MA, Levine M, Arslanian S, Ewing L, Houck P, Cheng Y, Ringham R, Sheets C, Marcus MD. Family-Based Treatment of Severe Pediatric Obesity: A Randomized Controlled Trial. Pediatrics 2009;124:1060-1068.
- Marcus MD, Foster GD, El ghormli L. Stability of relative weight category and cardiometabolic risk factors among moderately and severely obese middle school youth. Obesity 2014;22:1118-25.
- Marcus MD, Wilfley DE, El ghormli L, Zeitler P, Linder B, Hirst K, Ievers-Landis CE, van Buren DJ, Walders-Abramson N. Weight change in the management of youth-onset type 2 diabetes: the TODAY clinical trial experience. Pediatr Obes. 2017;12:337-345. PMID: 27161901

**Publications from others that are most applicable to the workshop objectives:**

*Papers focusing on lifestyle interventions and youth with severe obesity*

- Danielsson P, Kowalski J, Ekblom O, Marcus C. Response of severely obese children and adolescents to behavioral treatment. Arch Pediatr Adolesc Med. 2012;166(12):1103-1108.
- Reinehr T, Kleber M, Lass N, Toschke AM. Body mass index patterns over 5 y in obese children motivated to participate in a 1-year lifestyle intervention: age as a predictor of long-term success. Am J Clin Nutr. 2010;91:1165-75.
- Savoye M, Nowicka P, Shaw M, Yu S, Dziura J, Chavent G, O'Malley G, Serrecchia JB, Tamborlane WV, Caprio S. Long-term results of an obesity program in an ethnically diverse pediatric population. Pediatrics 2011;127:402-410.

# *Julie A. Mennella, PhD*
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**Biosketch**

Dr. Mennella obtained a Ph.D. from the Department of Behavioral Sciences at The University of Chicago in Chicago, IL. She joined the faculty at the Monell Chemical Senses Center in Philadelphia, PA in 1990 where she is now a Member. Her major research interests include investigating the timing of sensitive periods in human flavor learning and growth; uncovering how children are living in different taste worlds than adults and their vulnerabilities to the current food environment as well as medication adherence; and the development of psychophysical tools to study individual variation in taste and flavor perception. She is the recipient of several grants from the National Institute of Deafness and Other Communication Disorders and the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the author or co-author of numerous peer-reviewed research papers and an internationally recognized speaker on the ontogeny of flavor preferences and its implications for health and nutritional programming.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Relevant to the workshop, my research has focused on the ontogeny of taste perception, how to measure it and how it relates to what children eat. For example, although obese children and adolescents often are assumed to differ in their taste preferences from normal weight individuals, this claim has received little evidentiary support. On the contrary, the level of sweetness of sucrose most preferred by obese children does not differ from those who are normal weight. What differed was the efficacy of sucrose in blunting expressions of pain and children's motives for eating sweets.

**Publications from your own work that are most applicable to the workshop objectives:**

- Pepino MY, Mennella JA. Sucrose-induced analgesia is related to sweet preferences in children but not adults. Pain. 2005;119(1-3): 210-8.
- Mennella JA, Bobowski NL, Reed DR. The development of sweet taste: From biology to hedonics. Reviews in Endocrine and Metabolic Disorders. 2016;17:171-8.

# Aviva Must, PhD

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**Biosketch**

Dr. Must is a nutritional epidemiologist who has worked in population-based obesity research since 1988.  She focuses on the epidemiology of obesity across the lifespan with a particular interest in physical and psychosocial health consequences during adolescence and in vulnerable populations. She developed the first BMI percentiles based on nationally representative data for identification of overweight and obesity in children—a precursor of the 2000 CDC growth standards.  Additional research foci include the development of valid survey measures and surveillance systems for pediatric obesity and proximal modifiable behaviors (nutrition, physical activity, sedentary behavior). Recent efforts have been directed towards developing the descriptive epidemiology and health promotion for children with developmental disabilities. Her preventive intervention work includes community-based research projects in pre-school and primary school populations.  Dr. Must directed the Clinical and Community Research Core of the Boston Nutrition Obesity Research Center, a cross-institution NIH-funded Obesity Center (2002-2016). She is co-director of the Healthy Weight Research Network for Children with Autism Spectrum Disorders and Developmental Disabilities, funded by the Maternal and Child Health Bureau of HRSA, USDHHS (2014-present).

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

I have led research investigations that used historical cohort datasets, including the Third Harvard Growth Study, Newton Girls Study, and Children in the Community Study to elucidate the long term physical and psychosocial impact of early obesity. I used the heights and weights collected for other purposes to identify weight status and to link them to health consequences (all-cause mortality, cardiovascular morbidity and mortality, cancer morbidity and mortality, activities of daily living) as well as psychosocial and outcomes (depression, generalized anxiety disorder, conduct disorder). This work has contributed to our understanding of the health impact of pediatric obesity, and the importance of life-course perspectives in the natural history of obesity.  My more recent work in this area has helped professionals rethink adolescence as a critical period in the development of obesity and its consequences.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the most clinically meaningful measures of weight change--for the clinician, for the patient, and for the family?

- How can we tailor treatment to produce outcomes that are meaningful to the adolescent?

- How can "standard" approaches be adapted for special populations of children, such as children with developmental disabilities, psychiatric conditions, other special health care needs? Similarly, for race/ethnic minority adolescents who are at greatest risk for severe obesity?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Barriers include lack of common definitions of severe obesity itself, measures to account for weight change in growing children, and, in the context of interventions, definitions of success. For severe obesity that this secondary to medically indicated medications, competing issues need to be managed. The need to support the autonomy of the developing adolescent is often at odds with treatment protocols that necessarily involve parents and run counter to independence.

Ideas include testing novel treatment support models that leverage digital technologies – for data collection of primary and secondary measures (diet, PA, sleep), motivation, peer coaching. Qualitative and mixed methods approaches with adolescent patients undergoing treatment would better understand adolescent preferences and concerns and inform development of novel treatment models.

**Publications from your own work that are most applicable to the workshop objectives:**

- Anderson SE, Cohen P, Naumova EN, Jacques PF, Must A. Adolescent obesity and risk for subsequent major depressive disorder and anxiety disorder: Prospective evidence. Psychosom. Med 2007;69:740-7.
- Goodman E, Must A. Depressive symptoms in severely obese compared with normal weight adolescents: Results from a community-based longitudinal study. J Adolesc Health. 2011;49:64-9.
- Must A, Phillips SM, Naumova EN. Occurrence and timing of childhood overweight and mortality: Findings from the Third Harvard Growth Study. J Pediatr. 2012;160:743-50.

**Publications from others that are most applicable to the workshop objectives (up to 3 papers):**

- Suchindran C, North KE, Popkin BM, Gordon-Larsen P. Association of adolescent obesity with risk of severe obesity in adulthood. JAMA 2010;304(18):2042-7.
- Wang YC, Gortmaker SL, Taveras EM. Trends and racial/ethnic disparities in severe obesity among US children and adolescents, 1976–2006. Pediatric Obesity. 2011;6(1):12-20.
- Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689-712.

# *Cynthia L. Ogden, PhD, MRP*
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**Biosketch**

Dr. Ogden is an epidemiologist at the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) overseeing the analysis branch within the National Health and Nutrition Examination Survey. Her research interests relate to nutrition, and in particular, growth and obesity. She worked on the revision of the 2000 CDC growth charts for children that are used to define obesity in US children. Dr. Ogden has published extensively and given numerous presentations on obesity and dietary intake in the US. She joined CDC as a member of the Epidemic Intelligence Service (EIS). Before joining CDC, she worked in the Nutrition Division at the New York State Department of Health where she researched obesity among school children in New York counties. She has also worked on nutrition related projects for the Food and Agriculture Organization of the United Nations and currently is an adjunct professor at the George Washington University Milken Institute School of Public Health, teaching courses on nutritional and obesity epidemiology. She earned her Ph.D. and Master's degrees from Cornell University where her research focused on social contributions to malnutrition among young children in Kigali, Rwanda

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

The most significant findings from our research relate to trends in obesity prevalence and changes in the distribution of BMI in the United States. Results show that the distribution of BMI has shifted to the right and become more skewed indicating increasing prevalence of severe obesity. These results have been seen in adults and adolescents. Trends in prevalence show that the prevalence of obesity and severe obesity in adolescents has been increasing steadily between 1988-1994 and 2013-2014, unlike what has been seen in younger children. The prevalence of severe obesity among adolescents more than tripled from 2.6 to 9.1% over this time period.

Our research has also provided evidence at the national level of sex and race/Hispanic origin disparities in severe obesity prevalence among adolescents. In 2011-2014 the prevalence of severe obesity was 10.7% and 12.2% among non-Hispanic black boys and girls, while among non-Hispanic Asian boys and girls it was 3.3 and 0.5%. The same cut points may not be appropriate in all race/Hispanic origin groups, but sex differences do not appear to be the same in all subgroups.

Our team developed the CDC growth charts and has made suggested about how to define extreme values of BMI using the charts (see Flegal et al 2009 below).

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

For this question and the next one I consulted with Dr. Craig Hales, a physician colleague who is working with me on obesity projects.

- In many cases, the choice of treatment is determined by the likelihood of successful implementation. Will different treatment options be studied only among those where implementation is most likely to be successful, or will research include interventions to increase likelihood of success, so that more treatment options are available? If some treatments are not available to all participants (due to lack of insurance coverage, family support, etc.) will associations between individual characteristics and therapeutic outcomes be generalizable?
- There are a multitude of individual characteristics that could influence the effectiveness of a given treatment, and given the complex interactions among them, how can we determine the influence of individual characteristics?
- What harms could occur if the "wrong" treatment is selected and how can they be mitigated?
- What outcomes are adequate to assess the success of an intervention? Longer term outcomes are desirable, but may slow progress.

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

Some adolescents may not have adequate psychosocial or family support to implement certain treatments. Community organizations, schools, and/or faith-based organizations/churches could be leveraged for support.

Changing the adolescent's food environment is challenging. Research on individual treatments and outcomes could be integrated with existing or planned community-level intervention and evaluation programs.

**Publications from your own work that are most applicable to the workshop objectives:**

- Flegal KM, Wei R, Ogden CL, Freedman DS, Johnson CL, Curtin LR. Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. Am J Clin Nutr. 2009 Nov;90(5):1314-20.
- Freedman DS, Butte NF, Taveras EM, Lundeen EA, Blanck HM, Goodman AB, Ogden CL. BMI z-Scores are a poor indicator of adiposity among 2- to 19-year-olds with very high BMIs, NHANES 1999-2000 to 2013-2014. Obesity (Silver Spring). 2017 Apr;25(4):739-746 .
- Ogden CL, Carroll, MD, Lawman, HG, Fryar, CD, Kruszon-Moran, D, Kit, BK, Flegal, KM. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. JAMA. 2016;315(21):2292-2299.

**Publications from others that are most applicable to the workshop objectives:**

- Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR; American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689-712.

# *Thomas N. Robinson, MD, MPH*
Irving Schulman, MD Endowed Professor in Child Health,
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**Biosketch**

Dr. Robinson is Professor of Pediatrics and Medicine at Stanford University and Director of the Stanford Solutions Science Lab and Center for Healthy Weight at Stanford and Lucile Packard Children's Hospital Stanford. He focuses on designing solutions to help children and families improve their health- and sustainability-related behaviors. He originated the *solution-oriented* research paradigm and is known for his obesity prevention and treatment research, including the concept of *stealth interventions.* Dr. Robinson focuses on solution-oriented research to develop and evaluate health promotion and disease prevention interventions for children, adolescents and their families to directly inform medical and public health practice and policy. His research is largely experimental in design, conducting family-, school-, and community-based randomized controlled trials to test the efficacy and/or effectiveness of theory-driven behavioral, social and environmental interventions to prevent and reduce obesity, improve nutrition, increase physical activity and decrease inactivity, reduce children's screen time, and promote energy efficiency and environmental sustainability. Robinson's research is grounded in social cognitive models of human behavior, uses rigorous methods, and is performed in real World settings with diverse populations, making the results of his research more relevant for clinical and public health practice and policy. Robinson's received his B.S. and M.D. from Stanford University, M.P.H. in Maternal and Child Health from the University of California, Berkeley, internship and residency in Pediatrics at Children's Hospital, Boston and Harvard Medical School, and postdoctoral training as a Robert Wood Johnson Clinical Scholar at Stanford and UCSF.  He has been a faculty member at Stanford since 1991. Dr. Robinson also is Board Certified in Pediatrics and practices General Pediatrics at Lucile Packard Children's Hospital Stanford.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

- Individual variation and individual responsiveness to treatment is the norm. There is broad variation in responses to behavioral and community-based treatments.
- Behavioral and community-based treatments do work well in some individuals – some do lose substantial weight and BMI, improve their metabolic profiles, and make changes in their behaviors in response to treatment, while others do not.
- There are few baseline individual characteristics (moderators) or changes during treatment (mediators) that predict treatment response that account for a substantial amount of variance in treatment outcomes.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- What are the socio-demographic, behavioral, psychological, environmental, and biological factors that strongly predict future responsiveness to different treatments (i.e., moderators)?
- What are the early treatment changes (i.e., mediators) that strongly predict long term benefits from different treatments among different groups of patients (i.e., moderators)?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

- Barrier: Reductionistic, often linear, scientific thinking
- Barrier: Insufficient emphasis on solution-oriented research
- Barrier: Belief that modeling of observational data can substitute for experimental studies to accurately represent complex systems dynamics in the real world
- Opportunity: Recent advances in developing targeted interventions for social psychological barriers to change.

**Publications from your own work that are most applicable to the workshop objectives:**

- Robinson TN, Sirard J. Preventing childhood obesity: A solution-oriented research paradigm. *American Journal of Preventive Medicine.*2005;28:194-201.
- Robinson TN. Stealth Interventions for Obesity: Strategies for Behavioral, Social and Policy Changes. Chapter 99, in: Brownell KD, Walsh BT. *Eating Disorders and Obesity: A Comprehensive Handbook, 3rd Edition.* New York, NY: Guilford Publications, Inc., 2017, pp 609-613.
- Mummah SA, Robinson TN, King AC, Gardner CD, Sutton S. IDEAS (Integrate, Design, Assess, and Share): A framework and toolkit of strategies for the development of more effective digital interventions to change health behavior. *J Med Internet Res.* 2016 Dec; 18(12): e317.

**Publications from others that are most applicable to the workshop objectives:**

- Li-Pook-Than J, Snyder M. iPOP goes the world: Integrated personal omics profiling and the road toward improved health care. *Cell Chemistry & Biology* 2013;20:660-666.

## *Marian Tanofsky-Kraff, PhD*

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**Biosketch**

Dr. Tanofsky-Kraff, Ph.D. is Professor in the Department of Medical and Clinical Psychology at the Uniformed Services University of the Health Sciences and Researcher in the Section on Growth and Obesity at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development at the National Institutes of Health (NIH). Prior to receiving her PhD in Clinical Psychology from the Catholic University of America, Dr. Tanofsky-Kraff was a Research Associate

at the Yale Center for Eating/Weight Disorders at Yale University. Her research program involves the intersection of obesity and eating disorders in pediatric samples and addresses questions about the risks, protective factors, maintenance, consequences, and prevention of childhood excess weight gain, with a particular focus on disinhibited eating behaviors. Dr. Tanofsky-Kraff has extensive experience in the assessment of aberrant eating in youth, ranging from structured interviewing to laboratory feeding paradigms. She has carried out pediatric intervention trials aimed at preventing adult obesity and eating disorders in targeted populations. Dr. Tanofsky-Kraff has published over 150 empirical papers/chapters, has received research funding from the several NIH institutes and other agencies, and is the recipient of numerous awards. She is a Fellow of The Obesity Society, Fellow and Past Board Member of the Academy of Eating Disorders, and is Board Member and Past-President of the Eating Disorders Research Society.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

To date, we have identified disinhibited eating phenotypes that appear to be associated with, and in some cases, promote excessive weight gain. These phenotypes can be reliably distinguished from uncomplicated overeating. While there is still a great deal of work to understand how these phenotypes are linked to underlying physiology, we have gained some clarity on their presentation and whether they place individuals at risk for excessive weight gain. Central to our efforts has been our work on "loss of control" (LOC) eating. Our data suggest that LOC eating may be associated with genetic (*FTO*) and neural (involving limbic and prefrontal regions) underpinnings. LOC eating also appears to be associated with hormonal, metabolic, and inflammatory markers, above and beyond the contribution of obesity. Importantly, we have found that LOC eating is predictive of excessive weight and fat gain, components of the metabolic syndrome, and worsening psychological symptoms. While we have studied a number of other disinhibited behaviors, most appear to interact with LOC eating to produce adverse associations and outcomes. LOC eating may play serve as an important marker for risk of severe obesity.

Although LOC eating may be an important marker for adverse outcomes, it may not be the necessary behavior to target for reducing excess weight gain. Our initial intervention studies suggest that other factors – potentially underlying psychological traits (for example, internalizing symptoms) that promote LOC eating – are most relevant for reducing excessive weight and fat gain. As a result, we believe that efforts to better endophenotype disinhibited eating behaviors and traits are required. Our current program is attempting to fill this gap.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- How can we disentangle the overlap of disinhibited eating behaviors to determine who is at greatest risk for excess weight gain and severe obesity?
- Can endophenotyping disinhibited eating behaviors to better identify groups at high risk for excess for excess weight gain?
- Based on the answers to questions 1 and 2, can we determine treatment responsiveness based on well-defined disinhibited eating patterns?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

A primary barrier* for advancing research to develop more effective and targeted treatments for adolescents with severe obesity involves the erroneous belief that there is still a "one size fits all" approach to weight loss. It has become increasingly clear that many individuals develop severe

obesity due to a myriad of psychological and behavioral factors. These factors need to be addressed and resistance to unconventional approaches needs to be overcome. Furthermore, the field should be to be open to the possibility that multiple interventions, several of which may be intensive, may be warranted.  *Above and beyond funding reductions and resistance to implementing policy to improve the food environment.*

New ideas for advancing research may involve focusing on endophenotyping and addressing the underlying deficits that promote overeating among adolescents with severe obesity. Addressing such deficits may involve treating behavioral, cognitive, and psychological factors, and interventions likely need to go beyond healthy eating and physical activity education. Technology may be useful for behavioral and cognitive deficits, while psychotherapy might be especially effective for those whose obesity is promoted by emotional distress.

### Publications from your own work that are most applicable to the workshop objectives:

- Tanofsky-Kraff M, Shomaker LB, Wilfley DE, Young J, Sbrocco T, Stephens M, Brady S M, Galescu O, Demidowich A, Olsen CH, Kozlosky M, Reynolds JC, Yanovski JA. Excess weight gain prevention in adolescents: Three-year outcome following a randomized controlled trial. J Consult Clin Psychol. 2017;85(3): 218–227.
- Tanofsky-Kraff M., Cohen ML, Yanovski SZ, Cox C, Theim KR, Keil M, Reynolds JC, Yanovski, JA. A prospective study of psychological predictors for body fat gain in children at high risk for adult obesity. Pediatrics. 2006;117:203-1209.

### Publications from others that are most applicable to the workshop objectives (up to 3 papers):

- Field AE, Camargo CA, Ogino S.The merits of subtyping obesity: One size does not fit all. JAMA. 2013;310: 2147-8.
- Carnell S, Gibson C, Benson L, Ochner C N, Geliebter A. Neuroimaging and obesity: Current knowledge and future directions. Obes Rev. 2012;13:43-56.

## *Elsie M. Taveras, MD, MPH*
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**Biosketch**

Dr. Taveras, MD is Professor of Pediatrics and Associate Professor of Population Medicine at Harvard Medical School, and Professor in the Department of Nutrition at Harvard School of Public Health. She is a board certified pediatrician, clinical epidemiologist, and an obesity researcher. She is the Chief of the Division of General Academic Pediatrics as well as the Director of Pediatric Population Health Management at Massachusetts General Hospital. She co-directs a multi-

disciplinary pediatric obesity management clinic at Massachusetts General Hospital for Children. Dr. Taveras has extensive expertise in epidemiologic investigations into the early life origins of obesity, pediatrics, obesity prevention and treatment, examining racial/ethnic disparities, health services research, and direction of randomized trials. She has led several randomized controlled trials to prevent and manage obesity in different settings including primary care, homes, and communities. Her interventions have included use of health information technology applications for clinicians, remote and mobile technology-enabled health educators, motivational counseling, and linkages to community resources.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

Interventions that include high-quality clinical care for obesity and linkages to community resources result in improved family-centered outcomes for childhood obesity and improvements in child BMI. In the MA-CORD quasi-experimental trial, body mass index (BMI) outcomes were improved for low-income children ages 2-12 years in a comprehensive clinical intervention delivered at two federally qualified community health centers as part of the MA-CORD initiative.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

What is the comparative effectiveness of different strategies for treatment of severe obesity among adolescents?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

- Barriers – severe obesity is difficult to treat.
- Adolescents are sometimes difficult to engage.
- How to involve parents?

**Publications from your own work that are most applicable to the workshop objectives:**

- Taveras EM, Marshall R, Sharifi M, Avalon E, Fiechtner L, Horan C, Orav J, Price SN, Sequist T, Slater D. Connect for Health: Design of a Clinical-Community Childhood Obesity Intervention Testing Best Practices of Positive Outliers. Contemp Clin Trials. 2015 ;45(0 0): 287–295.
- Taveras EM, Marshall R, Horan CM, Gillman MW, Hacker K, Kleinman KP, Koziol R, Price S, Simon SR. Rationale and design of the STAR randomized controlled trial to accelerate adoption of childhood obesity comparative effectiveness research. Contemp Clin Trials. 2013;34(1):101-108.

# *Jack A. Yanovski, MD, PhD*

Chief, Section on Growth and Obesity
Division of Intramural Research,
Eunice Kennedy Shriver National Institute of Child Health and Human Development,
National Institutes of Health

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**Biosketch**

Dr. Yanovski is Chief of the Section on Growth and Obesity, in the Division of Intramural Research of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, one of the National Institutes of Health.  Dr. Yanovski obtained his MD and PhD degrees at the University of Pennsylvania, completed residency training in Pediatrics at the Children's Hospital of Philadelphia and fellowship training in Pediatric Endocrinology at the National Institutes of Health. Dr. Yanovski has carried out clinical studies on the evaluation and treatment of overweight and obesity in children and adults, as well as laboratory investigations of the molecular etiologies of obesity including studies of brain-derived neurotrophic factor and the melanocortin 3 receptor.  Dr. Yanovski has authored over 250 published manuscripts, has served as Chair of The Obesity Society's annual Scientific Meeting, was a member of the expert panel that developed the 2017 Endocrine Society Clinical Practice Guideline on Pediatric Obesity Assessment, Treatment, and Prevention, and has received the Bar-Or Award for Excellence in Pediatric Obesity Research from The Pediatric Obesity Section of the Obesity Society and has twice received the Public Health Service's Outstanding Service Medal for his studies on obesity.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

My laboratory has conducted clinical trials of pharmacotherapy combined with lifestyle modification in adolescents and pre-adolescents with severe obesity that demonstrate the limitations of treatment approaches that are nonselective. In general, such treatments are less efficacious in adolescents than in adults and have not been able to generate weight losses in most participants that are of significant magnitude to improve comorbidities. We have also investigated behavioral phenotypes associated with excessive weight gain in pre-adolescence. A hyperphagic phenotype (sometimes termed loss-of-control or binge eating) can be identified that is associated with greater attentional biases to food stimuli and with undue weight gain over time.  Targeted behavioral approaches to reduce such weight gain have so far not been successful. Finally, multiple genetic loci influence body weight; for some individuals, single gene defects that lead to obesity offer excellent targets for specific therapies expected to lead to better outcomes from therapy.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

- Can we predict with great certainty who will develop severe obesity in adolescence? If not, what research is needed to develop such knowledge, so as to be able to select appropriate pre-adolescents for prevention or early treatment?

- What are the most promising approaches for treatment of severe adolescent obesity? Under what circumstances can we leverage knowledge obtained about adults with extreme obesity to prioritize research into treatments or prevention efforts, and when will this approach not be helpful?
- Can we predict with great certainty who will fail to maintain weight loss among adolescents with extreme obesity who do so by behavioral approaches? If not, what research is needed to develop such knowledge?

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

- Limited funding for pharmacotherapy studies – study sections seem to think drug companies should fund these investigations. Suggest: RFP specifically for treatment approaches for extreme obesity.
- Limited support for long-term observational studies that can be hypothesis-generating. Requires multi-center, team science to negotiate what specific hypotheses will be investigated from many potential genetic, physiologic, behavioral, and psychological realms.
- Waning efficacy of most treatment and prevention approaches. Research needed into how to maintain motivation for long-term behavioral change. Does this require neuromodulation? Is it possible? Support animal model research and translation.
- Difficulties maintaining cohorts of patients with extreme obesity and keeping them in treatment. Could non-traditional (e.g., adaptive) trial designs of combinatorial therapies be supported? Also needed: Research into how to minimize attrition in adolescent samples with low SES (often observed in families with extreme obesity).

**Publications from your own work that are most applicable to the workshop objectives:**

*Limitations of pharmacotherapy for treatment:*

- Sherafat-Kazemzadeh R, Yanovski SZ, Yanovski JA. Pharmacotherapy for childhood obesity: present and future prospects. Int J Obes (Lond). 2013;37(1): 1-15.
- Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, Yanovski JA. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102: 709-757.

*Limitations of diet therapy for treatment:*

- Mirza NM, Palmer MG, Sinclair KB, McCarter R, He J, Ebbeling CB, Ludwig DS, Yanovski JA. Effects of a low glycemic load or a low-fat dietary intervention on body weight in obese Hispanic American children and adolescents: a randomized controlled trial. Am J Clin Nutr. 2013; 97: 276-85.

*Limitations of targeted behavioral therapy for prevention:*

- Tanofsky-Kraff M, Shomaker LB, Wilfley DE, Young JF, Sbrocco T, Stephens M, Ranzenhofer LM, Elliott C, Brady S, Radin RM, Vannucci A, Bryant EJ, Osborn R, Berger SS, Olsen C, Kozlosky M, Reynolds JC, and Yanovski JA. Targeted prevention of excess weight gain and eating disorders in high-risk adolescent girls: a randomized controlled trial. Am J Clin Nutr. 2014;100: 1010-1018.

**Publications from others that are most applicable to the workshop objectives:**

*General state of the art:*

- Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, Urbina EM, Ewing LJ, Daniels SR, American Heart Association Atherosclerosis H, Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young CoNPA, Metabolism, Council on Clinical C. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013;128(15):1689-712.

*Possible better outcomes from specific pharmacotherapy:*

- Kuhnen P, Clement K, Wiegand S, Blankenstein O, Gottesdiener K, Martini LL, Mai K, Blume-Peytavi U, Gruters A, Krude H. Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. N Engl J Med. 2016;375(3):240-6.

*Epigenetics/Genetics of Obesity*

- Locke AE et. al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518: 197-206.
- Kuehnen P, Mischke M, Wiegand S, Sers C, Horsthemke B, Lau S, Keil T, Lee YA, Grueters A, Krude H. An Alu element-associated hypermethylation variant of the POMC gene is associated with childhood obesity. PLoS Genet. 2012;8: e1002543.
- Ding X, Zheng D, Fan C, Liu Z, Dong H, Lu Y, Qi K. Genome-wide screen of DNA methylation identifies novel markers in childhood obesity. Gene. 2015;566(1):74-83.

## Meg Zeller, PhD

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University of Cincinnati College of Medicine
Cincinnati Children's Hospital Medical Center

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**Biosketch**

Dr. Zeller is Professor of Pediatrics at Cincinnati Children's Hospital within the University of Cincinnati College of Medicine and Co-PI/Co-Director of an NIDDK T32 post-doctoral training program in Child Behavior and Nutrition (T32DK063929-14). She is a licensed pediatric psychologist as well as a clinical researcher in the area of pediatric obesity. Dr. Zeller's program of research aims to significantly improve the health and quality of life (QOL) of youth who are obese by identifying psychosocial correlates of pediatric obesity at the child/adolescent, caregiver, or family level that are potential barriers to successful weight loss and maintenance. Dr. Zeller has been continuously funded by the NIH (NIDDK, NIDA; K23, R03, R01s, U01-UM1) with 74 peer-reviewed publications in pediatric obesity. Dr. Zeller leads the field in studies on the psychosocial correlates and risk behaviors that characterize adolescents with severe obesity. She served as the

Behavioral Science Lead/Co-Investigator for the development and launch of the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) Consortium (2007-2016). Her ongoing Teen-LABS ancillary studies are tracking psychosocial health and emerging risks in adolescents with severe obesity who did/did not undergo bariatric surgery into young adulthood. Dr. Zeller has made significant contributions to the pediatric obesity QOL literature, including the development of three condition-specific instruments (i.e., weight/obesity) that are actively being used in clinical programs as well as NIH and industry-sponsored outcome studies.

**What are the most significant findings from your research that could inform our understanding of the development and treatment of severe obesity in adolescents?**

We are utilizing a controlled multi-site U.S. sample of adolescents with severe obesity in clinical weight management settings (bariatric, behavioral) to (1) describe psychosocial characteristics of adolescents with severe obesity, and (2) observe the psychosocial changes and any emerging risks when an adolescent with severe obesity does/does not undergo surgical weight loss and as they age into young adulthood. Key psychosocial/risk domains include psychopathology, social functioning, child maltreatment, family functioning, as well as maternal psychological health and weight status. Across several initial publications, we have demonstrated that, with few exceptions, rates of any of these characteristics are significantly higher (i.e., greater dysfunction) in adolescents in the non-surgical group. This was admittedly unexpected. We speculate these group differences are due to that achieving surgical candidacy involves navigating a complex process with multiple levels of decision-makers (i.e., supportive caregivers, a referring physician, the clinical team, and ultimately, insurance approval) and necessary steps. Adolescents with poorly managed psychosocial health and/or greater family dysfunction may not seek or be referred for surgery, drop out of this intensive clinical care pathway during the preoperative phase, or are subsequently deferred or denied access by the clinical team, all which are important areas for future research. Taken together, our data suggest that adolescent bariatric samples may indeed be a highly selective psychosocial group, yet there is a clinically impaired minority subgroup who undergo surgery. Analyses and publications focused on outcomes are ongoing, with an initial report demonstrating that family factors (pre-/post-/change in) being unrelated to the % of weight lost across the first two post-operative years.

That said, our program of research is also uniquely positioned to publish critically important data that characterize the more typical adolescent with severe obesity – the comparison group of treatment-seeking adolescents with severe obesity not pursuing surgery. Briefly, approximately 40% present with psychological symptomatology outside of the healthy range, with depressive/anxious symptoms the more common subtype. One in every 2-3 females report some form of child maltreatment (i.e., physical, emotional, and sexual abuse and/or neglect), with emotional abuse the most common, and 1 in 10 reporting a history of sexual abuse, specifically. Nearly 3 out of every 4 adolescents (and 1 out of 2-3 caregivers) reported family dysfunction in a clinical range, with notable deficits in family communication, challenges to how the family works together to complete daily tasks, family members showing less interest and investment in each other. In addition, nearly 1 in every 2-3 female caregivers met criteria for her own clinical range psychological distress, with measured rates of female caregiver overweight, obesity (Class 1), and severe obesity ($\geq$ Class 2) at 20.5%, 16.9%, and 55.5%, respectively. These data paint a bleak picture of psychosocial health and risk that should be considered as potential barriers to successful study recruitment and retention, as well as weight loss outcomes and maintenance over time.

**What are 2-3 most pressing questions that need to be addressed in order to advance the development of more effective and targeted treatments for adolescents with severe obesity?**

From a psychosocial health perspective, do we understand this population well-enough? Much of the extant literature is based on clinical samples, and in large part, small subsamples of adolescents with severe obesity considering or undergoing bariatric surgery. Our understanding to date is

potentially biased by a highly selective sample, one that also lacks racial/ethnic diversity and is heavily female.

Based on extant data, both epidemiologic and bariatric, there are clear yet opposing health disparities in adolescent severe obesity, and the majority demographic who seeks and undergoes bariatric surgery (i.e., non-Hispanic White females). What are the drivers of this and how can we get more adolescents to bariatric care? Moreover, current practices and guidelines may not appreciate there may be unique cultural or gender-based nuances to care.

**What are the barriers to and creative ideas for advancing research in order to develop more effective and targeted treatments for adolescents with severe obesity?**

There is a remarkably small literature which examines adherence to prescribed treatment or adherence promotion techniques in the context of weight loss intervention outcomes in adolescents in general, and those who are severely obese, specifically. This is a critical gap, which can be informed by applying theoretical models, standardized definitions and language, actual versus "proxy" measures, and in samples with high retention over time. Moreover, the emerging literature in the role of executive functioning as it relates to adherence to medical regimens in other disease populations, and its potential role in obesity care, are promising steps.

**Publications from your own work that are most applicable to the workshop objectives:**

- Reiter-Purtill J, Gowey MA, Austin H, et al. Peer victimization in adolescents with severe obesity: The Roles of Self-Worth and Social Support in Associations With Psychosocial Adjustment. *J Pediatr Psychol.* 2017;42(3):272-282.
- Zeller MH, Hunsaker S, Mikhail C, et al. Family factors that characterize adolescents with severe obesity and their role in weight loss surgery outcomes. *Obesity (Silver Spring, Md.* 2016;24(12):2562-2569.
- Zeller MH, Noll JG, Sarwer DB, et al. Child maltreatment and the adolescent patient with severe obesity: Implications for clinical care. *J Pediatr Psychol.* 2015;40(7):640-648.

**Publications from others that are most applicable to the workshop objectives:**

- Hayes JF, Eichen DM, Barch DM, Wilfley DE. Executive function in childhood obesity: Promising intervention strategies to optimize treatment outcomes. *Appetite.* 2017. May 26. pii: S0195-6663(17)30154-X. doi: 10.1016/j.appet.2017.05.040. [Epub ahead of print]
- Tanofsky-Kraff M, Shomaker LB, Wilfley DE, et al. Excess weight gain prevention in adolescents: Three-year outcome following a randomized controlled trial. *J Consult Clin Psychol.* 2017;85(3):218-227.

# PARTICIPANT REAKOUT SESSION ASSIGMENTS

*(in alphabetical order by last name)*

| | LAST NAME | FIRST NAME | Break Out Session |
|---|---|---|---|
| A | Alnaim | Lubna | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Appleton-Knapp | Sara | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| B | Bernstein | Shanna | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Bjarnason | Ragnar | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Bremer | Andrew | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Browne | Allen | Treatment Approaches for Severe Obesity in Adolescents |
| | Burke | Nastasha | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| C | Camp | Diane | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Casagrande | Sarah | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Chao | Ariana | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Chung | Stephanie | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Courville | Amber | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Cowie | Catherine | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Curtis | Leslie | Treatment Approaches for Severe Obesity in Adolescents |
| E | Eichen | Dawn | Treatment Approaches for Severe Obesity in Adolescents |
| | Esposito | Layla | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| F | Fay | Monica | Treatment Approaches for Severe Obesity in Adolescents |
| | Fiedorek | Fred | Treatment Approaches for Severe Obesity in Adolescents |

| | | | |
|---|---|---|---|
| | Fischer | Dena | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Fisher | Rachel | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | FitzSimmons | Stacey | Biomarkers and Phenotypes that Predict Response to Treatment |
| **G** | Gannot | Gallya | Treatment Approaches for Severe Obesity in Adolescents |
| | Gowey | Marissa | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Grammer | Anne | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Green | Melanie | Treatment Approaches for Severe Obesity in Adolescents |
| | Greenwel | Patricia | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Gross | Amy | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| **H** | Haft | Carol | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Hales | Craig | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Horlick | Mary | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Hunsaker | Sanita | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Young-Hyman | Deborah | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| **J** | Jaramillo | Manuela | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Jenkins | Todd | Treatment Approaches for Severe Obesity in Adolescents |
| | Joseph | Paule | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| **K** | Karp | Bob | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Kelsey | Megan | Treatment Approaches for Severe Obesity in Adolescents |
| | Kowtha | Bramaramba | Treatment Approaches for Severe Obesity in Adolescents |
| **L** | Lightbourne | Marissa | Treatment Approaches for Severe Obesity in Adolescents |

| | | | |
|---|---|---|---|
| | Lipsky | Leah | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Lubna | Alnaim | Biomarkers and Phenotypes that Predict Response to Treatment |
| **M** | Mackey | Eleanor | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Maruvada | Padma | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Mirza | Nazrat | Treatment Approaches for Severe Obesity in Adolescents |
| | Moghadam | Yasmin | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| **N** | Nadeau | Kristen | Treatment Approaches for Severe Obesity in Adolescents |
| | Nansel | Tonja | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| **P** | Pratt | Charlotte | Treatment Approaches for Severe Obesity in Adolescents |
| | Pratt | Janey | Treatment Approaches for Severe Obesity in Adolescents |
| | Price | Paula | Biomarkers and Phenotypes that Predict Response to Treatment |
| **R** | Rhee | Kay | Treatment Approaches for Severe Obesity in Adolescents |
| | Rose | Meredith | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Ross | Sharon | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Ryder | Justin | Treatment Approaches for Severe Obesity in Adolescents |
| **S** | Santos | Melissa | Treatment Approaches for Severe Obesity in Adolescents |
| | Saslowsky | David | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Sato | Sheryl | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Schvey | Natasha | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Shaibi | Gabriel | Treatment Approaches for Severe Obesity in Adolescents |
| | Shank | Lisa | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |

| | | | |
|---|---|---|---|
| | Sim | Leslie | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Sisley | Stephanie | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Smith | Jaime | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Stoeckel | Luke | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Sweeney | Brooke | Biomarkers and Phenotypes that Predict Response to Treatment |
| **T** | Teff | Karen | Biomarkers and Phenotypes that Predict Response to Treatment |
| **U** | Unalp-Arida | Aynur | Biomarkers and Phenotypes that Predict Response to Treatment |
| **V** | Vargas | Ashley | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| **W** | Weinstock | George | Biomarkers and Phenotypes that Predict Response to Treatment |
| | Wilkins | Kenneth | Treatment Approaches for Severe Obesity in Adolescents |
| | Winer | Karen | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| | Woo | Jessica | Epidemiology and Subgroups at Risk including Disparities and Special Populations |
| **Z** | Zappala | Giovanna | Biopsychosocial and Behavioral Factors Associated with the Development of Severe Obesity |
| | Ziss | Randy | Biomarkers and Phenotypes that Predict Response to Treatment |

# NOTES

# NOTES