

Obesity is a multifaceted condition that involves the interplay of diet, genetics, and many other factors, even the microbiome. In a recent study in mice, highlighted in this chapter, researchers found that small, antenna-like projections called primary cilia (shown here in green) on brain cells (shown here in purple) have a critical role in a known “hunger circuit,” which receives signals from the body to control appetite. Changes in these antenna-like structures could produce a “short circuit” leading to overeating. The researchers provide evidence showing that two proteins work together specifically in primary cilia of brain cells to regulate appetite and body weight and provide new insight into the role of primary cilia in obesity. This recent discovery could lead to new approaches to treating and preventing obesity.

Image courtesy of Christian Vaisse, M.D., Ph.D., University of California San Francisco.

Obesity

Obesity has risen to epidemic levels in the United States. Individuals who have obesity may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders within the NIDDK's mission. Nearly 40 percent of U.S. adults are considered to have obesity based on body mass index (BMI), a measure of weight relative to height.¹ More than 18 percent of children and adolescents also have obesity, and thus are at increased risk for developing serious diseases both during their youth and later in adulthood.^{1,2} Obesity disproportionately affects people from certain racial and ethnic groups and those who are socioeconomically disadvantaged.

The high prevalence of obesity in the United States is thought to result from the interaction of genetic susceptibility with behaviors and factors in the environment that promote increased caloric intake and sedentary lifestyles. Diet, activity, and aspects of our environment may also modify biologic factors in ways that promote obesity. Research is providing the foundation for actions to address this major public health problem by illuminating the causes and consequences of obesity, evaluating potential prevention and treatment strategies, and providing an evidence base to inform policy decisions.

The NIDDK supports a multi-dimensional research portfolio on obesity, spanning basic, clinical, and translational research. NIDDK-funded studies investigate a variety of approaches for preventing and treating obesity. These span behavioral and environmental interventions in families and in health care and other settings, using a variety of approaches and technologies; surgical interventions; and combinations of strategies. In parallel, Institute-supported investigations into the biologic processes associated with body weight have continued to spark new ideas for intervention approaches. To help bring research results to those affected by obesity and their families, health professionals, and the general public, the Institute sponsors health information programs.³

The NIDDK also continues to play a leading role in the NIH Obesity Research Task Force. The NIDDK Director co-chairs the Task Force along with the

Directors of the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The Task Force includes representatives from these and numerous other NIH Institutes, Centers, and Offices.

Highlights of recent advances from NIDDK-supported research on obesity are provided in this chapter.

THE BRAIN'S REGULATION OF APPETITE, ENERGY BALANCE, AND OBESITY

“Sensing” a Genetic Predisposition to Obesity: New research suggests a mechanism by which antenna-like sensory projections, called primary cilia, located on brain cells play a role in the genetic predisposition to and development of obesity. Primary cilia are found on many types of cells, and defects in these structures contribute to a wide range of human diseases collectively called ciliopathies. For reasons that have

¹ Hales CM, et al. 2017. CDC. National Center for Health Statistics Data Brief No. 288.

² For children and adolescents, obesity refers to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).

³ NIDDK Weight-control Information Network, <http://win.niddk.nih.gov/index.htm>

remained unclear, certain ciliopathies typically result in obesity. Mutations in some genes that produce proteins located in primary cilia cause obesity in both mice and humans, and recent studies have suggested a role in human obesity for the protein ADCY3, which is specifically found in primary cilia of brain cells.

In this study, scientists investigated whether another protein, MC4R, which is found on the surface of brain cells and transmits appetite-regulating information, could be involved in a primary cilia signaling pathway. Several known mutations in the gene encoding MC4R cause severe obesity in people; similarly, in mice, deletion of the gene that produces MC4R induces severe obesity. For the first time, the researchers were able to visualize the precise cellular location of MC4R in the brains of male and female mice by using a fluorescent tag along with imaging technology. The scientists discovered that, in a group of brain cells whose job it is to communicate information about appetite to the rest of the brain, MC4R is located in close proximity to ADCY3 on the primary cilia. Furthermore, when they introduced a known human obesity-associated mutation into the gene encoding MC4R in mice, MC4R no longer traveled to the primary cilia with ADCY3, suggesting that the mutation may cause obesity by disrupting the protein's localization to cilia. To determine if MC4R and ADCY3 work together at primary cilia to regulate body weight, the researchers blocked the function of ADCY3 specifically in MC4R-containing brain cells in mice. The mice increased their food intake and gained significantly more weight than mice with functional ADCY3.

Taken together, these results suggest that ADCY3 and MC4R work together specifically in primary cilia of brain cells to regulate appetite and body weight, and provide new insight into the role of primary cilia in obesity. Further research could determine if additional proteins have a role in the brain's primary cilia and may suggest new approaches to treating or preventing obesity.

Siljee JE, Wang Y, Bernard AA, ...Vaisse C. Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity. Nat Genet 50: 180-185, doi: 10.1038/s41588-017-0020-9, 2018.

Your Brain on Food—How Genetic Variants Increase Obesity Risk Through Impaired Brain Signaling and Augmented Appetite: In the largest study of its kind to date, researchers used imaging technology to show that certain DNA sequence variants in a gene called *FTO* (fat mass and obesity-associated) raise obesity risk in humans by disrupting brain processing, leading to a weakened sense of fullness and subsequent overeating. It is well-known that DNA variants in a particular region of the *FTO* gene increase obesity risk, and people with “high-risk” variants prefer high-fat foods and tend to eat more. However, a direct link had not been established between these genetic variants and how the brain processes rewarding aspects of food and feeling full after a meal.

The team of scientists recruited both men and women with high-risk and lower-risk variants of the *FTO* gene. While the participants had a range of body mass indexes (a measure of weight relative to height), the majority had obesity. The investigators compared subjective reporting of appetite between the groups with high-risk and lower-risk *FTO* gene variants, in addition to comparing appetite-regulating hormones, food intake, and brain response to visual food cues before and after a meal. They found that the group with the high-risk *FTO* gene variant consistently reported feeling less full than their counterparts with lower-risk *FTO* variants. Compared with the lower-risk group, high-risk individuals rated calorically dense, “fattening” foods as more appealing. Moreover, when presented with a buffet meal, those with the high-risk *FTO* variant consumed approximately 350 more calories compared to individuals with a lower-risk genetic variant. Using brain imaging technology, the researchers found that the high-risk group experienced greater activation in certain brain regions with known roles in food reward and food motivation when they were presented with images of fattening foods both before and after a meal; this activation was directly linked to greater food intake. In contrast, participants in the lower-risk group experienced greater brain activation when presented with images of low-calorie food, especially after a meal. Blood sample analysis provided no evidence that appetite-regulating hormones were responsible for differences in brain processing.

Taken together, these findings point toward a brain processing mechanism associated with certain *FTO* gene variants driving decreased satisfaction after a meal, which can lead to overconsumption of food in individuals with these high-risk genetic variants. However, the researchers point out that it is also possible that genes other than *FTO* that predispose for obesity act upon the same brain pathways and contribute toward the overall effect. In addition, it is possible that individuals' dietary habits prior to this study influenced results, based on prior research showing that access to a high-fat diet in rodents increases activity of *FTO* in certain brain regions. Additional studies could provide greater insight into the role of *FTO* genetics, brain processing, and obesity.

Melhorn SJ, Askren MK, Chung WK,...Schur EA. *FTO* genotype impacts food intake and corticolimbic activation. *Am J Clin Nutr* 107: 145-154, doi: 10.1093/ajcn/nqx029, 2018.

From Body to Brain and Back Again—How the Hormone Leptin Utilizes Brain Cell Circuits To Regulate Appetite, Calorie Burning, and Glucose Levels: Scientists have used a new genetic tool in mice to map out the cellular brain circuits used by the hormone leptin to control energy balance (calories consumed versus calories burned) and blood glucose (sugar) levels. Leptin, which is produced in fat tissue, acts in the brain to regulate food intake, promote calorie-burning, and control blood glucose levels following a meal. Leptin deficiency or dysfunction of leptin receptors (molecules on the cell surface with which leptin interacts) results in severe obesity and diabetes in humans. It has been widely suggested that certain types of brain cells called “AGRP” and “POMC” cells, which contain leptin receptors, are essential to carrying out leptin's effects. However, selectively deleting leptin receptors in these cells in mice using traditional genetic manipulation methods has failed to reproduce the obesity and diabetes seen in mice completely lacking leptin receptors, suggesting that other cells may play a key role.

To identify leptin's primary target, researchers used a chemical agent to induce diabetes in male mice, which subsequently leads to leptin deficiency. They then determined the brain region primarily affected by the loss of leptin by measuring brain activity: during leptin deficiency,

one brain region became intensely active, and when they administered leptin, the activity subsided. This finding led the researchers to investigate if this area contained AGRP cells because it is known that leptin suppresses AGRP cell activity. After administering an agent that selectively suppresses AGRP cell activity in diabetic, leptin-deficient mice, the mice experienced significantly reduced blood glucose levels, indicating that AGRP cells play a primary role in leptin responsiveness and blood glucose control. But, why had previous studies deleting leptin receptors in AGRP cells failed to induce diabetes in mice? The answer could lie in the limitations of older, traditional methods.

To explore this further, the researchers used a powerful, new genetic engineering tool—one that had not been used in the previous studies—to selectively delete leptin receptors in AGRP cells of non-diabetic male and female mice. This deletion induced severe obesity and diabetes, increased food intake, and reduced calorie burning. These results suggest that leptin is acting through its receptors on the surface of AGRP cells to induce widespread metabolic consequences. Interestingly, when they performed a similar experiment by selectively deleting leptin receptors in POMC cells, they observed no effect on body weight or blood glucose, indicating that leptin acts primarily on AGRP cells to maintain blood glucose control and prevent weight gain and diabetes. They further investigated the mechanism by which leptin suppresses activity of AGRP cells and found that by acting through its receptor, leptin modifies the function of nearby proteins on the surface of AGRP cells to reduce the cells' activity and modulate communication between cells.

Taken together, these findings identify the critical elements of a brain cell circuit through which leptin governs energy balance and blood glucose levels. Importantly, this study shines a light on the disparity in experimental results that can occur when different gene-altering methodologies are used and suggests a critical need to reexamine previous conclusions drawn from past studies.

Xu J, Bartolome CL, Low CS,...Kong D. Genetic identification of leptin neural circuits in energy and glucose homeostases. *Nature* 556: 505-509, doi: 10.1038/s41586-018-0049-7, 2018.

NEW INSIGHTS INTO THE MOLECULAR REGULATION OF BODY WEIGHT

Genes Newly Associated with Body Weight:

Scientists' recent analysis of hundreds of thousands of human genomes has identified new links between certain gene sequence variations and body mass index (BMI), a measure of weight relative to height. Obesity is a complex condition that can be caused by multiple factors, including a person's genes. Identifying the genes (and the specific natural variations in those genes) that contribute to body weight regulation can provide new information on what causes obesity and how best to treat it. Genome-wide association studies (GWAS) have been used to rapidly scan the DNA of large groups of study participants, with the aim of finding genetic variations linked to differences in BMI. Previously, analyses of common variations identified through GWAS have led to identification of some of the mechanisms involved in regulating body weight. It has been challenging, though, to identify what specific genetic variants govern this regulation, as identified variants were sometimes outside the "exome"—regions of the genome that code for proteins—making it unclear how those variants affect cell function. Further, most GWAS to date have identified fairly common variations, and less common variations may also shed light on the biology of obesity.

To identify more BMI-specific genes and gene variants, researchers scanned only the exomes of over 700,000 individuals who participated in 125 clinical studies, looking for uncommon or rare gene variants that correlated with higher or lower BMI. The study identified 14 uncommon gene variants in 13 genes, with one of the variants only being associated with BMI in females. Eight of these genes had never before been implicated in human obesity. Further investigation of these variants showed that the four that were least common affected BMI on average about 10 times more strongly than more common, previously identified obesity-related variants. Researchers found that many of these newly BMI-associated rare gene variants coded for proteins that are enriched in the brain, and further research is needed to fully understand their role in body weight. None of the identified variants contributed significantly to BMI variation in the overall population, but they may substantially affect the weight of individual

people. Overall, these findings provide new insight into the causes of obesity, which could lead to new therapeutic targets and more personalized obesity treatments.

Turcot V, Lu Y, Highland HM, ...Loos RJF. Protein-altering variants associated with body mass index implicate pathways that control energy intake and expenditure in obesity. Nat Genet 50: 26-41, doi: 10.1038/s41588-017-0011-x, 2018.

Examining the Effects of Weight Gain and Loss—Multiple Molecules at a Time: In a controlled study of weight gain and loss, researchers have assembled a comprehensive molecular profile of dramatic changes that occur in humans during short periods of weight fluctuation. By using a variety of different analytical methods on a large scale, they collected more than 2 million measurements that provide a window into the dynamic nature of the molecular, metabolic, and gut bacterial changes in study participants during weight gain and loss.

The team of scientists selected 23 men and women who volunteered for the study and were overweight or had moderate obesity. While none of the participants had diabetes, they differed in their levels of insulin sensitivity or insulin resistance. People who are insulin-resistant (IR) require greater amounts of insulin, a hormone made by the pancreas, to maintain blood glucose (sugar) levels than people who are insulin-sensitive (IS), and they are more likely to develop type 2 diabetes and associated complications later in life. Therefore, the researchers performed a weight gain/loss intervention on weight-matched individuals with different insulin-sensitivity profiles to identify specific molecules and signaling pathways that could be involved in weight-related insulin resistance. At the study's onset, the investigators analyzed participants' biological samples (blood and stool) and found that differences in protein levels and gut microbial populations already existed between IR and IS individuals. For example, IR individuals exhibited molecular markers for inflammation in their blood. Because people with type 2 diabetes are known to have inflammation, this could potentially be an early warning sign for future disease. All participants then went on a controlled, high-calorie diet for 30 days, during which time each individual consumed approximately 880 excess calories daily and gained an average of 6 pounds. With just this modest amount of weight gain, molecular markers for fat metabolism, inflammation, and heart disease

increased in both IR and IS participants, potentially providing a biological explanation for the link between weight gain and heart failure. In addition, the researchers observed a dramatic increase in numbers of a type of gut bacteria known to protect against insulin resistance in response to weight gain in animal models, but this increase only occurred in IS individuals. The weight gain period was followed by a 60-day period of calorie restriction designed for participants to return to their original weight. Notably, most biomolecules, pathways, and microbes that were disrupted by weight gain returned to normal levels with weight loss, suggesting that deleterious effects of short-term, modest weight gain can be mitigated with dietary intervention. Some effects, however, continued post-weight loss, indicating some longer-lasting consequences of even a brief period carrying extra pounds.

Taken together, these results provide a dynamic picture of the human body's molecular response to weight fluctuation and illustrate how even short-term periods of modest weight gain can affect metabolism, the gut microbiome, and heart health. Moreover, this research highlights the fact that individuals are unique at the molecular level and emphasizes the need for personalized analysis in medicine. Further studies with the publicly available data generated by this study could lead to personalized, predictive molecular signatures for type 2 diabetes and other weight-related conditions long before a disease manifests.

Piening BD, Zhou W, Contrepois K,...Snyder MP. Integrative personal omics profiles during periods of weight gain and loss. *Cell Syst* 6: 157-170, doi: 10.1016/j.cels.2017.12.013, 2018.

Restricted Feeding Leads to Metabolic Benefits

in Mice: Scientists found that feeding mice twice a day, with complete food restriction in between, improved metabolism and prevented age- and obesity-associated metabolic defects compared to allowing them 24-hour access to food. Previous research demonstrated that fasting can lead to improved metabolic health and extended life. Fasting has been shown to activate a cellular process called “autophagy” that removes damaged parts of cells, and this process decreases with obesity and/or aging. If autophagy is responsible for the metabolic improvements associated with caloric restriction the scientists hypothesized that a feeding strategy that induced robust autophagy—without needing to

restrict calories or alter the type of food consumed—might lead to metabolic benefits.

To test this hypothesis, the researchers developed a twice-a-day (TAD) feeding model where mice were fed only during two intervals—one early and one late in a 24-hour period. TAD mice were compared to a group that had 24-hour access to food, but were otherwise identical. Importantly, both groups ate the same amount of food. The scientists found no difference in body weight between the two groups of mice fed a healthful diet after 1 year, but observed that the TAD mice had less body fat and an increase in muscle mass. Additionally, TAD mice fed a diet that typically causes weight gain and metabolic problems were protected from these. TAD mice also showed lower blood glucose (sugar) and lipid (fat) levels and an increase in energy expenditure. By comparing young TAD mice to old TAD mice, the scientists observed that the TAD feeding prevented metabolic defects associated with aging. Studying the impact of the TAD feeding in multiple tissues—liver, fat, muscle, and brain—the scientists found that the diverse metabolic benefits of TAD feeding were linked to changes in daily cycles of autophagy. The results raise the possibility that twice-a-day feeding could have similar benefits in humans, although it remains to be tested; and many other factors, such as genetic makeup, may influence the benefits in people.

Martinez-Lopez N, Tarabra E, Toledo M,...Singh R. System-wide benefits of intermeal fasting by autophagy. *Cell Metab* 26: 856-871., doi: 10.1016/j.cmet.2017.09.020, 2017.

CIRCADIAN RHYTHMS AND OBESITY

The Timing Is Everything—Understanding How Obesity Alters the Liver's Circadian Clock:

Researchers have gained new insights into how obesity influences the “circadian” activity of genes in mouse liver, and found that administering medicine at a certain time of day—to align with that circadian activity—results in better metabolic outcomes. It is known that in animals and humans, biological “circadian clocks” regulate behavior and bodily processes, harmonizing them with daily, rhythmic changes in the environment, most notably day/night cycles. In humans, altering normal circadian rhythms with changes in the

timing of behaviors such as sleep and eating—for example, during night shift work—increases susceptibility to diabetes, obesity, and other metabolic disorders. In new research, scientists studied the underlying mechanisms by which obesity affects circadian rhythms in the liver, an organ that plays a key role in metabolism.

First, the researchers examined global gene activity in the livers of male mice throughout the day and night, comparing obese mice eating a high-fat, high-sugar diet with control animals eating a normal chow diet. They discovered that global circadian gene activity was significantly altered in the obese mice compared to the control mice. Next, they studied the new circadian gene activity patterns in the obese mice, making the surprising finding that genes involved in the opposing metabolic processes of producing and burning fatty acids (key components of both solid fat and fat in the blood) developed a circadian rhythm that was not present in control mice. Further experiments allowed them to “zero in” on proteins that were playing important roles in these processes—SREBP and PPAR α . Both proteins are transcription factors, which control whether genes are “turned on” or “turned off.” Previous research had shown that SREBP is an important regulator of cellular processes related to fatty acid production, while PPAR α plays a key role in fatty acid burning. In fact, PPAR α is targeted and activated by drugs used clinically to lower fat levels in the blood. In the study, the scientists showed that the levels of SREBP and PPAR α varied much more throughout the day and night in obese mice compared to control mice. Based on this observation, the scientists questioned whether giving obese mice a PPAR α -activating medicine would be more effective when PPAR α was at its highest level. Indeed, administering the drug at the time when PPAR α levels were at their peak resulted in improved metabolic outcomes in mice after 3 weeks, including reducing fat in the animals’ liver and blood, compared to animals getting the drug at a time of day when PPAR α levels were lower.

These results show that obesity causes major changes to circadian gene activity in mouse liver, and these changes influence fatty acid production and burning. They also suggest that the timing of administering some drugs that lower fat in the

blood may be an important factor to consider related to maximizing their effectiveness. Further research could help determine if the results hold true in people, toward finding novel ways to combat obesity-associated conditions.

Guan D, Xiong Y, Borck PC, ...Lazar MA. Diet-induced circadian enhancer remodeling synchronizes opposing hepatic lipid metabolic processes. Cell 174: 831-842, doi: 10.1016/j.cell.2018.06.031, 2018.

RESEARCH TOWARD IMPROVING HEALTH IN PREGNANCY

Understanding Calorie Burning in Early Pregnancy—Moving Toward Improving Health for Mothers and Children: New research is shedding light on calorie consumption and calorie burning in early pregnancy in women with obesity, which could inform strategies to promote healthy gestational weight gain and reduce racial disparities in pregnancy outcomes. Because of increasing rates of obesity, larger numbers of women than ever before are entering pregnancy with obesity. Pregnant women with obesity are more likely to have excess gestational weight gain. They are also at higher risk of developing other complications, such as gestational diabetes, disorders related to high blood pressure (e.g., preeclampsia) and having a baby with high birth weight. Racial disparities during pregnancy also exist. For example, pregnant African American women are more likely than White women to have complications such as gestational diabetes, preeclampsia, stillbirth, preterm birth, and weight retention after giving birth. In new research, scientists examined calorie (energy) intake and energy expenditure (calorie burning) in early pregnancy in women with obesity to identify factors that could promote healthy pregnancies and reduce racial health disparities.

Researchers studied healthy, pregnant women with obesity from different racial/ethnic backgrounds at 13 to 16 weeks of gestation. In their first analysis, which included data from 72 women, the researchers sought to identify factors that may influence excess gestational weight gain. They found that 88 percent of participants were sedentary, 12 percent were moderately active, and none were highly active. Furthermore, they found that energy expended

during sedentary activities (e.g., rest and sleep) accounted for nearly 70 percent of the women's daily total energy expenditure, and that energy expenditure from activity (e.g., exercise) was low. The researchers also discovered variability in the rate at which the participants burned calories regardless of their activity level: over a quarter of them had a low metabolic rate, which means they burned fewer calories than women with average or high metabolic rates and thus may have been more susceptible to excess gestational weight gain. Based on the energy expenditure measurements from their experiments, the researchers determined that the number of calories that the women should be consuming to maintain appropriate gestational weight gain was lower than what is estimated based on currently used models; those models were developed based on data primarily from women without obesity. Together, these findings identify three factors that could be contributing to excess gestational weight gain in women with obesity: current recommendations related to caloric intake during pregnancy may overestimate the needs of women with obesity, pregnant women with obesity have low activity levels, and some women have a low metabolic rate.

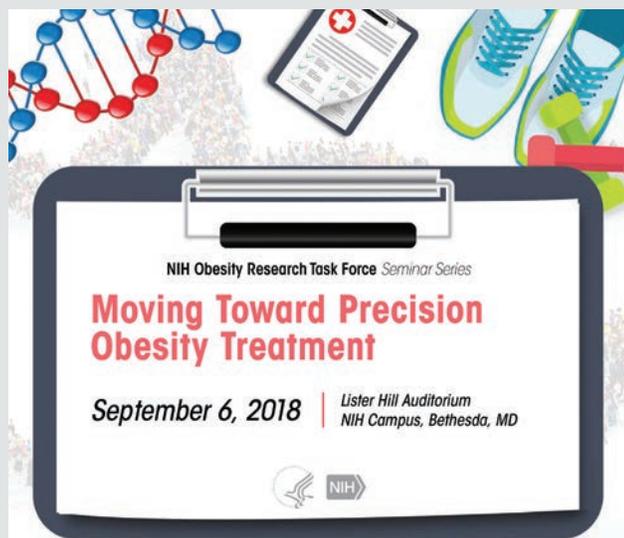
In their second analysis, which included data from 66 African American and White women, the researchers sought to identify biological factors that predispose African American women to worse pregnancy outcomes. They found that African American women consumed fewer calories than did White women, but there was no racial difference in physical activity levels, which were low in all women. However, after

adjusting for individual differences in body weight and body composition (proportions of fat and lean mass in the body), African American women were found to burn significantly fewer calories than White women. Based on that finding and similar to results described in the first analysis, the researchers calculated that current recommendations for caloric intake during pregnancy, which do not differ by race, may overestimate the needs of African American women with obesity. Although studies have shown that African American women do not have higher rates of excess gestational weight gain than White women, it is possible that the lower energy expenditure in African American women may contribute to their higher risk of excess weight retention after giving birth—making it more likely that they will have higher levels of obesity in subsequent pregnancies. Further research to develop interventions to address the newly identified factors associated with energy expenditure during pregnancy, such as personalizing guidelines related to caloric intake and developing strategies to promote physical activity during pregnancy, could help support healthier pregnancies, reduce racial disparities, and improve health outcomes for mothers with obesity and their children.

Most J, Vallo PM, Gilmore LA, ...Redman LM. Energy expenditure in pregnant women with obesity does not support energy intake recommendations. *Obesity* 26: 992-999, doi: 10.1002/oby.22194, 2018.

Most J, Gilmore LA, Altazan AD, ...Redman LM. Propensity for adverse pregnancy outcomes in African-American women may be explained by low energy expenditure in early pregnancy. *Am J Clin Nutr* 107: 957-964, doi: 10.1093/ajcn/nqy053, 2018.

NIH Obesity Research Task Force Seminar Series: Moving Toward Precision Obesity Treatment



A significant challenge in developing better obesity treatment strategies is the large amount of individual variability in treatment response, and it has become clear that a one-size-fits-all treatment plan is not the most effective approach. Precision or personalized medicine is defined as medical care that is designed to optimize therapeutic benefits by targeting the needs of the individual based on differences in people's genes, environments, and lifestyles. Four leading scientists—Mr. Eric Dishman and Drs. Michael Snyder, Elizabeth Speliotes, and Nancy Sherwood—highlighted their research on precision medicine in general and on precision obesity treatments at a September 2018 seminar at the NIH in Bethesda, Maryland. Dr. Penny Gordon-Larsen moderated a panel discussion following the presentations. The research presented was supported by several NIH Institutes, including NIDDK. The seminar was organized as part of the NIH Obesity Research Task Force seminar series.

As the Director of the *All of Us* Research Program at the NIH, Mr. Dishman leads the agency's efforts to build a national cohort of one million or more U.S. participants to advance precision

medicine. But, it is his personal journey that set him out on this path. After battling a rare form of kidney cancer for more than two decades, Mr. Dishman became cancer-free thanks to early access to precision medicine that clarified the right treatment plan for him. But, not everyone has such access to state-of-the-art medical care. Therefore, a major goal of *All of Us* is to focus on health disparities, enrolling volunteers from communities that have been historically underrepresented in research to make the program the largest, most diverse resource of its kind. The *All of Us* Research Program launched nationally in May and currently has more than 100,000 participants enrolled from all 50 states. As the program continues to grow, Mr. Dishman hopes the study will accelerate the path from bench research to bedside medicine for many conditions, including obesity, ultimately getting the right treatment to the right person at the right time. People interested in signing up for the *All of Us* Research Program can find more information at www.joinallofus.org/en

Dr. Snyder's research is centered around the "omics" revolution in which entire complements of molecules such as genes and proteins (genomes and proteomes, respectively) in an organism can be readily characterized. Using a variety of approaches to "omics" profiling, Dr. Snyder and his group are increasing understanding of variation in individual human health that could ultimately lead to more effective ways of predicting disease risk and managing personalized treatment plans. For example, in a recent study, Dr. Snyder's group provided a dynamic picture of the human body's molecular response to weight fluctuation and illustrated how short-term periods of modest weight gain can affect metabolism, the gut microbiome, and heart health. This work could lead to predictive molecular signatures for weight-related conditions, such as type 2 diabetes, long before a disease sets in. A complete write-up of this study can be found earlier in this chapter.

As obesity has reached epidemic proportions in the United States, Dr. Speliotes has focused her research on why some people do not develop obesity in an obesity-promoting environment and why some people with obesity do not develop its complications, including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. Shining a light on variations in human disease processes is critical for precision care. To that end, Dr. Speliotes and her team have carried out large-scale analyses in humans to identify genetic variants that are associated with body fat distribution. Because different regions of body fat associate with different obesity complications, identifying genetic variants associated with body fat deposition can potentially lead to new therapeutic targets.

Standard behavioral weight loss programs can help people achieve meaningful weight loss. However,

only about half of participants typically achieve that goal, illustrating once again that a “one-size-fits-all” intervention is not the best strategy. To increase the amount of people who experience significant weight loss, Dr. Sherwood and her colleagues are conducting Sequential Multiple Assignment Randomized Trials (SMART), which are clinical trials that include adaptive interventions that allow the investigators to alter treatment type throughout the trial. In other words, these trials seek to find which intervention being tested works best for each individual participant. Personalized adaptive interventions have the potential to increase weight loss and improve health outcomes for people with obesity.

Continued research in this important area of precision medicine can potentially reveal better ways to personalize obesity treatment plans and deliver the right treatment to the right person at the right time.