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Advances in Genetic Obesity Management Across Syndromic & Monogenic Obesity

Announcer Introduction:

Welcome to CME on ReachMD. This activity titled, Advances in Genetic Obesity Management Across Syndromic and Monogenic Obesity, is provided by Clinical Care Options, LLC, and is supported by an educational grant from Novo Nordisk Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Stanford:

It's a delight to be here to talk to you today about advances in genetic obesity management across syndromic and monogenic obesity. I do want to introduce our faculty for today. I have Dr. Stephanie Sisley, who's an Assistant Professor in the Department of Pediatrics at Baylor College of Medicine in Houston, Texas, and myself, Dr. Fatima Cody Stanford, an Obesity Medicine Physician Scientist at Massachusetts General Hospital, and Harvard Medical School where I serve as an Associate Professor in the Neuroendocrine Unit and Pediatric Endocrinology in the Department of Medicine.

Our disclosures are listed here. And the fact that we've reported the relevant financial relationships or relationships to products or devices, you can see them listed here. And I do want to go over our four learning objectives for today, which include the following, we want to recognize the clinical features that warrant further diagnostic workup for rare genetic causes of severe childhood obesity. We do want to apply strategies that support patients with genetic obesity in their families. We want to evaluate the current clinical efficacy and safety evidence of the melanocortin 4 receptor agonist treatment in the management of genetic obesity. And finally, we want to identify patients who would benefit from setmelanotide treatment as a part of holistic management of genetic obesity.

Now, this is an outcomes analysis presentation, and so we're going to be assessing what did you learn. Some questions in this activity will be presented twice, once before the content and then again later in the activity. So you can see we have the question, which was the pre-education, the educational content that we'll be presenting here today, and then finally, a post-education question. All responses will only be measured in aggregate, meaning you will not be identified with your individual responses. And we want to thank you so much in advance for helping us to assess the impact of this educational activity on your learning.

And we're going to start with a quick survey. How many patients with genetic causes of obesity do you provide care for in your practice? Is it 1 to 5 patients; 6 to 10 patients; 11 to 15 patients; 16 to 20 patients; greater than 20 patients; or the final responses, I do not provide care for these patients. Please, vote now.

Alright, moving on to our next question. Which of the following would indicate screening for genetic causes of obesity in a pediatric patient? Is it, 1, family history of overweight; 2, hyperphagia, this insatiable desire to eat; 3, an interests in pharmacotherapy for obesity management; or 4, obesity onset at greater than or equal to 10 years of age. Please vote now.

Alright, moving on. Setmelanotide is approved for treatment of which of the following genetic causes of obesity? Is it Alstrom syndrome, POMC, pro opiomelanocortin deficiency of obesity, Prader-Willi syndrome, or SRC1 deficiency obesity. Please vote now.

Alright. When initiating setmelanotide, patients should be counseled on which of the following common adverse events? Is it 1, constipation; 2, dizziness; 3, drowsiness; or 4, skin hyperpigmentation. And please vote now.

Diagnosis of genetic obesity diseases may benefit patients and caregivers in which of the following ways? Number 1, to decrease insurance premium; Number 2, increase access to social services; 3, to reduce stigma; or 4, to eliminate the need for multidisciplinary care. And please vote now.

Alright, so that was all of our questions. Those are going to be very helpful as we navigate now the content of this presentation.

We're going to start with an overview of genetic orders of obesity. And what I want to start off with, always, is thinking about obesity as a disease. We know it's a multifactorial disease with various phenotypes, clinical presentations, and treatment responses. There are a variety of environmental factors that contribute such as diet and lack of sleep, increased stress, overeating, physical activity, and medications that cause weight gain. And there's common genetic factors. There are some common genetic variants along with impairment of gene expression or function and rare genetic variants. I do also want to put in a plug here for deleting the word obese from your vocabulary. Obese is a label, obesity as a disease; we want to call people appropriately a patient with obesity. And I want us to make sure that we do that as we think about the care of this patient population.

Now, it's important for us to distinguish between syndromic versus monogenic obesity. And so when we're looking at syndromic obesity, this is associated with severe early onset obesity with neurodevelopmental disorders, and a polymalformative symptom - syndrome. So this is including Prader-Willi, Bardet-Biedl syndrome, Alstrom syndrome. And when we're looking at monogenic obesity, this is associated with extreme behaviors related to hyperphagia and insatiable hunger. This is caused by autosomal recessive variants in genes such as leptin, leptin receptor, POMC, PCSK1, and melanocortin 4 receptors.

When we look at the estimated prevalence of rare genetic diseases of obesity, I do want to indicate here what we're seeing, particularly as the U.S. prevalence, so for those of us joining us from out of the country, we don't necessarily have that information available in this presentation. What you can see is POMC deficiency is less than 1,000 individuals. For leptin receptor deficiency, we don't really know. Bardet-Biedl syndrome, 1 out of 140,000 to 160,000 individuals; Alström, less than 5,000; melanocortin 4 receptor mutation, 1 out of 1,000; Smith-Magenis is less than 50,000 individuals; and then Prader-Willi greater than 7,000 individuals, which could be really any number, right?

When we're looking at the clinical characteristics that are indicative of genetic cause of obesity, I really want us to think about this in these four quadrants. We have severe early onset obesity, this hyperphagia or that insatiable hunger, and then genetic variants that are in this green thing. So this is affected by key neuronal circuits that regulate appetite and satiety, and some have multiorgan effects. And then finally, these syndromic features that include developmental delay, failure to thrive, renal, eye, and cardiac disease.

Now, these symptoms do differ depending upon what your genetic disease we're talking about. And Prader-Willi is one that we've been all familiar with for quite some time. It's characterized by failure to thrive in infancy, and then characterized by hyperphagia which onsets between 3 and 15 years of age. It continues until adulthood and may lessen with age. Denial of food, causing distress and behavioral issues. Bardet-Biedl syndrome is characterized by food-seeking and overeating. Melanocortin 4 receptor deficiency is variable severity of hyperphagia and obesity, depending upon whether or not you're homozygote versus a heterozygote. PCSK1 deficiency is persistent diarrhea and failure to thrive in infancy, followed by this hyperphagia. And then the Smith-Magenis syndrome, hyperphagia that occurs in adolescence and continues into adulthood.

And what we have to recognize is that hyperphagia does lead to severe early onset obesity. With this hyperphagia, this is a history of food-seeking behavior, they may be searching for stealing food, waking up at night to find food, eating food when others leave it behind, or even eating non-food items. This leads to, of course, severe early onset obesity and distress for family and caregivers. And we also know that this increased hunger leads to excess energy intake, which contributes to obesity, and this extreme food-seeking behavior can create stress on families, caregivers, and support systems.

Now we do know that obesity is a disease that causes over 200 diseases. Some of them are noted here, including type 2 diabetes, hypertension, dyslipidemia, over 14 cancers, mood disorders, heart disease, reproductive disorders, and liver disease.

And we do know that there's a higher risk of mortality with obesity, and this is particularly looking at obesity in young adulthood. And what we can see here is that there's a 64% higher risk of mortality in those with obesity, and 89% higher risk of later-life cardiovascular disease-related death. And so childhood and adolescent obesity significantly is associated with the risk of premature death because we're starting even earlier than our adults that are developing obesity.

But there are challenges related to monogenic and syndromic obesity. First of all, genetic testing is underutilized. The definition of severe early onset obesity is unclear. There's a lack of awareness amongst health professionals, and clinical features are poorly understood as a relates to both monogenic and syndromic obesity.

So let's talk about this testing for rare genetic diseases of obesity. And you do want to consider testing persons with early onset obesity

and hyperphagia. And these are the clinical practice guidelines particularly related to testing individuals. If they have a history of early onset obesity, which is greater - weight greater than the 97th percentile by age 3 to 5 years old; insatiable hunger, which is characterized as what we call hyperphagia; a family history of severe obesity; obesity with syndromic etiology, so certain neurodevelopmental abnormalities; and resistant to traditional weight management strategies. Adults with severe obesity may have misdiagnosis of genetic obesity despite early onset symptoms. Indeed, I'm seeing that in my practice, where I care for pediatric and adult patients with obesity, some I'm diagnosing in their 30s, 40s, and even 50s that were missed from screening.

So now let's turn over to an assessment question based upon what we've talked about. Which of the following would indicate screening for genetic causes of obesity in a pediatric patient? Is it a family history of overweight; is it hyperphagia; is it an interest in pharmacotherapy for obesity management; or is it obesity at the age of 10 or more of age. So I'm going to give you a chance to weigh in. So let's look at what we find in the next slide. The correct answer is hyperphagia. This would indicate screening for genetic causes of obesity in pediatric patients.

So let's look at the gene panels and testing strategies when we're looking at patients that present as we just discussed. We do have gene panels for certain variants, POMC deficiency, PCSK1 deficiency, leptin receptor deficiency, Bardet-Biedl syndrome, and melanocortin 4 deficiency. There's also genetic testing for Prader-Willi syndrome. And this is a DNA methylation analysis and tests that are assessing deletions, uniparental disomy, and imprinting defects that can be used to confirm a diagnosis and differentiate Prader-Willi syndrome from other syndromes.

Now, this is really important when we're discussing these genetic test results with patients, and I am routinely testing my patients for genetic diseases associated with obesity. And so, you first want to start with that pretest counseling, which you want to include information on what the potential results might be, discuss the risks, the benefits, and limitations of testing. And you want to inform patients on how genetic testing could affect insurance premiums or eligibility. Patients can decline testing, even if you do offer it to them. And then in that post-test counseling, what we want to do is present results in a clear objective and non-directive manner to allow patients to understand information and make their own informed decisions. If a significant pathogenic variant with heritable potential is identified, we do want to encourage patients to share their results with at-risk family members. And we want to refer to a genetic counselor if available if the provider cannot provide further counseling. And so this is really important, I would say that last point, because some people don't feel comfortable as a clinician really explaining this to their patient and need some additional assistance.

So let's look at the role of melanocortin 4 receptor. And as we look at this, we're going to get into some of the pathophysiology. And part of my really exciting part is to really teach you about the melanocortin pathway in the regulation of food, energy, and intake and expenditure. We're going to focus on adipose tissue, so adipose or adipocytes, and leptin, which is a hormone that signals from adipocytes and crosses that blood-brain barrier and can signal down the bottom pathway. Now if it signals down that pathway, we have leptin binding to a receptor. And what we can see is that it actually affects the melanocortin 4-expressing neuron. When we go down the alternate pathway, and I want you to see a minus in that, we're going down the AgRP, or the agouti-related peptide pathway, that happens in the paraventricular nucleus of the hypothalamus. And you can see that that can express in the melanocortin 4. Now when we express down this pathway kind of on the bottom, it leads to decreased hunger and food intake, increased energy expenditure, and decreased weight. So we're going to say that POMC, or the pro-opiomelanocortin pathway, is the more beneficial pathway.

And when we look at this and kind of look at this and expand this, particularly as we're looking at these rare genetic forms of obesity, I want you to kind of hone in on what we're seeing, and people that may have some difficulty seeing what we're kind of, you know, kind of magnifying here, is we're seeing that leptin receptor, and we're seeing several things along this continuum. We have gamma melanocyte stimulating hormone, ACTH, beta melanocyte-stimulating hormone, and alpha melanocyte-stimulating hormone. But it's important to look at the ALMS, which is the Alström syndrome, which is right there on the leptin receptor, the PCSK1, which is specifically they're targeting the POMC pathway, and this being activated in the downstream regulation. And so this is where that that mechanism is happening.

Of course, in these particular situations, particularly when we're looking at these genetic and monogenic forms of obesity, we don't have these things working in the way that they should. And so you can see that these are being crossed out. And so we're not able to stimulate that POMC pathway, that pathway that tells us to eat less and store less in the same way.

So let's talk about setmelanotide, particularly as we just talked about the melanocortin 4 pathway and how this is downregulated when we don't have, you know, we're not traveling down that POMC pathway. So when we can see a setmelanotide is a melanocortin 4 receptor agonists. And it's approved for chronic weight management in patients that are greater than or equal to the age of 6 with monogenic or syndromic obesity due to pathogenic or in certain POMC, PCSK1, leptin receptor deficiency, and confirmed by genetic testing, or Bardet-Biedl syndrome. It's not effective in heterozygous individuals, and it's not approved for polygenic forms of obesity.

Now, when we look at setmelanotide in pediatrics, remembering that 6 is the earliest age that we would prescribe this in patients, this is

looking at 6 to 17 years of age. And what I want you to do is note that when we're looking at POMC, leptin receptor, and Bardet-Biedl syndrome here on our left, we're looking at the mean change in the BMI percent. And we can see that the numbers are small because we have, you know, small numbers of individuals, but see, POMC is most affected, right, we have the greatest mean change in BMI, followed by Bardet-Biedl syndrome and leptin receptor on our left side. What we can see is that mean change in BMI for the 95th percentile also have not just the Z score, but the 95th percentile, with really similar outcomes. And then in patients achieving this BMI Z score change criteria, I want you to notice what we're seeing in the column for POMC, 100% will see a BMI Z score change. With leptin receptor deficiency, 75%, and with Bardet-Biedl syndrome, between 70 and 86%.

So let's talk about setmelanotide, and this is a question for you guys. Setmelanotide is approved for the treatment of which of the following genetic causes of obesity? Is it Alström syndrome? Is it POMC deficiency obesity? Is it Prader-Willi syndrome? Or is it SRC1 deficiency obesity? So I'm going to give you a chance to weigh in.

Reductions are recommended if you have a low glomerular filtration rate characterized by between 15 to 29. And so that's really important for us to know. The common adverse events associated with setmelanotide include skin hyperpigmentation, injection site reactions, headache, GI adverse events, and spontaneous penile erection, which you guys may not have known. When we're doing patient monitoring and counseling, it's important for us to recognize that when we're using this for POMC, PCSK1, or leptin receptor deficiency, we want to discontinue if the patient has not achieved at least 5% of total body weight loss after 12 to 16 weeks of administration. With Bardet-Biedl syndrome, we want to discontinue if the patient has not achieved 5% weight loss after 1 year. So notice that there's some differences there when you compare Bardet-Biedl syndrome to POMC, PCSK1, and leptin receptor deficiency.

The counseling points are the storage and proper administration and possible adverse events and when to seek treatment.

So let's see if you have the answer to this: When initiating setmelanotide, patients should be counseled on which of the following common adverse events? Is it number 1, constipation; is it number 2, dizziness; 3, drowsiness, or number 4, skin hyperpigmentation. So I'm going to give you a chance to weigh in. And so moving over. What we see here is that the correct answer is of course skin hyperpigmentation.

Now I'm going to turn it over to Dr. Sisley, who will give us information about treatments in genetic forms of obesity.

Dr. Sisley:

It's an honor to be here. So we don't have a lot of data unfortunately, on exactly for these rare genetic forms of obesity of other treatments. But this is the average weight loss on kind of the key clinical trials for these particular drugs that are currently approved. So everything above the red line is currently FDA approved for obesity management. And you can see that the ones with asterisks are the ones that are approved in pediatrics. So you have three in pediatrics. The ones below the red line have some weight loss-reducing effects, but they are not currently FDA approved for obesity management.

Now, there are some case series or case reports of the GLP1 receptor drugs in some of the genetic forms of obesity. So what you can see on the left is that people who have melanocortin 4 receptor variants, when you give them liraglutide and compare them to controls, there's no statistical difference. So people who have melanocortin 4 receptor variants should respond to a GLP1 receptor the way you would expect another person to respond.

Now, this is just one case report. But in a BBS person, they gave a liraglutide and then switched to semaglutide, probably because it's an easier administration at once a week. And you can see a really nice decrease in both weight, which is in the blue line, and BMI, which is in the red line. The yellow bars are the change in A1c. So you can actually see as the weight loss came down, that the A1c improved as well. So also showing some effectiveness, actually a fair amount of effectiveness with a GLP1 receptor agonist. So again, we don't have a lot of really great phase 3 clinical trials. But we do have some data that should give you some confidence in trying some of these in someone who has a genetic form obesity.

But just to remind you of the effectiveness of liraglutide. This is not genetic obesity, this is just kind of standard adolescent patients. When they were given in the clinical trial, liraglutide, less than 50% respond. So it's really important to talk to patients when you start these medications, that it's not 100%. And so it's really important to actually assess how are they doing after the 12 or 14 weeks. And if they're not responding, they're just not a responder, right, and you want to pull them off the medication.

Now, I will say the one caveat is when you have genetic forms of obesity, like Dr. Stanford just kind of showed you, the criteria are different because some of the genetic forms of obesity are so complicated. There's so much else going on with them. And so in truth, if I'm treating someone with a drug, even though the FDA approval criteria might say, 'hey, if they don't lose X amount, by this time, stop the drug,' if I see a clinical benefit, for instance, they were gaining 5 pounds a month, and now they stop and they've actually maintain their weight, I would actually say that's probably a clinical win. And I might continue. So you do have to use some just personal

knowledge of the patient and their family when you're doing some of these treatments.

So could you combine setmelanotide with a GLP1 receptor? It's not been currently studied. However, there are some rodent studies that indicate it should be beneficial. And theoretically, the combination of the two drugs should be beneficial. They act on different receptors, they should stimulate different things, and so theoretically, you should be able to actually get a beneficial effect with both of them. But there's no data to support it at this time.

Now, tirzepatide. So the adult effectiveness of tirzepatide came out in June or July of this year. And this is the weight loss trial. And so what you can see is that over three different doses, patients respond very well. Now what I want to point out is right here, even at your kind of lowest target of 5% body weight reduction, the percentage of patients that respond in the adult trials is 85% or greater. And this is kind of the big distinguishing factor, I think, between this drug versus some of the other GLP1 drugs that we currently have available. However, this is not FDA approved right now for obesity management. Hopefully that will come in the near future. And it is certainly not currently approved specifically for any of the rare genetic disorders.

Now, what about bariatric surgery? Because one of the most effective treatments we have right now for obesity management is bariatric surgery. There is a little bit of discord in the literature on this. So if you look at melanocortin 4 receptor variants, if they are heterozygous, there seems to be good evidence that they respond the same way as controls. So you can, you know, confidently talk to a patient and if they have a heterozygous variant and a melanocortin 4 receptor, you should be able to counsel them the same way you would any other person. If they have homozygous variants and the melanocortin 4 receptor though, and I chose this particular graph because it just shows you the individual responses. So these are patients who had vertical sleeve gastrectomy and then what happened after them. And you can see that two of them with those arrows actually converted to a Roux-en-Y because they weren't having as much effectiveness as they wanted. And so there's some case reports out there that show that if you're homozygous for a melanocortin 4 receptor variant, bariatric surgery is really not effective. There's others here where, hey, there is some effectiveness. So I think with that, you really have to counsel your patient, and say that it may not work. And you might want to actually think, kind of think again, about whether or not you're going to send the patient for bariatric surgery, if they're homozygous for the melanocortin 4 receptor.

For all of the other genetic variants out there, we're talking case reports at best. Some of the different genetic variants don't have any case reports. There's, you know, fears of what if you take someone who's cognitively delayed and has hyperphagia, right, and you do bariatric surgery, what's going to happen? And so there's some case reports that say that, indeed, some of these patients struggle and then there's case reports to say they did great. So unfortunately, we need a lot more data on how surgery is going to work in some of these patients.

There's a lot of cool investigational therapies. And so hopefully in a future meeting, we'll be able to talk about a lot of different options. So semaglutide is currently in trials for diabetes in pediatrics. It is – and then for obesity and pediatrics, the trial, I'm not even sure it's started actually but hopefully it will come as well. There's actually, so tirzepatide is a GLP1/GIP dual agonist. There's some GLP1 receptor glucagon dual agonists that are currently in trials. Oxytocin, especially for hypothalamic forms of obesity, is in clinical trials. And then just some other interesting, like intragastric Botox.

Now, how do you manage? So you have someone who's in your clinic, right? How do you manage this person? And I think it's really important to manage the whole person in a holistic manner. You really need to focus first on treatment goals. So typically, if someone comes in and you're managing obesity, your treatment goal is probably weight loss. However, if you have someone who has a genetic form of obesity, because it's such a complex situation, because they may have symptoms like hyperphagia that have to be addressed before you can really even talk about lifestyle changes, you may have different treatment goals. So your first goal, for most of us who do pediatrics, our first goal is weight maintenance. I'm not looking for weight loss, I just want you to maintain your weight for a while because that's a huge clinical win.

For some, it's symptom treatment. So like I said, if you have really bad hyperphagia, all the lifestyle therapies in the world are not going to be effective, because you haven't actually addressed the underlying hunger that is driving that person. If you can address that, then maybe you can actually address different parts of how to eat better, or how to exercise more. So you want to actually consider what is your treatment goal and make that very clear with a family.

What are your options? Well, the currently FDA approved treatments are setmelanotide, the GLP1s, or orlistat. You also though, consider drugs that have weight-reducing effects for their other comorbidities. So for instance, if they have diabetes and they're an adult, more than likely my first-line therapy is going to be to talk about tirzepatide, because it's the best thing that we currently have for weight loss and diabetes at the same time. If they have diabetes, you could get a SGLT2 inhibitor, which has some weight loss-reducing property. So that's going to be maybe my second-line diabetes treatment. And I'm going to use that because I also want to get some of the weight-reducing effects. If they happen to have headaches, might want to try topiramate, or talk to their neurologist and say, 'Hey, do you think we could try topiramate on this individual?' You can also consider off-label therapy. And for anyone who does pediatrics, you

kind of almost are forced to consider off-label therapy if you want to do obesity management.

The one thing you do want to note though, is to check your state laws, especially when dealing with controlled substances. There are certain states that are very, very picky about what they allow for controlled substances with weight - with regard to weight treatment. So you just want to make sure you check your state laws. But you can try some off-label therapy, you just want to make sure that the patient knows this is off label, it is not approved. You want to make sure you document it very clearly in your note, I'm prescribing this for weight. This is – I talk to the patient, they know it's not FDA approved for the indication that I'm using it for.

Obviously, you want to screen for the other comorbidities. And we've already showed you briefly that there are many comorbidities. The guidelines differ on when or what to screen for. It depends on which guideline you're reading. In general, people mostly would agree that you would do an ALT, an A1c, and a lipid panel at least yearly. When do you repeat it? If it hasn't, you know - when would you repeat it less than a year? With significant weight gain or significant weight loss. Sometimes it's actually really beneficial for a family to actually show that, 'hey, you know what, you actually lost this weight, you had this BMI change, and hey, look, your ALT has actually improved, you have become metabolically healthier.' So sometimes that can be really helpful for families to actually see that they're actually improving metabolically. And then you want to do symptom screening for the other comorbidities.

One of the things to note is, especially for obstructive sleep apnea, it's well known that if you have a circadian rhythm disorder, if you are not getting good sleep, then the leptin in your body, the insulin in your body, the GLP1 in your body is not working the way it's supposed to work. So someone who's trying really hard to do lifestyle changes, if they have obstructive sleep apnea and they're not getting good sleep, they're not getting the most benefit from all the changes that they're doing. And so for sleep apnea, specifically, you want to really make sure that that has been addressed and that you talk about that with the patient.

Now, dietary considerations. We know that diet is kind of king when it comes to trying to actually have a healthier weight. If someone has hyperphagia, one of the best resources you can send them to is actually the Prader-Willi Foundation, as they have some resources that you can print out or that the your patient can print out regarding hyperphagia. Essentially, what it comes down to, is making sure especially for patients who have some of these syndromic disorders, if they really never feel full, they basically don't, and they don't know when food is coming, then they feel panicked. And so basically what the recommendation is, is that you schedule the meals. And if you talk to any of these patients and their families, like if they say supper is supposed to be on the dinner table at 6, and it's 6:02, like their child is like, where is the food? You really have to like, stick to the schedule, there's no like kind of play in it. But actually scheduling we are going to have spaghetti at 6 o'clock on Monday, that is what our dinner is. This kind of scheduling and knowing that food is coming is actually really beneficial for them to kind of reduce the anxiety around when am I going to get food again, because they don't ever feel full.

There's little evidence to support specific dietary intervention. So what diet should you say? Or how should you tell them to eat? We don't have any good evidence for specific forms of genetic obesity. We do know that in non-genetic forms, we don't have any data to show superiority of one particular macronutrient composition versus another. This data is 10 years old now, but it's a really good study where they randomized patients to four different diets that are very different in macronutrient composition. And what you can see is that in every single diet, people lost weight. And in every single diet, people gained weight. So there's nothing here that's magic about this. Now what I would say is, when you look at this, why did someone not respond? I don't know. Maybe they couldn't actually stick to it. Maybe their body just didn't respond to it. And so when we're recommending things for our patients, if they tell you this didn't work, or 'I just can't do it,' right, 'This just doesn't fit with my lifestyle,' then 'Hey, no problem. Let's switch to something else. Let's figure out a way that works for you.'

Now, in the adult literature, we know that these particular behavior changes had been linked to successful weight outcomes. So monitoring weight or food diaries, having really good sleep hygiene, family meals, minimizing unprocessed foods, and decreasing screen time. For genetic forms of obesity, you have to take these a little bit with a grain of salt. No one's going to be disrupted by this decreased screen time, that's probably a go no matter who you are, minimizing unprocessed foods also beneficial regardless of who you are. But family meals, you wouldn't think this would be a problem, but we actually just finished focus groups with a group of Smith-Magenis families, and they actually said that it's actually detrimental for their child to sit at a family meal. Because since they have hyperphagia, they are so consumed with what their sibling is eating, how much of that their sibling got, right, 'Who got seconds? I didn't get seconds,' that it's completely disruptive. And in fact, then they want to eat from all of their sibling's plates. And it actually causes more stress for the family and probably increases their own food intake because they're trying to eat everybody else. So for them, it's actually healthier for them to actually have their own plate and eat alone.

So I only bring that up as a story to tell you that when you're looking at things that work in maybe in a general adult or a general kind of pediatric population, you have to really take it back to the individual with genetic forms of obesity because it just might not work in that particular situation.

So the bottom line is treatment has to be individualized. Now, none of us in the 15 to 20 minutes that we get with our patients can go through this entire wheel. But I think what's important to know is that more than likely your patients have more than one thing on this wheel that's actually preventing them from having a healthy weight. And so if there's six things going on that need to be addressed, there's no way you can do that in one visit. But you can address one or two of the things that you feel or they feel like are the most pressing. But then to just continue to encourage them. This is going to be a process over time. And we're going to keep adding to this, as well as when they come back, if they haven't had success, and they're frustrated, and you're frustrated, going back to think, 'What am I missing? What else could be going on here that I just haven't thought through yet?' Something might have changed in their, you know, life, they might have switched schools, or switched, if they have, you know, they may have gone from being home with their family to being in like a group home. And maybe those changes could be affecting what's going on. They could have had someone else start a different medication, and you just - we haven't noticed it, right, didn't happen to bring it up, might have been 6 months ago, but 6 months of that medication has slowly brought on some weight gain, and is preventing them from having the success that they want to have.

It was mentioned that there's significant impact of having obesity on the family and on the patient. And so this is data that we just published, where we took 20 families of - these were all mothers - that had children who had severe early onset obesity. Some of them had known genetic forms of obesity, some of them had presumed genetic forms of obesity where they had a variant of unknown significance, and we can't prove whether it's causal or not. Some of them have negative testing to date. But they all have suffered from severe obesity from a very early age. And what we found was that these families face barriers everywhere. They get pushback from their spouses, from the extended family, they'll want to do a healthy dinner, the child will go to grandma's house. The child can get whatever they want at grandma's house. They will have - or the siblings will be whining about why can't I have this in the house anymore, right? So the moms are constantly having, you know, like people come to them within their own family telling them like it's not right. You know, where's all the food in the pantry? Why can't we eat this anymore? People will say it's their fault that we can do this, right? So there's fighting within the siblings.

There's conflict with schools. Two of our families had CPS called on them because of their child being overweight. They carry a lot of the burden. They feel a lot of guilt. So they really feel like every time they're going to the doctor, they're like, 'What have I done wrong? What are they going to yell at me for?' Sadly, one of the things that came out as one of their primary concerns was protecting their child's self-esteem, and not from other people, but from us, the medical community. They're hesitant to bring their child to us, because they don't want us to call their children names. They don't want us to put ideas into their child's head that they're not good enough, they're not healthy enough. And so there's this battle with them of trying to get the help they need, but also protecting their child, which is heartbreaking for me.

So these are just two of the quotes. And I was trying to tell them like it felt like something was wrong. But I felt like nobody was listening to me. The most frustrating part is that there's not enough education on the situation. There's nothing that can be done to fix the situation. None of the doctors wanted to really tell us anything. Their only answer was always Oh, well, she's overweight.

So now we're going to go into a few cases. So if you have a 6-year-old girl who has early onset obesity, and she presents with hyperphagia and facial abnormalities. Her mother reports that she had swift weight gain after about 2.5 years of age and her current BMI is 31. And we don't have the percentages there, but for a 6-year-old, a BMI of 31 is off the charts. Genetic testing reveals that she has Bardet-Biedl syndrome. She had some comorbidity screening that confirms prediabetes, and then genetic testings for the relatives was recommended. So medical management options, lifestyle modification and supportive care for the family and patient are all offered.

So which of the following medications would you recommend for this patient? Number 1, phentermine/topiramate; number 2, semaglutide; number 3 setmelanotide; number 4, tirzepatide. Vote now. Alright, so you say setmelanotide. I would agree. In this 6-year-old, none of the rest of these are approved. And she has Bardet-Biedl syndrome. So, for Bardet-Biedl syndrome, setmelanotide is one of the drugs that – or is one of the diagnoses that setmelanotide is approved for. Now, if we had it available, tirzepatide should theoretically work, and semaglutide should theoretically work and might be good options, but in a 6-year-old, they are not available to you as an FDA treatment. And unless your patient is willing to spend between $1,500 or more a month, dollars a month on it, it's just not cost effective for most of our patients. So in this particular answer, yes, I think setmelanotide is the best option to go with.

Dr. Stanford:

Alright, so I'm going to cover case number 2. So this is a 25-year-old woman with obesity who struggled with hyperphagia and weight gain starting at 4 years of age. So one of the questions that had come through was talking about like, when do you test adults with obesity? And so this woman began to have this hyperphagia and weight gain very early in life. She has a family history of obesity in her brother and sister, and genetic testing has confirmed that she has PCSK1 deficiency. There's recommended screening which includes, of course, for cardiovascular disease, diabetes, thyroid, and liver function tests. The treatment options, of course, can be medical management, both acute and maintenance, metabolic and bariatric Surgery, behavioral and lifestyle modifications.

Now, what would you think would be a good consideration with regards to this patient for her treatment? Would you recommend for this patient a naltrexone/bupropion? Would you recommend semaglutide? Setmelanotide? Or tirzepatide? Vote now.

Now technically, you know when we look at this, we do know that setmelanotide is approved for those with PCSK1 deficiency; however, these other answers are not necessarily incorrect. When Dr. Sisley was speaking, she was talking about the use of combination therapy. And while we don't necessarily see a lot of data on these things, I can tell you in clinical practice, many of us are using combination pharmacotherapy agents. But I think it's important for us to recognize that different agents could be utilized. Now, of course, you wouldn't be able to sema and tirzepatide concurrently, because they're both GLP1, of course, the GIP being in that tirzepatide component. But I think it's important for us to recognize that different people will have different strategies. And then it's important for us to recognize that there may be different accessibility in certain areas. And so I want to bring that up.

Now I'm going to hand this back over to Dr. Sisley.

Dr. Sisley:

So if you have a 12-year-old boy with obesity, and he also happens to have hyperphagia and rapid weight gain since 2 years of age, his BMI is currently 34. He has type 2 diabetes diagnosed at 10 years of age, and genetic testing at 5 years confirm Prader-Willi syndrome. Medical management for treating diabetes and obesity, the family supportive care and behavioral challenges due to Prader-Willi syndrome are present.

So which of the following medications in this child would be most appropriate for this patient? Number 1, liraglutide; number 2, phentermine/topiramate; number 3, orlistat, or number 4, setmelanotide? Vote now.

In this particular case, this child has Prader-Willi syndrome, is 12 with obesity, so setmelanotide actually isn't FDA approved. There's some data that it might be helpful, but it's currently not FDA approved. So setmelanotide probably isn't an option actually in this child. Liraglutide and phentermine/topiramate would both be FDA approved for obesity treatment, just the obesity, nothing to do with the Prader-Willi because the child is 12. If the child were 10, you would have none of these options. I would agree that I would probably choose liraglutide. Phentermine/topiramate, though, is another really good option. And the one thing is phentermine/topiramate is a pill. So if the child can swallow pills, and liraglutide is a shot, so while liraglutide has a lot of really beneficial things with it, it may be that the child doesn't want to take a shot or actually may have significant behavioral issues if you start giving them a shot. So depending on the family and how they're going to handle that, might actually change which one of these two I would choose. But I think actually either one of those top two options would potentially be an option in this patient. And then Prader-Willi syndrome, hyperphagia is that - is a key component. And both of these medications should actually treat the hyperphagia, or at least would have some impact on it.

So just to summarize our case studies here, the common factors included severe early onset obesity and hyperphagia in all three of these cases. Typical management strategies may not be effective. Right? So if you have someone and they've gone to the dietician, and they're trying to work out, and it's just not working, you might be dealing with a genetic form of obesity. Recognition by healthcare professionals is crucial. It's crucial so that we can actually get them the help that they need. I will say the one patient in our study who – or one of the patients in our study where CPS was called, the pediatrician was instrumental in getting that case resolved, because the child did have a melanocortin 4 receptor variant.

And then diagnosis can actually help with individualized management. So obviously, if you get a diagnosis for a genetic form, then us as providers can go back, we can go to, you know, things like this, and we can learn from each other as to what works and what doesn't work, and what things could come together, what order could you do things, or what other things could be - could come along to actually help someone that may not be kind of general obesity treatment.

And I will let Dr. Stanford close us out.

Dr. Stanford:

So when we're talking about challenges facing diagnosis and treatment of obesity, we know that this - there are many challenges, and Dr. Sisley spent a lot of her time really focused on the challenges that individuals and their families face, particularly with syndromic and monogenic obesity. And this diagnosis really can provide some significant help to those patients and their caregivers.

We talked about stigma. And it's important for us to recognize that there are two common forms of bias in the U.S., and they are weight bias and race bias. So what we know about this weight bias also is that for physicians, based upon which study you're evaluating, that we have the highest likelihood of having bias towards patients with obesity. Based upon studies, it shows that we have 79 to 90% of us that will show either implicit or explicit bias towards patients. So the very persons that they're supposed to be getting care from are the ones that are treating them the worst in these settings.

We want to help families alleviate this feeling of guilt or blame. This is really important because people believe that this is their fault. And we think about obesity as something that someone chooses. And it's really important for us to recognize that in these – the disease of obesity at large, particularly in these genetic forms, that we want to help reduce these feelings of guilt or blame.

We do want to initiate multidisciplinary and specialized care. Many individuals are often involved in the care of these individuals. And so we want to make sure that we want to have the best team for them and prevention of future unnecessary testing is really also key.

So let's finish with the assessment question. The diagnosis of genetic obesity diseases may benefit patients and caregivers in which of the following ways? Is it 1, to decrease insurance premiums; 2, to increase access to social services; 3, to reduce stigma; or 4, eliminate the need for multidisciplinary care. Vote now.

Alright, so we talked about reducing stigma, and this is extremely important in these individuals; spent a little bit of time talking about that. And I'm thankful to see that as one of the responses here. And of course, the answer here is reduce the stigma. And I think it's really important for us as individuals that care for individuals that may have obesity, whether it's a rare form of genetic obesity, to treat patients with the dignity and respect that they deserve, along with their families and other caregivers.

So we have a few conclusions for today, and they include the following, and part of this is what we've done today, we want to educate health professionals about the identification of severe early onset obesity. It's very crucial. Genetic testing can help with proper diagnosis and management of rare causes of obesity, there is free genetic testing for rare forms of obesity. Setmelanotide and other weight loss medications may be beneficial in helping patients with syndromic and monogenic obesity, achieve weight loss and happier, healthier lives.

Moving on to our question-and-answer session, we're going to - actually can you guys go back and pull up the – we're going spend some time talking about some Q&A. And then we're going to go back and forth.

Dr. Sisley:

Alright, so you want me to read you a couple of these that went with your session? So actually something you just had mentioned, where do you typically send patients for genetic testing? Local hospital labs?

Dr. Stanford:

So there - actually, there's a company that actually has a rare form of obesity testing called Rhythm Pharmaceuticals. This is for anyone here in the United States. It is free to us as healthcare providers to register on their system. I can't remember the actual name of the website, was it common genetic?

Dr. Sisley:

Uncommon.

Dr. Stanford:

Uncommon.

Dr. Sisley:

Uncommon Obesity.

Dr. Stanford:

Uncommon Obesity. If you go to that particular site, you can register. I do this for my patients that are presenting in the ways that we talked about earlier today. I think it's important for us to recognize. And really, when we get back, sometimes we get back, not necessarily PCSK1 or POMC, we may get some of these heterozygotes for which we don't know necessarily what to do. I will tell you that there are clinical trials that are underway looking at some of these heterozygotes, particularly for some of the deficiencies that we've talked about today. They are just starting up around the country. And so if you happen to have one of these trials, in your area, I would highly encourage, if your patients do come back with one of these heterozygote forms of obesity. I have - we are not doing that trial at Mass General, the University of Massachusetts actually is running that trial. So we're referring our patients that may benefit to their site for consideration. And so I would encourage you guys to do the same for wherever you're located.

Dr. Sisley:

For the - when seeing adults, when do you test for monogenic obesity?

Dr. Stanford:

So that's a very good question. So when we're looking at adult patients, I think we have to look at their whole history. And what was mentioned is we don't really have a lot of time within a short office visit to often glean what we're doing. But if we see a patient that has struggled with obesity, has tried many therapies, seem to have some of the things that we've talked about, really early onset obesity, significant hyperphagia, these are things that clue me into, I think there's something else going on here. This isn't presenting as simple obesity. And so for example, one of the patients that I just refer to that trial I talked about that's going on, is one of the sites at University of Massachusetts, was a 32-year-old woman that has struggled, she's had multiple forms of treatment, metabolic and bariatric Surgery, both a sleeve and a Roux-en-Y gastric bypass, we've tried her on all forms of both nonapproved and approved treatment of obesity that are FDA - medically - approved by the FDA, some for obesity and some for not. And her response has been minimal at best to many of these therapies. And when we did test her, several different things came back, five different things actually appeared in her genetic tests, which gave her some reassurance and made her understand that she's not someone that just has failed at these therapies, that the therapies failed her. And so when you change that thought process and get people to understand that, 'Look, this isn't about something you're doing wrong, this is about how your body is interacting,' it really is helpful. She does plan to enroll in this trial to get some answers. And so I'm hoping that we see some positive things that she gets randomized to treatment versus placebo.

Dr. Sisley:

And the one thing that we didn't mention in the talk is that if your patient has had a whole exome and it came back negative, that does not mean that you have ruled out all genetic forms of obesity, because you have no idea what gene is going to be discovered next year, and it won't have come out on that testing. So for patients who have had whole exome sequencing, and let's say it was 5 years ago and it was negative, you actually may want to actually have the genetic testing company rerun it, because new things might have come up. And now the way they actually do the algorithms, it might actually come up with a hit. So it's just one thing to note. Sometimes people will get genetic testing back and they're like, 'Oh, well, it was negative, I'm fine.' For whole exome or whole genome for that matter, a negative test doesn't necessarily mean that you've ruled everything out.

Are GLP1 inhibitors approved by insurance for use in patients with syndromic obesity? It is not covered in adults. Many kids are in unfavorable social economic groups. They are not. So the GLP1 inhibitors are only approved for obesity, and it's just obesity. So there's no secondary indication that, okay, it's approved if you have specific genetic forms of obesity; it's either obesity or not. And you're absolutely right, they don't get approved a lot. I'm not even sure I have a 50% rate of getting it approved in my patients. Not sure any –

Dr. Stanford:

So I live in Massachusetts where we tend to have a more favorable environment with approvals. All of our employer-sponsored insurance in Massachusetts do cover these agents. Now when we're talking about those that have Medicare or Medicaid as their primary insurance, which is MassHealth, which became the basis for the Affordable Care Act, we aren't able to get these medications approved. And that is definitely frustrating for those populations that tend to have high vulnerability and high rates of obesity at large, not just these genetic forms of obesity.

Dr. Sisley:

And kind of going with that, so most insurances are not going to cover Saxenda or Wegovy. Do you use Victoza or Ozempic for non-diabetic patients for weight loss? I will say, for pediatrics, it is not going to get approved either, so I don't. Now, if they have diabetes, yes, I do. But I can't get Victoza approved, if I can't get Saxenda approved if they don't have diabetes.

Dr. Stanford:

So sometimes I'm able to get these approved, and I have to finagle the system a little bit. So for example, if we're looking at Victoza, Trulicity, etc., I may be able to get those approved in individuals that don't have diabetes, but have obesity. And it does require some work. So I do work with the companies to try to see what I can do. It requires often a lot of back and forth with prior authorizations. We do have a whole team that works on that at Mass General. So I think we're able to have a little bit greater success because we have a team that is committed to that work. And so they sometimes know tricks of the trade that I don't even know that is able to get it across the finish line for my patients that don't meet criteria for using those medications.

Dr. Sisley:

Have you been successful using a diagnosis code of metabolic syndrome? I've had a couple of my adult colleagues use that one.

Dr. Stanford:

So I do use metabolic syndrome. But what I use often is multifactorial weight gain is my most commonly used ICD-10 code. So multifactorial weight gain is what I will use. And that, you know, really covers a lot of different things.

Dr. Sisley:

One of the questions is: How do you counsel families about drugs that are off label? So I basically tell them, here are the options that are FDA approved. And then if they're less than 12, I have none. So then I will say, 'I have no options for you.' And unfortunately, right, this is just where we're at. So I say, 'The possibility is we could use a drug off label, which means that the FDA has not approved this for how I want to use it. And then this indication I want to use it for your child to be able to help them with their weight gain.' I will say the most common thing that I use off label is going to be a stimulant, an ADHD stimulant, because the insurance companies don't fight back on it. If they're over 6, or over 5, I think there's so many thousands of children on them that they don't actually ever bat an eye at me prescribing an ADHD medication, even though it is very clear in my note that I am doing it for - because I often do it when I feel like the patient has hyperphagia, and so I will do it, and I'm very clear about I'm doing it for hyperphagia, this is how I am treating hyperphagia. I put it in my note. I have discussed it with the family that this is not approved for weight, but it is approved in pediatrics for ADHD. This is why I'm using it. And if the patient has agreed, I've documented in my note that the patient has agreed. However, I will say ADHD medications are controlled stimulants, so check your state laws.

Dr. Stanford:

Absolutely. And in addition to that, I've often used drugs like topiramate. What we find is topiramate is really great for that evening hunger, sometimes it becomes more pronounced in the evening. I do dose the topiramate in the evening, and I do discuss with the parents why we're using it. Often, unfortunately, in many of these situations, we're dealing with families with obesity. So even if we aren't dealing with genetic and syndromic forms of obesity, we know that obesity to be highly heritable. If we have parents with obesity, there's a 50 to 85% likelihood that the child will have obesity. And so in my care of patients that range in age from 2 to 90, I'm often caring for children, parents, grandparents, and in certain situations, I'm even caring for the great-grandparents. They often, because of the fact that I'm treating the family at large, will have trust in me in terms of using other agents that I may start even as early as 2 or 3 years old, for those that are presenting two or three standard deviations above the growth chart at that time, but coming in with a strong family history of severe obesity, but no genetic testing that confirms that this is secondary to any of the things we've discussed today.

Dr. Sisley:

And to follow with that, have you found that and when you dose the topiramate in the evening, that it decreases the kind of brain fog that can occur with it?

Dr. Stanford:

Absolutely. There's strategy. So I dose topiramate and zonisamide in the evening for both my pediatric and adult patients. You - there are actually, believe it or not, topiramate sprinkles that you can use, although I've heard they don't taste good. I still haven't tasted them, but I can use that in the pediatric population. And you can start at really low doses of course thinking about, you know, milligrams per kilogram if you're thinking about pediatric patients. And then of course, in adult patients, starting at a dose of 25 and a gradual titration up if you're using that as a solo agent, as you mentioned, for both migraines - it's approved for migraines, of course it's approved for persons that have a history of seizure disorder. And of course, we can use it in obesity as approved only, however, in combination with phentermine under the trade name of Qsymia.

Dr. Sisley:

And of course, if you're in pediatrics and you can't get Qsymia, then adding topiramate on to a stimulant, whether it's phentermine or a different ADHD med, is kind of like faux Qsymia. Right? So I know a lot of my colleagues will kind of try a faux Qsymia if they can't actually get the actual drug itself.

So how about the use of combo weight loss medications? So Contrave or Qsymia. So we just talked about Qsymia a little bit. Do you want to talk about Contrave?

Dr. Stanford:

Yeah. So you know, I think it's important to recognize that most of us that do this work, and I cannot not acknowledge Dr. Donna Ryan, who is - who I call my fairy godmother in medicine, who's really kind of one of the pioneers in this work, taught me a lot of kind of what I'm doing today, which is using a lot of combination therapy. Now when you're using combination therapy, it's important to use not the same agent within the same group. So you wouldn't use two stimulants and two GLP1s. You could use, however, a bupropion and naltrexone on someone that has a history of depression, or maybe has a remote history of opioid use disorder, you might consider that, plus you would consider, let's say a phentermine/topiramate. And those are, you know, agents that aren't working in the same pathways. I would say how I typically do this is I would start with one medication and see what benefit we get from that as an individual agent before adding on a second agent.

If you are using a second agent or a third agent, or even a fourth agent, you do want to tell the patient that we will be continuing this indefinitely if their body's responded - if their body's responded to this additional agent. Now, if they get no benefit, which is that 5 to 10% total body weight loss within 3 months, you do want to withdraw the agent, right, because this will be a long-term sustained use of these combination of items.

And the paper that you will not find if you want to look it up in PubMed is the use of combination therapies. The reason why Donna's group at Pennington, my group at Mass General, Aronne's group at Cornell, have not done that study is because it will be a very messy study, trying to look at, you know, people starting medications. I guess you could do a prospective trial to look at these things. But what we do in real life is often are using combination agents. I have patients that are on, let's say, semaglutide plus Metformin plus phentermine, for example. Those are different agents working in different pathways that are influencing the body in different ways with weight regulation.

Dr. Sisley:

So one of the questions says: Would you be concerned with cardiovascular side effects when using phentermine in children over 12?

Dr. Stanford:

Absolutely not. So I think what's important - actually I have a paper that just got and will be published in *Childhood Obesity* looking at phentermine use in the pediatric population. So, we have done this for quite some time. There are a few key things that I really think about when I'm using phentermine. First of all, I have my patients take their blood pressure and pulse Monday morning, Wednesday, midday, and Friday evening, for at least the first 4 weeks with starting the medication and with any dose increases. I have them send that on a weekly basis via the patient portal. So I have a sense of whether or not there were changes in blood pressure and pulse. Did those happen in the morning? Did those happen in the midday? Did those happen in the evening time? I also, however, do that with bupropion. And if you look at a recent article that came out in *JACC*, the *Journal of the American College of Cardiology*, what we do see is actually higher increase in blood pressure and pulse with bupropion versus phentermine. Phentermine scares people because it was part of the fen-phen combination that was approved back in the late 90s. And of course, withdrawn from the market because fenfluramine, which is f-e-n-f-l-u-r-a-m-i-n-e, caused heart valvulopathy. We did not see that with phentermine. It has remained continuously on the market since 1959.

Now, I want to go back to something Dr. Sisley said that was extremely important, and that is to look at your state-based laws. There are certain states, Ohio, Florida, for example, that are very stringent on long-term use of phentermine, even if it's approved for chronic therapy use by the FDA in combination with topiramate. So really check that because I have seen people have their licenses threatened and/or withdrawn for using the medications as they should be used, but just, you know, going against what their state individual laws are. So I would say really, really important to see what your state regulations are as it relates to particularly the controlled substances.

Dr. Sisley:

So someone said: Is there any suggestion for quantitative or semi-quantitative instruments for the assessment of hyperphagia? I can say what I use and then - so I will admit, I do most of it clinically. I kind of have my set questions. That's kind of what I ask. I have kicked myself often for not giving a questionnaire just so that I could publish the results later. But I do kind of do it clinically, for the most part. But if I'm going to use one, the one I tend to use is actually the CEBQ, the Children's Eating Behavior Questionnaire. And I like that one because it has an adult version of it. So if I have an 18-year-old or a 19-year-old, I can just switch to the adult version of it. It has multiple different scales, and one of them is a food satiety scale. So if you wanted to, you can just kind of look at specific questions. But that's the one I'm going to use one, I would use the CEBQ or the AEBQ.

Dr. Stanford:

So I mean, I think that - I think those are really great resources and tools. There are some things that you'll see on the Rhythm site, for example, that help you in terms of thinking about screening if you've never done that. But often the patients are giving you the answers, you just have to listen to them. They're telling me, 'I'm having to lock the refrigerator,' or if they're telling me, 'Gosh, I have to lock or, you know, make sure I place certain items out of out of reach.' Those are things that are giving you a sense that the patient has a really, you know, significant insatiable desire to eat and consume. And so even without asking questions, you're picking that up. If you're listening to the patient and their family giving you that history, which happens very quickly, because they're very frustrated with these things.

Dr. Sisley:

So one of my favorite questions, especially for kids, because I have kids who will say – their parents were like, 'They're hungry all the time, but they only eat pizza, chicken nuggets, and like French fries.' To me, that's not hyperphagia. Right? I don't doubt that they're

hungry. But my kids who have true hyperphagia, they haven't met a food they don't like. Like they will eat broccoli, they will eat salad, they will eat fruit, they will eat anything you put in front of them, they are happy with it. And so that's one of the questions I like to ask is, do they have favorite foods? Is it only with favorite foods or not? I don't know if there's specific questions that you'd like to ask.

Dr. Stanford:

know. I think those are great. I think you did a great job.

Dr. Sisley:

One of the questions is: How do you counsel patients when they end up with heterozygous forms of obesity?

Dr. Stanford:

You know, this is a really challenging one because most of the tests that I've sent off, do come back with heterozygotes. I told you that there's this new study that's now available testing heterozygotes with setmelanotide, for example. But many of the heterozygotes are often more likely to respond to more traditional forms of therapy, whether it be metabolic and bariatric surgery or pharmacotherapy or a combination thereof. And so that's really, really important. If we look at like homozygotes from melanocortin 4, I've actually had one of those in my practice. There are less than 20 documented in case reports, which is one of them is mine, from around the world. And this woman, this young girl was flown in from Saudi Arabia to be cared for by us. And we found out that she was homozygous for melanocortin 4, her parents were consanguineous. And that was part of how we got to that homozygous state. Both parents were heterozygous for melanocortin 4. They have less response compared to a heterozygote from melanocortin 4 to traditional therapies. So I just, you know, I tell them, like, look, we can try traditional therapies and see how effective they are. Let's not give up hope. Let's try and exhaust everything first.

Dr. Sisley:

And there's some data from multiple different groups, but Dr. Farooqi's group being one of them, that actually shows that if you are heterozygous for POMC, PCSK1, LEPR, you do have an increased weight. And so I think that just knowing that, even if you can't say okay, for sure, you can – here's your therapy that's going to treat you. It gives them validation, as you had mentioned, right, that they're fighting against something real. It's not them being a failure. It's not that they've made poor choices, like their body is literally fighting against them. And so I think just that knowledge to say, there's something here, it's not just you. It's not mental. Right? There's something physiologic going on in you, and it gives them some validation for what they've gone through.

Dr. Stanford:

Excellent.

Dr. Sisley:

Are there any studies of setmelanotide in polygenic obesity underway? Not to my knowledge. And I do not believe there will be in any of the near future.

There was also a question: Do you foresee that setmelanotide will be approved for Prader-Willi? Not that I know of.

When might we assume that a patient's chronic relapsing obesity is a natural body diversity for them when all their tests are normal? That's a really hard question. I don't know if there's a good answer to that, truthfully. We know that if you have obesity, there's really good animal studies on this - if you have obesity, your brain does not work the way it's supposed to work. And sadly, if you bring someone's weight down, you would assume that everything goes back physiologically normal, and it doesn't. And so I think if someone has, right, chronic kind of unremitting obesity, they - it might actually be kind of, yes, it is their body. Right? It is just kind of them, and that is how their body is responding to that. I think this kind of comes back to the whole weight bias and how we as the medical community interact with them, as opposed to saying, right, 'Well, clearly, you just haven't done the diet that I prescribed for you,' right? That, you know, taking into account that, 'Gosh, let me tell you what might be going on in your body.' Right? 'Let me, maybe not show you the data, but let me tell you the data of what happens to hormones when you lose weight, like all of the hormones that make you feel hungry go up, and the hormones that are supposed to suppress your hunger, go down.' So when you actually lose weight, and your patient says they feel like they're starving, they're not kidding, they feel like they're starving. And so I don't know if that truly answers the question. But I do think there are some people who just have disrupted physiology, and that might actually just be how their body is responding.

Dr. Stanford:

Yeah. I think one of the key things, particularly for using pharmacotherapy for the treatment of obesity is I actually show my patients

where are the medication is working in their brain. So if we're talking about GLP1 receptor agonists, we know that those work in four key ways in the body, they stimulate POMC within the body, they slow gastric emptying, they improve insulin secretion, and they actually increase resting energy expenditure, whereas topiramate inhibits norepinephrine reuptake within the hypothalamus. And then what we know about topiramate is that it stimulates GABA, or gamma aminobutyric acid. So I'm showing them this to understand that we're working on different parts of their brain.

But I think we're actually out of time for any questions. So I want to thank you guys for your attentiveness. Thanks for coming to hear us talk about rare genetic forms of obesity.

Announcer Close:

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