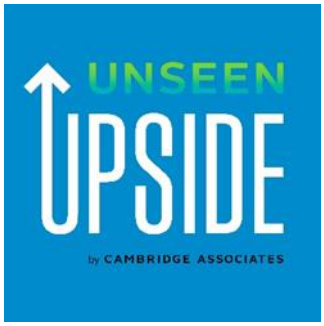

Season Four: Episode Four
Appetite for Change: The Obesity Epidemic Meets Biotech
Launch Date: March 2024

DISCLOSURE: All opinions expressed by host and podcast guests are solely their own opinions. The host, podcast guests, and/or Cambridge Associates clients and employees may maintain positions in the securities discussed in this podcast. This podcast is for informational purposes only and should not be relied upon as a basis for investment decisions. Please listen to the full disclosure at the end of the podcast for additional information.

Kathleen Mikaelian: I've always gone up and down in weight. you know, I've been really heavy in the past, lost, gained some back, lost it again.

Hillary Ribaudo: According to recent data by the World Health Organization, more than 1 billion people -including children- are struggling with their weight worldwide. Just in the United States, the Center for Disease Control and Prevention (CDC), says that about 4 out of 10 Americans are overweight.

Kathleen: People don't appreciate how difficult it is for overweight people to lose weight because so much of our social interactions are revolving around food.

Hillary: But people's relationship with food is just the tip of the iceberg. Obesity is a complex medical problem that increases the risk of many other diseases like diabetes, high blood pressure, heart and liver diseases, sleep apnea, cancer and many more.

Raymond Stevens: It is a real problem. A lot of people think obesity is cosmetic. It's not, it's a disease and we need to acknowledge that. That's the first step in solving the problem.

Hillary: Obesity is increasingly being recognized as a medical condition influenced by genetics, the environment, socioeconomic and psychological factors. And with that has come a new generation of pharmaceutical interventions.

Wegovy ad: *I've always had trouble with my weight. Now with Wegovy, I've seen real change. I've lost weight, and I'm keeping it off.*

Mounjaro ad: *Mounjaro helps your body regulate blood sugar. And Mounjaro can help decrease how much food you eat. 3 out of 4 people reached an A1C of less than 7%. Plus people taking Mounjaro lost up to 25 pounds.*

Ozempic ad: *O O O ZEM PIC! I got the power of three. I lowered my A1C, CV risk, and lost some weight.*

Hillary: These drugs belong to a class of medications originally intended to help with type-2 diabetes, they are called GLP-1s. They are disrupting the entire healthcare industry, but they are just the first wave.

Hillary: I'm Hillary Ribaudo and this is Unseen Upside by Cambridge Associates, where we explore investments beyond their returns. This season we're talking to leaders and investors behind healthcare innovations that could change how long, and how well we live.

And in this episode, we are looking at the efficacy of that first wave of GLP-1s and what the future of obesity treatment could look like.

Kathleen: I have managed to lose weight with diet and then I've gained it back again. I had lost quite a bit before COVID and then during COVID gained it all back again. It's been an up and down struggle ever since having six kids.

Hillary: Kathleen Mikaelian is in her early sixties, and she's also the mother of one of my close friends.

Kathleen: Yes, I'm Lauren's mom and five other people as well, which is pretty much what I'm known for.

Hillary: She lives in Rhode Island with her husband, two cats and a dog. And let me tell you, she's also a fantastic cook!

Kathleen: Oh yeah. I suppose that's another thing I'm somewhat famous for.

Hillary: Weight has been a concern for Kathleen for a while now, but at this stage of her life, she has been putting her energy into tackling other health issues.

Kathleen: I got diagnosis of type 2 diabetes about five years ago and at first my GP was managing it with medications. I was having a hard time getting my A1C under control.

Hillary: A1C, also known as hemoglobin A1C, is a blood test. Think of it as a sort of "report card" for your blood sugar levels over the past few months. It gives your doctor an idea of how well your blood sugar has been controlled during that time.

Kathleen: They just kept upping the medications, upping the medications, and I was taking, you know, a handful of pills every day, and still couldn't seem to get my A1C to come down.

At the same time as I got my diabetes diagnosis, I was trying to pursue treatment for atrial fibrillation. I wanted to potentially look into a new treatment for that, and the electrophysiologist said, you know, if you could lose some weight, that would help with whatever treatment we do for the AFib.

Hillary: So, in the fall of 2022, Kathleen decided to try something different. She went to an endocrinologist who recommended that she take a GLP-1 drug.

Kathleen: I had never thought about it before. But at that point I said, “heck, whatever I'm doing isn't working, maybe I should think about that.”

In my mind, I did want to knock off some weight in addition to getting my blood sugar under control.

Hillary: The World Health Organization describes obesity and being overweight as having too much body fat, which can be bad for your health. You can use a measure called Body Mass Index, or BMI, to figure this out. It's basically a way to see if your weight matches up with your height. If your BMI is over 25, you're considered overweight. If it's over 30, you're considered obese.

Roderick Wong: You can actually have folks that you would not consider as having a high BMI, but may actually be in the bucket of carrying significant risk of secondary complications.

Hillary: GLP-1s are often indicated for people with a BMI over 27 with at least one weight related problem.

Rod: Every individual is different, and it's figuring out from a medical perspective, which folks need treatment.

Hillary: Roderick Wong is Managing Partner and Chief Investment Officer at RTW, a life sciences investment and innovation firm. RTW is based in New York City and has offices in London and Shanghai.

Rod founded the firm 15 years ago. Before beginning his career, he simultaneously received an MD from the University of Pennsylvania Medical School and an MBA from Harvard Business School.

Rod: I think at the end of the day, what it's really about, is that folks don't want to be overweight. Part of that is cosmetic or a consumer preference, which is perfectly okay, but part of it is that there are significant medical consequences or comorbidities related to being overweight.

It's things like heart attacks and stroke, but it's also things that maybe some folks don't think about as much. For example, there are some relationships to developing things like dementia, obviously metabolic diseases like diabetes.

Hillary: So, this story is all about obesity and GLP-1 drugs, sure, but it's also a nod to the legions of scientists across generations who've hustled to bring us to where we are today. Along that journey is Raymond Stevens, the Chief Executive Officer and founder of Structure Therapeutics. A company creating life-changing medicines using advanced computational and structure-based technology.

Raymond: I am from the great state of Maine, I went to college at University of Southern Maine, I started out computer science, but had this really dorky professor that I just thought was the coolest, my freshman year: Ted Sottery. And he inspired me to switch my major to…

Hillary: He is my uncle!

Raymond: Holy. He passed away a couple years ago.

Hillary: Yeah! Oh my god.

Raymond: He's the whole reason why I became a chemist, He had this dorky Ti-55 calculator in his lab coat pocket. He taught me freshman chemistry and he's the one who inspired me to become a chemist. Oh gosh, I got goosebumps from that now.

Hillary: I was absolutely shocked to learn during our conversation that my great uncle Theodore Sottery had in part, inspired Raymond's career. Uncle Ted was a Chemistry professor at USM for almost three decades. He mentored Raymond, instilling a passion for chemistry that has since blossomed into the very foundation of Raymond's career. But the thing is, Uncle Ted also had type-2 diabetes and struggled with his weight. I know he would've been extremely proud of the work Raymond and his team are doing.

After Raymond studied under my Uncle Ted and finished his bachelor's degree, he went on to earn his PhD in chemistry and later, received his postdoc from Harvard University.

Raymond: I became an assistant professor at the University of California Berkeley, where I really got started with my independent career.

Hillary: Raymond has authored over 400 peer-reviewed publications and received several academic and industry awards. He has even worked with 2 Nobel prize winners. Raymond's work is focused on something called structural biology.

Raymond: … which means I use super resolution microscopes to see what molecules look like in our body.

Hillary: Through this work, Raymond and his students discovered big breakthroughs that led to the creation of a series of biotech companies.

Raymond: Each company that I have started has been with former students.

Hillary: Along this process, Raymond has been studying the history of obesity.

Raymond: It really is not that old of a disease. You can look at the data, the data's very solid globally. The curve of obesity, it was 13% in the 1980s, and it's jumped to now 42% today. That's in terms of just the United States. Almost half of our population is now defined as obese. It's an epidemic.

Hillary: Although some scientists have suggested an earlier origin, most epidemiologists attribute the roots of this problem to the proliferation of cheap, processed foods, sedentary lifestyles, and larger portion sizes, which can be traced back to the 1970s.

Raymond: We started adding things to food to make them last longer because they didn't want food to spoil. We started creating fast foods that made food more convenient for people.

But what's happened since the 1980s is ultra processed foods. We now add salt, sugar, and fat to the food from the food manufacturers because they want that food to be tastier, more addictive. It's very reminiscent of the tobacco industry adding nicotine to tobacco.

So that bag of potato chips, you just can't put it down. You wanna finish it because of the salt, the fat, the sugar, you want it. So that's where the obesity epidemic really got started, and then we started supersizing amounts of food.

Hillary: Diabetes and weight are closely connected. Being overweight or obese increases the risk of developing type 2 diabetes because excess body fat can make it harder for the body to properly use insulin -the hormone that helps regulate blood sugar levels.

In 1921, when this hormone was discovered, insulin injections revolutionized diabetes treatment. Since then, more classes of medications have been introduced to better control blood sugar levels in type 2 diabetes patients. Fast forward and we now have one of the latest classes, GLP-1s.

Part 2:

Raymond: These drugs were originally developed for type 2 diabetes. Then it was found if you increase the dose a little bit, you would get some significant weight loss. At the same time it was very safe.

Hillary: GLP-1s have been in the news lately in connection to their use for weight loss, but they are not new.

Rod: The first GLIP-I is called Byetta. And it was actually approved for the treatment of type-2 diabetes 19 years ago. That's a long time.

Hillary: Rod Wong again.

Rod: The issue back then was even though Byetta was potent enough to make a difference in type 2 diabetes, it did not have any meaningful impact on weight.

Novo and Lily continued to iterate and improve the potency of these modified GLP-1s. That's how we ended up with Ozempic and Monjaro.

Ozempic results in about 15% weight loss. Monjaro is closer to 20%. That is the efficacy profile that has really cracked open the obesity opportunity.

Hillary: GLP-1 stands for Glucagon-like peptide-1, often referred to as GLP-1 agonists, where "agonist" means a substance that triggers a response when it binds to a receptor.

These medications mimic a hormone by the same name, GLP-1, which is naturally found in the gut. GLP-1 binds to receptors on pancreatic cells, prompting them to release insulin when your blood sugar goes up.

Raymond: It was actually discovered from a lizard in the Arizona New Mexico desert. It's fascinating. These lizards have this spit that have GLP-1 in them. So that was the origin of where they came from.

Hillary: We are not exactly sure about how, but GLP-1s are helping people feel less hungry. They slow down digestion, so you might find yourself eating less.

Rod: At the end of the day what is happening in the simplest way when it comes to weight loss is that you are taking in less calories. That's the bottom line.

Kathleen: It definitely makes me feel full or, I don't know if I would describe it as feeling full. I feel like I'm just disinterested in eating. Not that like my stomach feels full or anything. It's just I don't feel like eating anything. I don't, I don't feel like chewing another bite.

Hillary: When Kathleen received her GLP-1 sample box in October of 2022, she was not ready to begin the treatment.

Kathleen: I was deathly afraid to start because I had heard about all the potential side effects. And, I had a lot going on in life at that point and I was scared to death. So I hung on to it.

Hillary: But finally, on January 29th, 2023, she decided to take the leap. We know the exact date because Kathleen keeps a notebook where she's been logging her experience.

Kathleen: So, I started with this tiny little dose and literally within probably a few hours, I had a headache.

[Reads her notebook]

I started with all kinds of side effects that same day- headache, nausea, dizzy, stomach upset. The next day, more of it, every single day, right up until my next dose a week later- more headaches, upset stomach, queasy, [laughs].

I did that for four weeks, constantly had upset stomach, headaches, and just not feeling like eating or anything.

Hillary: Raymond says not everybody has these side effects, but they are a normal reaction to the treatment.

Raymond: We have grown accustomed to continue to eat until we're completely stuffed, not when we sort of need to stop.

So we've adapted for years and years to consume more and more. All of a sudden, we're trying to train our bodies to eat just what we need in terms of the nutrients. Your body is evolving. It's trying to readapt down to a smaller level. This class of drugs will slow down your gastric emptying, the release of everything from your stomach. So you'll naturally get some degree of nausea and vomiting.

What we're trying to do, and what many people are trying to do now, is how do you minimize. It's what we call tolerability. The solution is we give people small amounts of the drug, one week, another week, and then we can start increasing dosage.

We constantly are working on trying to find ways to make the patient experience better so that they don't feel this nausea, but it's a natural part of your body adapting to just consuming less food.

Hillary: Kathleen started with 0.25 milligrams and 4 weeks later her dose was increased to 0.5 milligrams.

Kathleen: Then I had four more weeks of more illness. But then I had an appointment about 8 or 10 weeks into it, and my A1C had gone from 9.6 to 7.6. The nurse practitioner said, “well sounds like you're doing really well.” I lost about 17 pounds I think at that point, and, she said, “hey, do you want to bump up to 1 now?”. I think I had maybe another four, five, six weeks of still feeling sick pretty much every day.

But then I started to notice I was going more days without making a note in my notebook about feeling ill. Gradually, it's gotten to the point where now I don't really have any symptoms at all. I'm now like 45 weeks into it and occasionally I will get an upset stomach, but now I really don't have any ill effects.

Rod: There's kind of tail risks sorts of things that people are concerned about as well, most of it theoretical.

Hillary: Rod Wang again.

Rod: This idea that maybe the risk of cancer or issues with the thyroid might be elevated.

And while we don't have definitive answers to some of those questions, what I will say is that we've had our first outcomes study reported at a major medical conference in Philadelphia at the AHA.

Hillary: The American Heart Association.

Rod: That showed that in obese patients, you're reducing death, which is ultimately the most important end point. You see 20% plus reductions in heart attacks, in strokes, et cetera.

Hillary: Today, there are many GLP-1 drugs available for weight loss, and for their original use to treat diabetes.

Raymond: Novo Nordisk and Eli Lilly have been pioneers, groundbreaking work, in terms of developing this class of medicines.

Hillary: Raymond Stevens again.

Raymond: After Novo Nordisk, Ozempic, and Wagovi, Eli Lilly has Monjaro and now ZetBound- again for type two diabetes as well as obesity. The state-of-the-art is, we're starting to learn with this class of medicines, not only can they treat type two diabetes and obesity, but we're now finding with weight loss, it improves your cardiovascular health.

It improves, your kidney health, your liver health, and your major organs in a very profound way.

Hillary: And scientists are even looking into using GLP-1 drugs for other disorders tied to cravings beyond food, like smoking, gambling and even nail biting.

But no medication is a magic pill and besides the side effects, GLP-1s can change your body in ways that are not positive as well.

Raymond: It's been acknowledged that there's both fat weight loss as well as lean muscle loss. Now, some of that lean muscle loss is because you're losing weight and you don't have to have as much muscle to carry all that weight. But you are losing.

And if you stop taking the medicine, then what we find is the fat weight comes on really quickly. The lean muscle takes much more time. So, there’s a lot of work that's going on in the field.

Hillary: The hope is that a newer version of this medication in the future will accomplish fat loss with minimal lean muscle loss.

Another challenge for this wave of GLP-1 drugs is how they're delivered—they have to be injected. This might not be great if you're scared of needles, but at least you can do it at home without having to see a doctor.

Kathleen: I had done self injections before for blood thinners. I was used to the process. And I have a daughter who's a pharmacy tech. Kate held my hand through the process, when I first got started. It's really simple. I mean, these instructions are in the box, so it's not very hard to do.

Hillary: Today, between 5 to 6 million people in the United States inject these drugs.

Raymond: But we're talking about hundreds of millions of people needing it. This is going to be hard to do with the injectables, even if they scale up. These injector pens are made out of plastic. The amount of waste and everything that comes from that, the refrigeration that's required for that.

I think the next generation of the GLP-1's will be what we refer to as oral small molecules that can be taken in a pill form.

Hillary: And this is the work Raymond and his team are doing right now. Structure Therapeutics is the latest biotech company Raymond has founded, and one of the reasons for starting it has to do with his family.

Raymond: I have three children and my youngest child, my daughter, was diagnosed prediabetic. And we're lucky, we had access to good doctors and she went on medicines like metformin. She got her health, got her exercise, food really under control and she's doing wonderful now. But most people in the world, they don't have that access to healthcare. You don't get diagnosed often as pre-diabetes, you have full-blown diabetes. By then it's harder to get under control.

If we could make a true oral small molecule pill, we can make this accessible to everybody.

Hillary: A small molecule drug has a small number of atoms, which is ideal in the making of oral medications like pills.

Raymond: It would have lower cost of goods. It would have no refrigeration required, more stability with the molecule.

Hillary: GLP-1s are Structure's first target, so the team is actively working to bring this vision to life.

Raymond: Most everybody's looked in a microscope at some point. And, you know, microscopes allows you to see small objects bigger. We have a super microscope that allows us to actually see at the atomic level. We can see the individual atoms.

Our technology platform, by taking the GLP-1's, that is a large protein that binds to the receptor in the body, what we call the GLP-1 receptor. By looking at that interaction, it's like looking in a keyhole and seeing the ridges and then making a smaller key. By visualizing that, we can figure out what's the smallest possible molecule or the smallest possible key that'll have the same function.

But by making it a small molecule, you can dissolve it, that's why you can take it orally.

Hillary: Structure's technology platform is called Structure-Based Drug Discovery, and it benefits from the latest technology in AI and machine learning.

Raymond: If you look at a crowd-we've all seen this stuff on TV where facial recognition will pick out faces. We use the same facial recognition technology, so we look in a cell under the microscope, and with machine learning we can see, and we can pick out the different atoms, the different molecules, and how they're binding.

Hillary: Structure's technology looks inside the cells, not at people's faces.

Raymond: It's facial recognition at the atom level. It's pretty cool.

Hillary: In 2023, Structure Therapeutics had its Initial Public Offering, or IPO. They have a high-potency oral medication that is in the race to be one of the first oral GLP-1s on the market. And Raymond says that when it comes to drug development, safety is a top priority.

Raymond: If people are going to be taking this chronically for a long period of time, it needs to be really safe. In December we got what's called our tox data. In animal models, we're able to go to very high dose, with no safety issues whatsoever. Determining and learning that your drug is really safe was incredibly rewarding.

Hillary: Now, the glucagon-like peptide GLP-1 receptor agonist is just 1 class of G-protein–coupled receptor or GPCR.

Raymond: You have 826 of them in your body. You smell because of olfactory receptors, GPCR. You know your heart is beating, adrenaline is pumping, because of a GPCR. They're like your network nodes of your body. They allow us to communicate everything from vision to smell to neurotransmitters.

Hillary: Raymond says they allow communication between our 2 brains. Yeah, you heard right, 2 brains!

Raymond: We have the brain that's up in our skull that we're most familiar with, but we also have a brain in our gut, it's called the gut brain axis.

Those two brains talk to each other. So GPCR is control that signaling.

Hillary: Besides GLP-1s, there are many other receptors in your body that can play a role in obesity.

Raymond: I think one of the other areas that's really exciting is what we call combination therapies. When you can combine two different mechanisms. For example, Wigovie and Ozempic, from Novo Nordisk, that's what we call a selective GLP-1. It hits one receptor in the body and it's a great drug. Eli Lilly developed Monjaro and now ZepBound. It actually

hits two targets in the body. It hits GLP-1 and it hits GIP. It's believed that combination effect makes it actually a superior medicine. Eli Lilly last year at the American Diabetes Association meeting, they shared data with what they call their Triple G. Where it hits three receptors in the body.

Hillary: GLP-1, GIP and Glucagon.

Raymond: By combining these things, we can get more enhanced effects.

We can also get effects that will specialize on, for example, liver disease, and you really want to have both weight loss but also focus there.

Part 3

Rod: If we're in the first wave of products, this wave is basically an Ozempic, Wegovi, and Monjaro wave.

Hillary: From RTW, this is Rod Wong.

Rod: Now every pen that they produce gets sold, and there's no new products that are going to change who's dominating for a handful of years. In the second wave, you have multiple things happening simultaneously. So first, companies are trying to improve upon the injectables that we already have.

So, you have an oral form of semaglutide, which is the active ingredient of Ozempic and Wegovy that is approved, but at the current doses, it doesn't, result in much weight loss. In addition to pushing the dose with oral semaglutide, there are novel small molecule pills that are in phase two that are shooting to hit that kind of 15 to 20% weight loss range that the injectables have. That's happening at the same time as the next wave of injectables. Finally, is not just targeting absolute weight loss because there's obviously a limit to how much weight loss people need, and then focusing on the quality of the composition of that weight loss.

Hillary: Rod manages all the therapeutics investments at RTW, which is made up of scientists, entrepreneurs, and investors making investments at every step of a business's lifecycle.

RTW's mission is to identify and support transformative innovation.

Rod: Initially is primarily through capital, and now it's through both capital as well as different types of support, like operational governance, creative transactions, et cetera.

Hillary: Rod says the industry has been in a bear market for the last several years.

Rod: One of the things that led us into this period was a very positive development. Which was that we have a whole bunch of new modalities, or technologies from which you can develop drugs out of. Obviously, we're all familiar with mRNA with the Covid vaccine, things like gene therapy and cell therapy. But there's a fair number of other modalities too, that have matured during the same period. Prior to the bear market, there was a lot of excitement about the fact that we had these new technologies.

What subsequently happened is that excitement led to too many IPOs and especially of early-stage immature companies, which then had a fair amount of disappointment. And that disappointment coincided or led this time of rising interest rates, of the reversal of covid revenues, and of the passage of the IRA.

All these things came together at the same time, then to lead us, to where we are now. Importantly though, despite the fact that things feel very, very bearish, we shouldn't forget that that innovation is still here. You're seeing successful kind of maturation of some of the modalities. What we ultimately want to see, which is the emergence of new drugs that are showing positive data, getting approvals, and having successful commercial launches.

All that is happening now, which is frankly the thing that gives us the most optimism.

Hillary: An optimism that's shared by my colleague Dean Dimizas. Dean is a partner at Cambridge Associates and has been with the firm for almost 2 decades.

Dean Dimizas: We've known Rod for approximately 10 years now. He brings a strong scientific background, himself and his team, and they've navigated the ups and downs of the biotech markets with very good success longer term.

Hillary: Dean says investing in general is hard, but investing in life sciences is even harder.

Dean: You're dealing with human lives. You're dealing with biology, you're dealing with science, and there are many unknowns there.

Life science investing is about three things. Will this work? Will it sell? And how much is it worth? We're trying to understand how these managers approach these three questions.

Hillary: Dean and his team advise and manage diversified portfolios for high net-worth families, family offices, and nonprofit institutions around the world.

Dean: We help them manage their portfolios or we manage them for them in the discretionary capacity. This entails determining what's the right asset mix for these portfolios for the next 10 and 20 years. At the same time, we're very active in identifying emerging managers, smaller younger funds, what we call often PhDs- PhD standing for poor, hungry and driven people that can play a role in our portfolios and complement the large established managers.

Hillary: And every year, with his team, Dean meets with over 400 managers across all assets.

Dean: It's not only investing in the 10 or 20 smartest people in the world. It's figuring out what's the right mix of risk exposures, of factors, of geographies. A very big part of our focus is the portfolio construction part, not only vetting individual managers. It all has to work perfectly to achieve our objectives over long periods of time.

Hillary: Dean points out that Cambridge Associates was one of the first companies to help clients invest in venture capital in the late '70s.

Dean: As a firm we've had a 50 year presence of investing in innovation that has been longer term. We've always embraced innovation as a way to create value for our portfolios

Hillary: Cambridge Associates has been investing in biotech for more than 20 years, and it started around the time Dean joined the firm. But back then things were a bit different.

Dean: There were only a handful venture capital funds, barely a handful of public funds and fast forward to today, there are hundreds of life science focused firms of institutional quality, most of them in the US, a few in Europe, and a few in Asia. So, a much larger number of players. And at the same time, we're seeing more specialization. Today you can see funds that have a distinct seed focus. Others that have more of a traditional venture capital and growth equity focus.

Hillary: And for Dean, a widespread problem like obesity presents investment opportunities that could really make a difference.

Dean: The rise of these drugs that we've seen in the last 12-18 months have created a huge revolution in allowing probably millions of people being able to biohack themselves out of this challenge. You know, diet and exercise and behavior modification could play a role, but I think in many cases, there's a limit to what that can achieve. We're harnessing a phenomenal technological innovation to help improve millions of lives globally.

Together with AI, the rise of these drugs has been one of the hottest trends in the market. Thus far, most of the value has accrued to the large pharma companies that have develop them and commercialize them. But over time we think there's going to be room for more.

Hillary: In the race to create obesity drugs, both small and big companies play crucial roles.

Rod: If you think about how many patients you have to study to get an obesity or a type-2 diabetes drug approved, it's in the range of around 10,000 patients, and that's a big pharma kind of exercise.

Hillary: RTW's Rod Wong.

Rod: For small companies, I think the added consideration is, the best small companies will be positioned strategically to fill these kinds of unmet needs. They're ultimately going to need to partner up or in many cases, get sold to a larger company.

Hillary: But perhaps one of the biggest challenges this class of drugs face is that the vast majority of insurance still does not cover them. In Kathleen's case, she has to pay for a portion of her treatment.

Kathleen: I believe it's 240 a month out of pocket, but I have a card from the manufacturer that brings that down to 120 dollars per month out of pocket for one month supply.

Hillary: And that could be a lot for some people.

Kathleen: My husband and I both have chronic health problems other than the weight issue. You know, we spend a lot on medications. It's always a consideration and I can see where a lot of people would not want to pay that much.

Hillary: So, a big question here is who's going to pay for these drugs?

Raymond: We're just starting to see them getting covered. People are paying out of pocket right now and so there's an accessibility issue.

Hillary: Structure Therapeutic's Raymond Stevens again.

Raymond: If you look at the sheer demand for these medicines, the companies, Novo Nordisk and Eli Lilly, they right now can't keep up. They're trying to scale up. They're building more manufacturing plants, but right now they're only hitting 5 to 6 million patients in the United States. Again, we go back to that 42% number, 300 million people in the United States. It's only covering a very small percentage of the population. The challenge is the cost and the accessibility has to improve.

All of the medical associations have now come out and declared obesity as a disease and that was a really important step. There was a question from the in insurance industry as to whether this weight loss is really cosmetic or it really has a real effect on health.

In November of last year, Novo Nordisk data at the American Heart Association meeting clearly showed a cardiovascular benefit. That's hard data that shows, with weight loss, with this class of drugs, it improves your cardiovascular function. And the same thing we've now seen with kidney disease. With that increasing amount of data that shows that there's an improvement in health, that certainly is encouraging the payers that if they cover these, then you're improving health, you'll have less complicated issues down the road.

Hillary: This is Rod Wong again.

Rod: At the end of the day, what it's about is building up additional evidence that then makes it more and more difficult for insurers to deny coverage, and that's going to be a gradual process.

Hillary: And beyond insurance coverage here in the U.S., global access is also an issue. Here is Raymond Stevens again.

Raymond: There's all these great breakthrough medicines that we're seeing, but they're only available to about one third of the world. Two thirds of the world will not get access to these, not for 10 years, possibly not for 20 years. This is a real problem.

Rod: From a purely medical perspective, it's one of the biggest nuts to crack and it's going to have the biggest impact on life expectancy for our society as a whole.

Hillary: Rod says GLP-1s are the first breakthrough in medicine where the potential value creation should lead to companies possibly reaching trillion-dollar valuations.

Rod: We already have those in multiple other areas, right? You clearly have them in tech, but we've never had anything even close in medicine. It is the most significant innovation from a opportunity perspective on that need perspective in medicine, in history.

Dean: A blockbuster drug is considered a drug that exceeds 1 billion in annual sales. These drugs have already exceeded this by a wide margin, and experts expect this drug class to reach and exceed 100 billion in annual sales before the turn of the decade.

There's a huge number of unmet needs out there. We're very excited about the innovation that lies ahead in this space; drugs with better effectiveness, less side effects. I think we're going to definitely see more capital investment in this space and wider adoption within society, especially as affordability and reimbursement improve.

Hillary: Raymond says there's no way this work can happen without capital. And investors in this space are paying close attention.

Raymond: The NIH, the National Institutes of Health, which does a lot of the medical research in the United States, sponsored by the government They're now investing $1 billion into research, understanding how these medicines work. There's more than 2060 grants in the US alone, understanding how these molecules work. What are the new indications? Can we use these for addiction? Can we use these for other diseases? These are all the type of things that we need to continue investing in order to solve this problem.

Rod: I'm very, very confident that fast forward 10 years from now, you're going to have widely available a whole range of options from injectables to pills. And in a decade you'll probably have the first options that have a better mix of weight loss than what we have now.

Dean: I'm optimistic that over time a broader rollout of these drugs and improved affordability will enable millions of people to enjoy better lifestyles and extend their lifespans because they’re going to be healthier.

Hillary: But to solve this issue, we can't forget how it began.

Raymond: The root of the problem is back to 1980s, again, it's very solid, clear data. And it was in part the food industry trying to solve one problem but creating a new problem. I think this is going to require a multi-industry solution to this.

The GLP-1 class of drugs and the combinations are one solution, but I also think it's going to take the food industry to start to evolve as well so that we don't have as much salt and sugar and fat added to all the food. You think about, you go to a restaurant, they put all that in because they want you to enjoy it. They want you to eat it and finish your plate. It's not going to happen overnight. This is going to take a while.

Hillary: In the meantime, the first wave of GLP-1s has helped patients like Kathleen.

Kathleen: I haven't changed anything. I haven't added exercise. I haven't really changed what I eat. I just don't eat as much. And so the weight's been coming off very slowly, but it is dropping.

Hillary: At the time of our conversation, Kathleen had been on GLP-1s for about a year and had dropped 22 pounds.

Kathleen: Society is focused on weight all the time. I feel extremely conspicuous when I'm out in the world, I feel like people are looking at me. So losing the weight that I have lost, I see people that I haven't seen in a long time and they're like, wow, you've lost weight. you look good, you've lost weight.

Now, her AIC is down to 6.5, which is within in the normal range. And, she has lost 20 pounds.

Kathleen: Seeing that big change was enough for me to say, "okay, well maybe this is worth it". My grandmother had a huge heart attack and died secondary to diabetes. I didn't want that to be my future and I didn't want that to be my kids' future. So, taking this part of the health issue out of the picture has become super important so I can focus on the other things that I've got going on. And as it turns out, that was the right decision to make.

Hillary: If you want to learn more, please visit us at cambridgeassociates.com/unseenupside or check out the show notes. If you like what you're hearing, leave us a review and tell your friends and colleagues.

At Cambridge Associates, our podcast team includes Michelle Phan, and me, Hillary Ribaudo. And a special thank you to Megan Morrissey, Robert Scherzer, Krista Matthews, Deirdre Nectow, Josh Baldwin, Danielle Keatley, and Lauren Barry.

This episode was produced by Sandra Lopez-Monsalve with support from Isabel Hibbard and Emmanuel Desarme. Genevieve Sponsler is our editor with audio mastering by Samantha Gattsek. The executive producer of PRX Productions is Jocelyn Gonzales.

Next time on Unseen Upside, join us as we dive into the mysterious world of the dark genome where drug discovery holds the promise of revolutionizing treatment for autoimmune diseases like Lupus.

Speaker: *Human biology is just beautifully complex and I think in this darkness, we are just as the very beginning of finding some points of light that will give us new ways of treating disease.*

Hillary: Before you go, one of our colleagues has an important message about the contents of this podcast.

[DISCLOSURE]