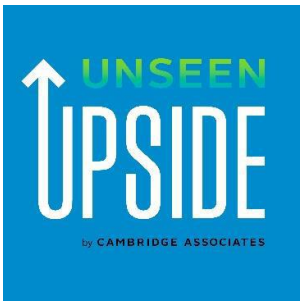

Season Four: Episode Two
Living Longer But Losing Our Minds: The Alzheimer's Emergency
Launch Date: Feb 2024

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Randi Casciano: I had worked for companies who sponsored Alzheimer's 5ks and stuff that I participated in. And I think in high school, like I had a couple of friends whose like grandparents had the disease, but I'd never encountered it firsthand. And I really just thought of it as this long-term memory issue that really impacted the elderly. I definitely thought it was something you didn't have to worry about until late in life.

Hillary Ribaudo: As of May 2023, 55 million people worldwide suffer from dementia. And Alzheimer's disease takes the lead as the most prevalent type of dementia, making up 60 to 70% of those cases.

Randi: Emotionally, it's a lot to confront the mortality of a parent, not only because you love them, but you know, that's traditionally the person that you turn to. It's your support system when things like this happen, so for that person to be the one that's ill, it really turns your world upside down.

Hillary: In a world where living longer brings new challenges, neurodegenerative diseases like Alzheimer's loom large over many of us. Currently 6 million Americans have Alzheimer's, a number that's expected to triple by 2050 if no new treatments are found.

But science has got this.

News Clip: *Major news in the fight against Alzheimer's disease. For the first time yesterday, the FDA fully approved a drug that has been proven to slow the progression of symptoms.*

Hillary: In July 2023, there was one new drug was all over the news.

News Clip: *In a clinical trial involving about 1800 patients in the early stages of Alzheimer's, the drug Leqembi slowed cognitive decline by 27% over an 18-month period.*

The drug is made by the Japanese pharma company Eisai and Biogen.

Hillary: Lecanemab is the generic name, and it was the drug that made the news, but it's not the only drug out there. And it definitely isn't working for everyone. However…

Carl Gordon: I think that's a huge shot in the arm for Alzheimer's and hopefully will lead to a resurgence of interest in this space.

[Theme]

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'll navigate the complexities of Alzheimer's disease and learn about novel drugs and approaches that hold the potential to change lives.

Randi: It was the end of February, but she kept asking about Halloween. She was confused about what state she lived in. She kept referring to a state that she hadn't lived in in 20 years.

Hillary: Randi is my colleague and Director of Global Public Relations at Cambridge Associates. She lives in Boston with her husband and their dog, Cruella. And back in 2020, just before the pandemic, her mother-in-law was diagnosed with Alzheimer's disease.

Randi: She was asking my husband about getting repairs to his car, and we like figured out that it was actually the car that he drove in high school that she was talking about. Alzheimer's wasn't apparent right away, especially because she was in her mid-fifties.

Hillary: Randi has always been close to her mother-in-law; we'll call her Susan for the purpose of this story. Randi describes Susan as this fiercely independent, single mom who loves cooking and athletics, and who climbed the ranks of a male-dominated industry in her career.

Randi: She has two boys, so as the daughter she never had, she really turns to me for fashion advice, helping her with interior decorating. We love to get mani-pedis together, gossiping over a bottle of Pinot Grigio. And I know the daughter-in-law-mother-in-law relationship traditionally is a pretty complicated one, but I'm so fortunate that I genuinely love spending time with mine.

Hillary: And they spent *a lot* of time together. As the matriarch of the family, Susan would host Fourth of July parties and Thanksgiving and Christmas dinners. But right before the pandemic, things started to feel a little different.

Randi: Thanksgiving 2019 was the first year that my husband and I were going to try and host dinner for the family. And I was really excited only to have her cancel on us a couple hours before she was supposed to arrive. And I remember being so angry at her, and especially because the excuse she came up with was not very realistic. And in hindsight, you know, you can tell that she had totally forgotten about the holiday.

Hillary: Randi and her husband also started to notice that she was getting weak.

Randi: She was low energy, she was barely eating, and she was complaining a lot about difficulty swallowing, which is actually a really common symptom of Alzheimer's. Once a patient loses the ability to swallow, it can lead to things like dehydration and malnutrition. And in real time, she was telling us that her throat issues, she thought, was a symptom of like an allergy. And she had made several visits to the doctor to get testing done and get to the bottom of it. And when an authority figure like your mom, you know, is passing along that information, you don't think to question it.

She's an adult, totally capable of, you know, arranging her own doctor's appointments. And we later found out that she had only been to one doctor's appointment and it was her lapse in her memory. She kept reliving that same doctor's appointment and repeating it to us. So from the outside, it created this appearance of a really robust healthcare journey that didn't actually exist.

Hillary: And unfortunately, the disease progressed until it was almost too late. That inability to swallow nearly took Susan's life.

Randi: After a few days of no one kind of seeing or hearing from her, my husband drove down to her house to find her unresponsive in her bed, and 911 was called. And the EMTs told my husband that if we had been a couple hours delayed in getting to her, she might not have lived through the rest of the day.

Hillary: Doctors did all kinds of tests before even thinking about Alzheimer's.

Randi: You know, I think the unknown was really scary. We knew she was really sick, but not being able to define it, I think, caused more stress. Your mind just keeps ruminating on the worst-case scenario, and that's not always healthy.

It was also heartbreaking to see my husband go through that. I felt an obligation to be his rock at home and turned on my PR crisis skills. It's literally my job to be the calm and the rational voice in moments of high stress and turmoil. But part of me felt, almost like it wasn't appropriate to have that kind of emotional response in front of my husband. I'm getting emotional just thinking about it. Um, it almost felt unfair for my emotional response to outweigh his, so I like let him take the lead. I think what you experienced in some of our first moments together was kind of the dam breaking and just unleashing the grief that I had felt at home.

Hillary: Alzheimer's disease is a type of brain disease that is caused by damage to neurons. Those are nerve cells that send messages all over your body to allow you to do everything from breathing to walking, even eating and thinking.

And the neurons in the brain regions in charge of memory, language, and how we process thoughts are the first to be damaged in Alzheimer's disease. And so, that's why the first symptoms tend to involve memory, language, and thinking problems.

Asa Abeliovich: So certain kinds of functions are especially impacted.

Hillary: Asa Abeliovich is a neurologist and molecular geneticist. He's also the founder and CEO of Leal Therapeutics, a biotechnology company developing novel therapeutics for patients with major disorders of the central nervous system.

Asa: Certain kinds of memories and capabilities over time are lost. For instance, short-term memory, the ability to remember things in the recent past, and certain functions like our ability to understand where we are in space and how to get from one place to another.

Hillary: While some everyday functions like the ability to communicate can gradually decline, others might be less impacted, like recalling distant memories. And this was the case for Susan right before her diagnosis. She could remember events that happened years ago, but she really struggled to meet her basic needs like eating and drinking until the disease almost took her life.

Asa: Over time as the disease progresses it really does essentially spread to different realms.

Hillary: Over a century ago, a clinical psychiatrist and neuroanatomist by the name of Alois Alzheimer led research that identified pathological changes that correlate with this disease.

Asa: There are certain kinds of changes, particularly called plaques and tangles, essentially the accumulation of debris that's associated with this disease.

Hillary: Our brains have their very own waste management system that prevents buildup of debris.

Asa: These debris are essentially components we believe of normal cellular components, normal processes that go awry over time.

Hillary: When working properly, the brain removes the debris regularly. But in brains impacted by neurodegenerative disease, that process is not as efficient and results in plaque accumulation.

Asa: Just as what happened here in New York City, over time you do have aggregation and accumulation of debris. You have garbage trucks that ideally come and pick it up. But as we grow older, unfortunately that process is imperfect.

Hillary: Asa shares that some indications of neurodegenerative disease were observed in Alois Alzheimer's time, like loss of neurons. But only in the last few decades have scientists been able to connect the dots.

Asa: There's a pathological underpinning that was noted over a hundred years ago, but it was not at all understood. And then since basically the '80s, the molecular biology and molecular genetic revolution allowed the identification of genes.

Hillary: Building on this revolution, scientists are now understanding more about the brain's changes through genetics.

Asa: Only really over the last decade do we have really effective tools to try to see these changes before patients die. So, before autopsy.

Hillary: These changes are called "biomarkers." Think of them like clues that doctors use to understand what's happening inside our bodies. Unlike symptoms that we feel, biomarkers are measurable signs that help doctors objectively see what's going on. They can range from very simple things like pulse and blood pressure to more complex lab tests, like MRI imaging, PET scans, and ultra-sensitive blood markers. Identifying the disease on time is one of the biggest challenges scientists like Asa face.

Asa: The early signs are subtle and really require pretty advanced tools. It's one of the things that's hindered over time the development of effective therapeutics. So, we absolutely need to understand it earlier and earlier. And there are better and better tools now, like psychological tests that enable the detection.

Hillary: Scientists have actually discovered that Alzheimer's disease begins 20 or more years before the symptoms start, and although that's a really scary fact, it gives science a significant window to work within.

Asa: But unfortunately, any one little thing is very hard to use to tease apart what's Alzheimer's versus what's essentially age-related memory decline, other kinds of dementias, or even for instance when people are depressed they certainly can be inattentive and that can lead to memory difficulties too. Teasing those apart by any one single minor criteria actually doesn't work well. To define dementia requires that multiple aspects and multiple realms are involved.

Randi: It was explained to us as kind of a poorly constructed staircase, which I thought was really helpful. You know, the disease could impact a patient's decline kind of steadily, small state increments one step at a time. You could even plateau and stay on one stair for a prolonged period, or you could take a step only to find out that several treads are missing and plummet many stairs all at once.

Hillary: So far, Alzheimer's has been understood as an incurable disease that progresses slowly. While it often affects older people, those in their 30s or 40s may also develop it. And according to the Mayo Clinic, approximately 5 to 6% of people with Alzheimer's disease develop symptoms before they reach the age of 65. This is known as "early onset." The remaining 95% have what's termed "late onset."

Asa has been working in this field for over two decades. He says that initially genetic studies were very difficult.

Asa: We had very few tools, but now with whole genome sequencing, with groups like 23andMe, there's just a remarkably large data set. And thankfully, very much of this is publicly available to scientists, of course, anonymized completely, but still can allow identification of genes that can underlie the disease.

Hillary: He explains that in very rare cases — about 1% — Alzheimer's is familial, meaning that the genes for the disease are passed along from generation to generation in an almost predictable way.

Asa: In the '80s and '90s, that allowed initial identification of genes underlying these very rare familial cases and that allowed us to start to unravel how these plaques and tangles are formed.

Hillary: Asa says that identification of these genes was critical to understanding Alzheimer's and other diseases.

Asa: Now, more recently, there are much, much larger studies that use much more sophisticated tools. And those have identified many other genes that don't have as big of

an impact individually, but at a societal level, at a population level, have a huge impact. So these are common variants that have a very small effect on any individual, on the risk, but they're important in the disease process.

Hillary: A well-known gene that affects the likelihood of Alzheimer's disease is the apolipoprotein E or APOE gene. This particular gene makes a protein that helps transport cholesterol and other fats through the bloodstream. Scientists think problems in this process could contribute to developing Alzheimer's.

Asa: Variants in these genes, and in that case it's APOE2, 3, and 4, can have an impact. That can be informative, but until the last couple of years when there were no real therapies, there was probably less interest in exactly whether individual patients have this variant and less focus on the mechanisms involved. But now that there are therapeutics and the therapeutics turn out to actually also relate to the APOE status. There's growing interest.

Hillary: There are currently seven medications approved by the US Food and Drug Administration to treat Alzheimer's. Of these seven, one is simply a combination of two of the approved treatments. And two others treat insomnia and agitation, which are symptoms associated with Alzheimer's disease.

These are by no means cures and may cause side effects, but for some patients they can really improve their overall quality of life. These treatments fall into two categories in terms of how they approach the disease. The first category of medications may temporarily lessen or mitigate some symptoms, like memory loss. So, in other words, these drugs treat the symptoms, but they do not slow the neurodegeneration, which is the brain cell damage that's caused by Alzheimer's.

Carl: Neurodegeneration does have some things going for it with respect to very strong science now, and also with respect to the approval of the beta amyloid antibody from Biogen and Eisai, Leqembi, and soon to be the approval of a similar antibody from Eli Lilly, most likely.

Hillary: Carl Gordon is a Managing Partner and Head of Global Private Equity at OrbiMed, which is an American investment firm focused on the healthcare and biotechnology industries.

Carl holds a Ph.D. in molecular biology from MIT and he was included on the Forbes Midas List of top venture capital investors.

Here, Carl is talking about a new wave of medications called anti-amyloids. These drugs actually work by removing a protein called beta-amyloid that accumulates into plaques on the brain. One of these drugs is Lecanemab, or Leqembi, by Biogen and Eisai. It was approved by the FDA just last year.

Carl: Leqembi does have real efficacy. It's very exciting to have the beta-amyloid drug that should be addressing a major cause of Alzheimer's disease get approved.

Hillary: Leqembi is an intravenous infusion therapy that patients receive every two weeks. It has proved that removing the beta-amyloid from the brain can slow cognitive and functional decline.

Two other medications of this kind are Aducanumab — approved by the FDA in 2021 and also created by Biogen and Eisai — and Donanemab from Eli Lilly, which is expecting FDA approval in 2024. As a note, Biogen announced Aducanumab will be discontinued this year, not because of efficacy concerns, but to reallocate resources to Leqembi and the development of more medications. Each treatment works differently and targets beta-amyloid at different stages of plaque formation, but they all aim to treat the underlying biology of the disease.

And that’s especially exciting because it means that these drugs could help a patient stay longer on one of those steps in the staircase that Randi described for us earlier.

Asa: I spent a decade or so working with Alzheimer's patients where we had very very little to offer.

Hillary: This is Asa Abeliovich again.

Asa: It's a tremendous advance that we have drugs now that have worked in large clinical studies, but they're really just coming online as of the last year or so. It's an almost cartoonish simple idea that we've known for a hundred years about these plaques, and lo and behold, you inject people with the antibodies, kind of like a vaccine, and after a lot of trial and error we now have ones that really work. And depending on how well they clear the plaques, it turns out that really does help.

Carl: What happened was a lot of companies came up with a lot of drugs that were aimed at reducing these plaques, but for the longest time they just didn't work. An incredible number of clinical trials failed and no one really knew why. Whenever something doesn't work, you don't know if it's because the hypothesis is wrong or if there was something wrong with the agent. And ultimately to their credit, you know, Lilly and then Eisai working with Biogen never gave up and then finally they got their drugs to work.

I think confirming that a key scientific hypothesis of Alzheimer's disease is right is pretty exciting because I think people were saying, if beta amyloid doesn't work in Alzheimer's, and that's like the most obvious thing, what is ever going to work? But no, now beta-amyloid does work, and so I think people can feel more confident that this disease is treatable.

Hillary: Again, it’s important to note that these drugs do not cure Alzheimer’s and they’re not appropriate for all people living with the disease. But they have been approved for people in the early stages that also show evidence of beta-amyloid buildup based on brain imaging.

These strides in understanding Alzheimer's disease offer so much hope. But there are still many challenges to address, like the side effects. For example, therapeutics that clear plaques can lead to inflammation on the brain.

Asa: In some of these patients, you get 10 to 30% of them having some changes. In many patients you don't even notice it. These are just seen on imaging.

Hillary: This is a side effect called Amyloid-related imaging abnormalities, or ARIA.

Asa: It's a bit of a conundrum. You have a therapeutic that's revolutionary, but it's certainly imperfect. It buys a few months and it has significant baggage essentially still. For your typical patient, the issue is this has to be started relatively early from what we know so far. And it's a conundrum because we know that probably the earliest we start, the better we're going to do, but it's hard to justify starting something that's potentially harmful in patients who don't have symptoms.

Hillary: The way these therapeutics are delivered also has limitations. The IV infusion requires regular visits to the doctor. And as we established before, early diagnosis of the disease is still hard.

Carl: These drugs have been shown to work well in the people with early-stage Alzheimer's, but you don't always find those people. Sure, when you find someone that's very confused and you find out they have Alzheimer's, but actually these drugs are going to work better in people that are just developing the symptoms.

Hillary: Detecting Alzheimer’s early gets at another concern about these therapeutics. As Carl and Asa note, the right candidate for these new therapeutics is someone in the early stages of the disease with excessive beta-amyloid buildup on the brain. Research studies show that African Americans are 35% less likely than white participants to be given the diagnosis of Alzheimer’s and related dementias, despite being twice as likely to develop neurodegenerative diseases. And for those who are diagnosed, it may be too late for the drug to have an impact.

The efficacy of these therapeutics for women has also been a point of concern. Almost 2/3 of Americans with Alzheimer’s are women, but based on the trial results Leqembi slowed cognitive decline by 43% in men, and only 12% in women.

Asa: The challenge now is how do we do better; we're now clearly so close. It's really changed the way patients think about this, how clinicians are thinking about the problem.

Hillary: Some scientists argue that this data raises questions for the next study and shows us exactly where to focus research efforts and where more investment is needed.

Carl: These beta amyloid antibodies are extremely exciting, but now we need to find a way to get them to patients and maybe to develop new drugs that perhaps wouldn't require IV infusion, wouldn't have as much imaging associated with them over time.

Hillary: As part of the drug discovery process, scientists look for a biological target — like the APOE gene that we heard about earlier — that plays a role in the disease. Then, they bring in a therapeutic that interacts with that target.

Asa: One can target these genes very directly. One can try to target these pathways. And I think it's very clear that one approach is to go after these high value targets.

Hillary: Besides APOE, one of the high-value targets is a protein called “tau.” In healthy brain cells, tau proteins help stabilize nerve cell structures. But in certain pathological situations, that can change in a harmful way.

In the brain of someone with Alzheimer’s and other neurodegenerative diseases, tau forms into these clumps that create tangles. Tau tangles are toxic to neurons and cause the cell structure to fall apart.

Asa: The challenge with tau, which is a little bit different from the amyloid plaques, is that it's intracellular, whereas the plaques are essentially extracellular, and antibodies don't really get into cells particularly well and far and away most of the tau is inside of the cells.

Hillary: Asa explained that RNA-based therapeutics, like one called antisense oligonucleotide or ASOs for short, are incredibly precise in engaging the target; in this case, the tau protein.

Asa: They're typically delivered, essentially, by spinal tap every three to six months or so. So far, seemingly look promising in being able to reduce that target. And then, this approach has actually been used in Lou Gehrig’s disease, or ALS.

Hillary: Asa’s company Leal is especially interested in exploring RNA-based therapeutics.

Asa: We started Leal about two years ago. We saw a tremendous opportunity, based on the continued advances in the genetics of diseases like Alzheimer's and Lou Gehrig's disease, particularly some of the genes involved in the late onset, and the advances in the capability to target the brain using approaches such as antisense oligonucleotides and small molecule therapeutics.

Hillary: Asa and Carl Gordon of OrbiMed met while studying at MIT, and together created two other companies previously: Alector and Prevail Therapeutics. Both are public

companies now, and after selling Prevail to Eli Lilly, they teamed up again to create Leal Therapeutics.

Asa: With Leal Therapeutics, we wanted to look broadly across the space, across opportunities. And it's a very different environment now where there's a lot of excitement around the fact that you have therapeutics in ALS, and we now have therapeutics in Alzheimer's, but it's the tip of the iceberg.

Hillary: Asa says that there's a lot of work to be done now, but there could be a future where we would be able to detect the disease early on.

Asa: Of course, the genetics can be done at birth and I think increasingly will be. The tools now are astonishing.

Carl: We need good diagnostics. Right now, if your main diagnostic is what they call a PET scan, which is a radioactive tracer that binds to beta amyloid to look for beta amyloid levels, it's probably not likely regular healthy people, everyone in the country is going to get that. But what if you had a blood test that you could take when you're getting your annual physical and just add that in there? You look at your cholesterol, your blood pressure, and here if you had a marker for Alzheimer's.

Hillary: There are teams currently working on this. In fact, a recent study published on February 12, 2024 in the journal *Nature Aging,* found that proteins in frozen blood samples could potentially predict various forms of dementia over a decade before diagnosis, which could aid in early detection. This research is part of efforts to develop a simple blood test for dementia risk, which could fast track the development of new treatments.

Carl: If you could do that, that would be fantastic and I think that's probably where the field needs to go, and then hopefully over time as we get the drugs they can be administered more easily. For example, the companies are moving to what they call subcutaneous injections versus IV infusions. You could take a shot, maybe give it yourself. I think over time the field will move in that direction.

Hillary: For patients like Susan and their families, access to treatment options for neurodegenerative disease is life changing. And to reach even more people, investment in research could make all the difference.

Carl: I've seen so much change in the field of medicine over the course of my career.

Hillary: For about two decades, Carl's career has been aligned with OrbiMed. The company’s name is actually a combination of “orbi,” meaning global, and medicine. So, the idea is for them to invest in the most innovative medical companies anywhere in the world. The majority of their business is in the US but they also have very active portfolios in Asia and Europe. Carl is a seasoned investor who understands this market well.

Carl: There are always new things that are happening, but there's always some sort of pattern to the investment landscape and there are times when people are more excited to invest in biotechnology and there are times when people are a little bit less excited. And right now, we're in a little bit of the more negative cycle for biotechnology.

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

Carl: As with all big economic ideas, there are a lot of different factors that play into it. I think most recently a rising interest rate environment has been the key reason that investors have pulled some capital out of the emerging biotechnology companies and invested it in other sorts of securities. But if you look at the biotechnology industry over long periods of time, you know, there are always ups and downs. It's a volatile industry. And what we try to do is to be successful across all cycles and to pay attention to the market environment and try to structure our investments and the strategies of our companies so that they can be successful no matter what the outside environment is.

Hillary: He lists three reasons for OrbiMed's excitement about investing in neurodegeneration work.

Carl: (A) It's a great medical need, (B) the approval of Leqembi, the beta amyloid antibody from Biogen/Eisai, and (C) the very strong scientific background that is creating new ideas for how to treat these diseases. At some point, neurodegenerative disease, led by Alzheimer's, will become a major area for the industry, I think in parallel to what happened with cancer. We're not there yet, but we're looking at it and we have invested in some neurodegeneration companies and we'll continue to do that. All of these problems in neurodegeneration are very hard and no one person is going to solve them. So, we all have to collaborate.

Hillary: OrbiMed manages 17 billion dollars across public and private company investments in a range of technologies including gene editing, AI and machine learning for drug development, and much more.

Carl: There will be a time for every technology. Maybe some technology is actually never going to work, like time travel. There's probably no time for time travel outside of science fiction. But most technologies that are realistic, they do work eventually. So, I think that's what we're trying to do: identify those technologies that with a little push can get over the hump and that can make a substantial difference in medicine, within a reasonable amount of time. And that reasonable amount of time can be long. It can be three years, it can be five years, maybe up to 10 years, but you know, it can't be 20 years.

Hillary: Ham Lee is my colleague and a Partner and Co-Head of the Healthcare Practice at Cambridge Associates, and in our interview I actually learned that he landed his job at Cambridge Associates fresh out of business school.

Ham Lee: When I was in business school, Cambridge Associates came interviewing and I was absolutely thrilled at the prospect of being able to not only work with an individual endowment or foundation but work with and have an impact on several of them.

Hillary: And twenty years later, he continues to do just that: managing custom portfolios for healthcare systems and other not-for-profit clients all over the country. And Ham says healthcare institutions have been paying close attention to the work that companies like Eisai, Biogen, and Leal are doing as it relates to neurodegenerative diseases.

Ham: Innovation plays a critical role. We have clients who have sort of realized that they are in a unique position as healthcare institutions to know exactly what they need in terms of innovation on the medical side and on the operating front. So what we're starting to see is that a lot of healthcare systems are intentionally investing in that innovation through their portfolios, either as part of the private investments program and the long-term portfolio. Or we're also seeing a lot of large systems dedicate separate pools to strategic, mission-related venture capital investments.

Hillary: Ham has also felt the impact of dementia in his personal life.

Ham: My parents are approaching their 90s and they are starting to show some signs of dementia. It's not a major problem yet, but these are highly educated, very accomplished people, and I know that they are living in fear of their bodies outliving their minds. So with the advent of some of these drugs that can slow the progression of Alzheimer's, I know for a fact that it has given my parents some hope and some peace.

Hillary: As an investor, Ham says the advances made in recent years to slow the disease progression are a huge positive for society.

Ham: This is a terrible and costly disease, but there is an economic side to it that the healthcare industry is going to need to grapple with. Nearly 300 billion dollars is spent every year treating Alzheimer's and taking care of people with Alzheimer's disease.

It's significantly more expensive to care for a person of a given age with Alzheimer's than it is someone who doesn't have Alzheimer's. So not a lot of that money is spent in hospital systems, but in assisted living, skilled nursing or nursing homes. And a lot of very large systems incorporate those into their business models, so there will be a financial impact.

To the extent drugs like Lecanemab or others slow the progression of disease and delay or even reduce the need for that care, it's going to have implications for the revenue and cost structures of health systems. And of course, the same is true for other diseases where there have been major breakthroughs that not only treat the disease, but also other diseases that are comorbid with it. Obviously that's fantastic news for all of us and very much in line with the mission of these health systems, but it is going to have ramifications for how they operate in the future.

Carl: I think we need to make the case as an industry that our medicines are creating a lot of value.

Hillary: That's Carl Gordon again.

Carl: And that the more society invests, the more medicines you're going to have. It's ultimately a sort of a societal investment decision.

Hillary: These advances are giving hope to patients like Susan. Eventually, she was able to move in with her sister and with support from her family they found treatment options for her.

Randi: We were able to get her in a clinical trial. Of course with those it's double blind, so we don't know if she's getting the medication or not.

Hillary: We don't know what drug is being tested in Susan's clinical trial, but in her case, the family has noted a real difference. A particular group of symptoms people with Alzheimer's disease can get is called "sundowning," and it refers to a state of confusion that occurs at night.

Randi: They have drastic shifts to their moods. They can sometimes get angry, sometimes violent. Luckily we haven't seen the violence from her, but there was another element to sisters bickering that was very prevalent in their day to day before the clinical trial. And we've seen a total elimination of her sundowner syndrome during the medical trial, which has been really great to see.

Hillary: That's incredible.

Randi: Her long-term memory is intact. It's just like day to day, week to week where she can't keep up. And if you have a conversation with her over the course of a couple hours, like you're going to repeat the same conversation a couple of times.

But while she's no longer hosting big holiday meals for the family, she still loves to cook. I think she gets a sense of purpose out of feeding others. So my freezer is always full of homemade meatballs and sauce. I think like reading, there's going to be a time where she can no longer follow a recipe, and it might be dangerous for her to be in the kitchen, but we hope that day is very far away. Day to day, I think she's living a pretty good quality of life.

Hillary: And while Susan and her family learn to manage the disease, investors and scientists are building on this momentum to further research and innovation.

Asa: We now have effective therapies that actually slow the disease. They're not at all perfect. Their effects are still limited. They slow the progression of the disease; they don't stop it, they don't reverse it. And they slow it quite incompletely, but it's a remarkable start

and certainly in the biotech space and in pharmaceutical companies. There's just tremendous excitement now that, you know, it's a foot in the door.

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.

You can find more information about Alzheimer's at the Alzheimer's Association website alz.org.

At Cambridge Associates, our podcast team includes Michelle Phan, and me, Hillary Ribaudo. And a special thank you to Megan Morrisey, Robert Scherzer, Krista Matthews, Deirdre Nectow, and Carter Neild.

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Next time on Unseen Upside, join us as we explore innovations and precision oncology that are both helping in the fight against cancer and making treatment more equitable:

Changing cancer is hard, like period. With the technology working where it is, the problems are people problems. We have to convince a doctor to do something different. We have to convince insurance companies and Medicare to do something different.

The world I want to live in is one where patients routinely respond to their cancer drugs. We're not there today, and we're not going to get there unless we do something different.

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

[DISCLOSURE]

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