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**Speaker 1:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast* and I'm Lynn Yoffee. During a year dominated in large part by COVID-19, another crisis continues to unfold across the globe. It's the increasing prevalence of dementia with Alzheimer's disease as its most common form.

As researchers for more than 110 countries gather for the Alzheimer's Association International Conference this week, we wanted to take stock of an important disease that, with its growing global incidents, touches millions of lives.

To discuss some of the most important issues under consideration at the meeting and in the broader field, BioWorld staff writer Lee Landenberger today is joined by Dr. Howard Fillit, founding executive director and chief science officer at the Alzheimer's Drug Discovery Foundation, which was founded by Estée Lauder heirs Leonard and Ronald Lauder to accelerate the discovery of drugs to prevent, treat, and cure Alzheimer's disease.

Dr. Fillit, a geriatrician, neuroscientist, and professor at Mount Sinai School of Medicine, has led the foundation since its founding in 1998. Thank you for joining us today, Dr. Fillit. Over to you, Lee.

**Lee Landenberger:** Thanks, Lynn. Welcome, Dr. Fillit. Thanks for spending time with us today.

**Dr. Howard Fillit:** Thanks, Lee.

**Lee:** You've helped broaden understanding of this disease. Tell us a little bit about the venture philanthropy approach the foundation takes and its role in advancing care.

**Dr. Fillit:** Sure. Thanks. Well, we were incorporated in 1998. In our incorporation papers, we told the Internal Revenue Service, which oversees all philanthropies in the United States, that we were going to do three things and only three things. They were all related to the development of new drugs for Alzheimer's.

Number one, we were going to develop new biomarkers that would lead to blood tests, but more importantly, would accelerate the development of new drugs. You saw that play out dramatically with recent approval, accelerated approval of aducanumab, Biogen's drug and I could talk about that later.

Secondly, that we were going to develop new prevention methods for preventing Alzheimer's disease, including drugs and lifestyle approaches.

Number three, that we would be heavily invested in developing new drugs for Alzheimer's disease.

As a result of that, we developed a business model because we realized that we were in a commercial space, basically, wanting to bring new drugs to market and accelerate their development.

With that, we adopted a model where we would, as we invested in biotechs, which we told the Internal Revenue Service that we intended to do, that as we invest in biotech companies, in programs, and in universities, that we would seek a return on investment that would lead to more revenue for us to invest in new research.

Finally, that we would take a very proactive approach to accelerating the development of new drugs for Alzheimer's disease, hiring scientists like myself, reaching out to scientists all over the world, funding internationally in over 20 countries now, and helping scientists to develop their ideas and their programs for new drugs for Alzheimer's disease, sort of like a venture model, but in the non-profit sector.

**Lee:** There's a new University of Washington forecast that was presented at the Alzheimer's Association International Conference this week that estimates the number of people with dementia globally is going to triple to more than 152 million people by 2050. What are some of the most important ways that research might help get ahead of the trend?

**Dr. Fillit:** Well, there have been studies looking at what the impact of treatment and prevention would be on the occurrence of the disease. I think it's an achievable goal. It's clearly achievable to reduce the prevalence and the incidence of Alzheimer's disease.

One study by one group showed that if you consider it in a simplistic way, let's say, the average age of death in the United States is 80 years old. Let's say that the average age of onset of clinical Alzheimer's disease, namely, dementia, is about 75. Let's say that there was a way that we could delay the onset of dementia by just five years.

If we did that, then the number of new cases of Alzheimer's disease would be reduced by 50%, which is huge because the reason being that people would live a full life without-- 50% of people would live a full life at that point without having ever developed cognitive impairment or dementia. I think that's an achievable goal. People would die from other causes like heart attacks, hopefully, in the middle of the night, and not have to suffer this nightmare. That's one way to do it and is that possible today? Well, not too long ago, the Lancet Commission, which is a very well-known group that does reviews of what evidence is out there, they came out with a very large report and a leading journal out of the UK called Lancet, which delineated all that we know about prevention of Alzheimer's disease.

They stated based on current research that 40% of cases of Alzheimer's disease and related dementias could be prevented, if people did simple things, like, don't smoke, don't drink excessively, exercise, watch your hearing, makes sure that your hearing is okay.

If you have comorbidities like diabetes and hypertension, manage them well because their risk factors for cognitive decline in late life in Alzheimer's disease, eat a healthy diet, a Mediterranean diet has been shown to reduce the risk of Alzheimer's disease.

The Lancet, a very prestigious group out of the UK and Europe, has already said that if people live this lifestyle and manage their medical comorbidities, that 40% of the cases could be prevented.

Then, **[unintelligible 00:06:36]** who's now one of our board members, a professor out of the University of Kuopio in Finland. She did a randomized clinical trial looking at whether or not if people who are basically well, but in mid-life and in late life, but not necessarily cognitively impaired, but just undergoing cognitive aging, if they adhere to these preventative measures, what would happen in terms of their cognition? She showed in a randomized trial where there was a control group that didn't adhere strictly to these methods, that the people who did adhere to these methods actually had a slow rate of cognitive decline.

We have a lot of data now that Alzheimer's is preventable and we like to say in a soundbite that doing all the things that people are currently aware of to prevent heart disease, including one more thing related to the brain, which is staying socially and or occupationally engaged, keeping your mind stimulated, doing all those things can help you to prevent or delay the onset of Alzheimer's disease in late life. I think that that's one thing that we can do.

The second thing that we can do is develop drugs and we're getting so much more progress in the development of drugs for Alzheimer's disease but what we really want to do is move those drugs into prevention and that's already being done as well.

For example, our foundation just funded the addition of a leading anti-aging drug that's out there, a drug called metformin, which is a diabetes drug, the leading diabetes drug in the world, but it's also an anti-aging drug and it's known to have effects on insulin sensitivity and glucose utilization in the brain, which is a huge user of glucose as a source of energy. Just like in diabetes, there's insulin resistance. There's insulin resistance in the aging brain.

What we're doing is in the next iteration of Dr. **[unintelligible 00:08:47]** prevention studies is adding on drugs like metformin to see if we can get further impact on preventing Alzheimer's disease but even drugs like the anti-amyloid antibody, aducanumab that was just approved for the treatment of people with mild dementia and mild cognitive impairment, there are studies using those kinds of drugs and people who are normal and seeing if we can prevent the progression of amyloid deposition in people who are cognitively normal.

The big breakthrough there was a biomarker called PET Amyvid where amyloid scanning, using PET imaging to identify people who are cognitively normal in mid-life, who have early Alzheimer's disease in their brain. We can do that now with modern techniques and identify people at risk and then get them into a treatment trial or a prevention trial, I should say, and see if we can prevent the progression of that amyloid accumulation or even reduce the amyloid accumulation.

The goal there is that before people even become symptomatic, we would prevent the disease. So, it's just amazing what's going on now. It's just incredible.

**Lee:** Biomarkers are a big focus of your work at the foundation and one that you invested $2 million in recently. Can you tell me a little more about work on developing digital biomarkers with the Alzheimer's Research, UK?

**Dr. Fillit:** Sure. Well, biomarkers come in a number of flavors. There is no imaging biomarkers which we could talk about that have really revolutionized the field and enabled the recent Biogen work that led to the first disease-modifying therapy, getting an accelerated approval.

An accelerated approval means that there was enough biomarker evidence in that trial that the FDA felt confident that the drug would have a clinical effect. Biomarkers really enabled the recent approval. You have neuroimaging biomarkers that are well-validated. We can see plaques and tangles in the living human brain of people. We have spinal fluid biomarkers that are really good biomarkers and a lot of innovative ones that can look at, again, beta-amyloid in that spinal fluid, tau in the spinal fluid, inflammation in the spinal fluid that affects the rate of progression of Alzheimer's disease.

Now, in the last few months, we had the approval in the United States through what's called a CLIA approval for the laboratory-developed tests by a company called C2N test called PrecivityAD, which is the first blood test for Alzheimer's disease, another company that we invested in another program that the foundation invested in.

Today, in my office, if a patient comes in with a memory complaint and, let's say, they're 65 and they want to know what they have, maybe they want to go into a clinical trial, I can send them for a brain scan. I can do a spinal tap. Now, I can do a blood test and there's other blood tests coming down the road.

The digital biomarkers that you refer to are adding a fourth component to our ability to detect changes very early and very inexpensively in patients, in people with, let's say, preclinical Alzheimer's disease, let's say, somebody is using their computer and they're in the earliest stages of Alzheimer's where if somebody met them on the street or even their spouse might just have an inkling that there's a little bit of a problem, but it's not really clear. They're not ready to go into the doctor, but they might go onto a website where the tracking of how they use the computer can be made and differences between normal people and people in the very earliest stages of cognitive impairment, a digital biomarker using your computer. It can be picked up on a passive or an active basis.

In other words, on a passive basis, it might be a program that monitors your computer use. I can pick up that as things are changing, maybe you need to go to your doctor and get an evaluation, or it could be active. Maybe you're concerned about your cognitive function and you have what we call subjective-cognitive decline, which is the earliest clinical stages of the disease where even doctors or neuropsychologists might not be able to pick up your cognitive impairment but you know that there's something going on. We call that subjective cognitive decline.

Now we have tests that can actually-- using digital technologies like computers, like smartphones, and so on, can pick up the very earliest changes. For example, we're developing, as another example, of speech and language consortium that will monitor the speech and language of individuals.

Again, one of the earliest changes that happens in people with very early Alzheimer's disease and related dementias is changes in their language, vocabulary declines. the complexity of sentences gets more simple, and grammar changes. The prosody, the use of emotion in language changes. We can pick all of these changes up using modern voice recognition technology.

Maybe you're talking into your phone, your smartphone, and were supporting digital technologies that will be able to, let's say, your doctor is concerned and you complain of subjective cognitive decline. Maybe instead of doing a blood test or an addition to knowing a blood test, your doctor could sign you up for an app that would measure your speech and language, and the doctor would get a report. That report would tell the doctor whether your speech and language predicts that you're going to get Alzheimer's disease. Another new biomarker category that's coming of age now are retinal biomarkers. In this case, the retina, the back of the eye is the mirror of the brain. We can see amyloid deposits and look at the microvasculature of the back of the eye in the retina. That predicts the early onset, that detects, I should say, the early onset of Alzheimer's disease in people.

Imagine one day when you go for, and that day is not far off, maybe a couple of years at most. You'll go for your routine annual eye exam. In addition to saying if you have cataracts and what your vision is, the doctor will have a device or the ophthalmologist will have a device, or maybe the optometrist will have this device where they can look in the back of your eye and see if you have Alzheimer's disease and what your vascular status is in terms of how it relates to cognitive impairment.

All of these biomarkers, these five categories that I've given you are going to change dramatically. They're already changing, but they're going to change dramatically. The landscape of cognitive decline with aging Alzheimer's early detection. Again, clinical trials, because all of these biomarkers will be used one way or another in clinical trials to make them more efficient, more rigorous, more sensitive, and less expensive.

**Lee:** Even with these great advances, it's still tough to differentiate between different types of dementia, like between Alzheimer's disease and frontotemporal dementia and dementia with Lewy bodies. Has there been any progress on differentiation? If there has been, what does that mean for patients?

**Dr. Fillit:** Well, it's difficult for the clinician and let's say a primary care setting to make that distinction. Let's compare the three that you mentioned just as a starting point because there's also vascular dementia, which is the second most common cause of dementia in elderly people and a few other kinds of dementia that we could talk about, but let's stick to the three that you mentioned which was frontotemporal dementia, Alzheimer's disease, and Lewy body disease.

On a clinical level, Alzheimer's disease is generally, and this is stereotypic, generally characterized by early memory loss, particularly specific type of memory loss that's created in a specific part of the brain called the hippocampus and the interveinal medial temporal cortex.

In the case of most people with Alzheimer's disease characterized by plaques and tangles, the clinical manifestation is what's called episodic memory loss. In other words, you forget things that are happening in your short-term memory, but your long-term memory remains intact. You generally don't have what's called executive dysfunction.

Executive dysfunction is based in the front of the brain, in the frontal lobes of the brain, executive function, human cognitive tests, like abstract reasoning, multitasking, planning, scheduling, emotional control, and those kinds of activities that make us human.

In that case, the pathology in the early stages is characterized in the frontal lobes because that's where the disease starts. The primary manifestations early on are executive dysfunction and not necessarily memory loss and often characterized in the clinic as a change in personality. Then, you have Lewy body disease, which affects the brain in a different part of the brain, generally in the parts of the brain where Parkinson's disease is affected and it's a continuum with Parkinson's disease.

Here, it's characterized by deposits of Lewy bodies that are composed of a molecule called alpha-synuclein. In this case, the progression of the disease is often beginning with memory loss, but people have other features, particularly hallucinations, and visual disturbances, and a lot of aggression in this kind of behavior.

We can distinguish patients of those three diseases by their clinical presentation. Then, we can look at their MRI imaging as the next test. If you do an MRI, particularly if you do what's called a volumetric analysis where you actually quantify the brain volumes of different regions of the brain. What you're going to see is what you expect for the three different kinds.

In Alzheimer's disease, you're going to see shrinkage of the hippocampus, which can be measured quantitatively using modern computer techniques. You can measure the volumes and the presence of disease in the frontal lobes. We can specifically see that there's frontal atrophy on the MRI and designate people as having frontotemporal dementia based on their MRI patterns. Similarly, with Lewy body disease, we see specific patterns of atrophy as well. Then, we can do a PET scan, Positron Emission Tomography. What that means is that we can look at, for example, glucose utilization in different parts of the brain.

We talked earlier about how the brain is 3% of the bodyweight uses 25% of the body's energy at any given time. Most of that energy comes from glucose and oxygen. That's why a diabetic that becomes hypoglycemic, within seconds, the first thing that happens is that they go unconscious, but we can use that fact that biology and use a certain form of glucose and inject that non-radioactive form of glucose called fluorodeoxyglucose, which is, sorry, radioactive, but very mildly radioactive. It doesn't affect anything.

We can use that fluorodeoxyglucose to look at metabolism in the brain. What are we going to see? In Alzheimer's disease, you're going to see metabolism of glucose in the hippocampus and the temporal lobes. In frontotemporal dementia, you're going to see decreased metabolism in the frontal lobes. Then, Lewy body, you're going to see it somewhat in the temporal lobes, but then you can do another test to look at where the Lewy bodies are affecting the brain in the basal ganglia and so on.

We can use imaging. More specifically, now we have FDA-approved tests, like the ones that we used in the Biogen trial, where we can specifically see the amyloid and that's specific for Alzheimer's disease. We can send people for a third form of neuroimaging and find the amyloid in their brain and specifically make a diagnosis of Alzheimer's disease. We can also detect tangles. Tangles aren't specific for Alzheimer's. They're seen in many different forms of dementia, but they do tell us something about what's going on with the disease.

Similarly, these blood tests and spinal fluid tests that I talk about can be used to discriminate. Long-winded answer, but the bottom line is actually that it's not as clear as we would like. What we're finding is that many people have mixed forms of dementia.

So 35% of people who are diagnosed with Alzheimer's disease had autopsy who have amyloid plaques and tangles in their brain also have Lewy body. A lot of people, as they progress through the stages of dementia will have frontal lobe disease and develop executive dysfunction, which is very disabling. We know now that there's many different mixed types of dementia and it's changed the way we look at drug development because we realized that it's going to be harder to get a magic bullet when most people have these mixed dementia.

**Lee:** Yes. Speaking of drug development, one of the big questions at the conference this year is about the approval of Aduhelm and how it might impact the way that clinical trials are conducted. I have a couple of questions for you. Might Aduhelm become the control treatment in new studies and might ongoing trials be affected by people dropping out to take Aduhelm in the future?

**Dr. Fillit:** Think about cancer. There, it's the case you're referring to in the extreme. We have many drugs on the market for cancer, but people still need to go into clinical trials. What we know for most diseases is that less than 5% of people with any particular disease want to go into a clinical trial. These are often unique people that really want to make a contribution and they want to try something new.

Sometimes, they have a form of the disease based on their biomarkers that doesn't fit well with the current therapies. So, they want to try something new. The 5% or less metric is true for cancer and it's true for Alzheimer's disease. I think what's going to happen with aducanumab is that a certain proportion of people with Alzheimer's disease will go on treatment, but we don't know how long they'll stay on treatment. There's a certain burden of receiving that drug. There's a lot of imaging. There's neuro-psych testing. There's monitoring of side effects with imaging. There's the monthly infusions. There's potentially the cost of the medication.

I think that there'll be plenty of people available for other clinical trials and particularly where there are small-molecule treatments available to be tested. When I say, "small molecules," I basically mean treatments that involve a daily pill rather than having to go for an injection once a month, that potentially 40% of the people who take that injection once a month are going to have side effects. There's a huge cost potentially for the people to take that drug.

The clinical efficacy is modest at best. I think you might get a lot of people starting on it, but I'm not sure how long, and how many people are going to stay on it over time. Aducanumab and some of the other anti-amyloid monoclonal antibodies that hopefully may come to market, they're not going to be the end.

The other thing is that that's one target, amyloid. Just like in cancer, you have to have combination therapy based on precision medicine as determined by multiple biomarkers. We knew we're going to have the same thing in Alzheimer's disease.

For example, if somebody is found to have a tumor in their lungs, the old days where you get an x-ray, you see the tumor, you put people on chemotherapy, mostly often shotgun, and you hope the tumor shrinks. If the tumor shrinks, you think you have a win, but cancer is nothing like that anymore.

Now, we do a biopsy of the lung cancer. We type the cells according to multiple cellular biomarkers, and we design a rational combination therapy for all the pathways in that cancer cell that are deranged that will lead to that cancer. Then, we monitor those biomarkers over time with this combination therapy.

That's where we're going now in Alzheimer's disease. I described all the multiple biomarkers that we're going to have inflammation, epigenetics, metabolic, mitochondrial, and so on. We're going to have multiple biomarkers, not just amyloid plaques and tangles for Alzheimer's. We're going to subtype people according to, again, the Lewy bodies, the TDP 43 subtypes, the amyloid subtypes.

Then, we're going to have precision medicine for Alzheimer's where people will be on combination therapy. Maybe some of the people that are on aducanumab, what can we add to aducanumab to make that therapy better in an incremental way? The benefit right now with aducanumab and these other anti-amyloid **[unintelligible 00:28:07]** is modest at best.

Actually, imagining a world in the coming year or two, let's say, or whatever, where the standard of care might be some monoclonal antibodies, but what will we add to that to get them more clinically meaningful clinical response?

One thing we do know, for example, is that inflammation in the brain around the plaques causes a faster rate of progression and even causes symptoms, and people who don't have inflammation around the plaques may be asymptomatic. They may be able to tolerate those plaques, those amyloid deposits.

I think another high chance of the next round may be, okay, we'll put people on monoclonal antibodies for amyloid, but maybe we need to add an anti-inflammatory, a very specific brain anti-inflammatory that's going to, not only help to remove the plaques with the aducanumab and other monoclonals, but it's going to reduce the inflammation in the brain that leads to cognitive impairment in most people. That might be the next incremental step. Now, you're on two drugs.

I really don't think it's going to have a huge impact on clinical trials. I think there'll be a blurb, an upswing in people that will go on the monoclonal antibodies but eventually, I think there's going to be plenty of room for other clinical trials.

By the way, we have over 120 drugs in clinical trials today for Alzheimer's disease, and more than half of those drugs are not amyloid-related or even tau-related drugs. There's a lot of innovation going on in the field now.

**Lee:** My last question for you is about money. Financing is a huge issue, obviously. A very small percentage of public and private financing dollars we estimate it to be about 3% to 4% of the billions that are invested annually is actually focused on Alzheimer's or dementia. It seems like a low number. Does it seem that way to you?

**Dr. Fillit:** Well, yes and no. It's one reason why we need venture philanthropy to take risks. Yes. Investors have been afraid of investing in Alzheimer's disease because we've had such a high rate of failure. We haven't had a drug approved since 2003. Now, we finally have one. What we're seeing now is a marked increase in investor interest. I think it's very timely. I think it's a perfect storm of good things happening right now.

We've been at this. I've been at this since about 1980, so over 40 years. When I started, we knew nothing. I mean, literally, nothing about Alzheimer's disease. The initial budget for the National Institute on Aging in 1975 at a time when the National Institute on Aging was started, and we were having the war on cancer and the war on heart disease and billions of dollars in 1975 dollars, attributed to those fields of research. We spent, as a nation, $625,000 on Alzheimer's research.

Now, the National Institute on Aging is spending $3.5 billion on Alzheimer's research. It's one of the largest institutes at the national institutes of health, one of the largest programs. Pharma has spent many tens of billions of dollars over the last 20 years on Alzheimer's research and they failed, but let's face it, 90% of people, who work in the pharmaceutical industry will spend their entire careers never working on a drug that comes to market for most indications because developing a drug, developing a little pill to prevent or treat a disease is really hard to do.

What we had to do over the last 40 years is build the basic science so that we can start translating that basic science into new drugs and we're just seeing an exponential increase. Like I said, there's over 120 drugs in development now. We're seeing lots of biotechs entering the field, IPOs, and a lot of investor interest in Alzheimer's. The reason for it also is because of those biomarkers.

We can show target engagement now. We have biomarkers that can show a pharmacodynamic effect of drugs to show that these drugs are working in the brain which is hard to do. We're able to do modern, efficient, rigorous, clinical trials in Alzheimer's disease. We've established the template for how to do clinical trials. There can be confidence that when we do clinical trials in Alzheimer's disease now, we know what we're doing. I think that makes a lot of difference for investors to know that there's a pathway here, not only to approval, but to getting the right information and making **[unintelligible 00:33:11]** at decisions.

The upside is huge. That's always been the case. In the past, a lot of investors were making investments because the upside was huge, even though the science was not necessarily there. This will be the largest pharmaceutical market in the history of the world.

Biogen's drug already is being touted as that and it's a problem. It could bankrupt Medicare, but the difference today is that, yes, it will be the largest pharmaceutical market, but, also, we have the science now to deliver on these clinical trials and this multitude of different kinds of drugs that are going to be coming through the pipeline.

I think it's very clear. We're seeing investors now having more confidence in investing in Alzheimer's programs. I hope that that's going to continue, I think, frankly, it will only increase. It's expensive.

One Phase 3 clinical trial in Alzheimer's cost about $400 million. Let's say you need two or three of those. We're talking about a billion and a half dollars all in to bring a drug to market, maybe more for Alzheimer's. It's expensive but the return on investment is huge.

Why is it expensive? There's all this neuroimaging, but we're going to be able to reduce the amount of neural imaging because we have blood tests now, that reduce the cost of screening, and monitoring of therapy by maybe almost tenfold. We're going to have digital markers where we can detect people's cognitive impairment and measure it over time instead of very expensive neuropsychological testing which has to be done now.

I think it's a really exciting time to be in our field in developing drugs for Alzheimer's and I think investors is looking to us. The amount of money coming in is increasing. It may be a small percentage now, but I think it will grow and I'm very optimistic about the future.

**Lee:** This Is fascinating. Thanks, Dr. Fillit. It's been a pleasure talking to you today.

**Dr. Fillit:** Thanks a lot. Same here.

**Lynn:** Thank you, Dr. Fillit and Lee. As always, BioWorld will continue to report on the incremental scientific, clinical, and business updates in this field. That's our show for today. If you need to track the development of drugs, turn to bioworld.com. Follow us on Twitter or email us at newsdesk@bioworld.com. Thanks for joining us.

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**Speaker 1:** BioWorld published by Clarivate is a subscription-based news service, but all of our COVID-19 content, more than 5,000 articles, and data entries since the start of the pandemic are freely accessible.

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