REVERSE ALZHEIMER'S SUMMIT

Retinal Amyloid Imaging And Blood Biomarkers - A Combination Approach To Alzheimer's Disease

Dr. Heather Sandison, N.D. interviewing **Steven Verdooner**

Dr. Heather Sandison, N.D.
Welcome back to the Reverse Alzheimer's Summit. I'm your host, Dr. Heather Sandison. And I'm so thrilled to have Steve Verdooner with me today from Neurovision. Steve is a seasoned, results driven executive with over 30 years of experience in the ophthalmology, neurology and medical device markets with the proven track record of launching and leading successful startup businesses.

He has expertise in a diverse range of business management, including sales and marketing, research and development, operations, and regulatory management, as well as business development and strategic planning. Steve has a proven ability to lead an interface with key opinion leaders, advisory boards, customers, scientists, engineers, company boards, and the financial community. Steve serves as the co-founder and CEO of Neurovision Imaging, a company developing retinal and fluid biomarkers for neuro-degenerative diseases. Welcome, Steve.

Steven Verdooner
Thanks Heather

Dr. Heather Sandison, N.D.
It's so great to have you here because you are the type of person having just shared your bio with everyone. You're the type of person that can make someone's ideas a reality, right? Like you put all of these pieces together so that when a patient is struggling, they can get the answers they need to make those really critical medical decisions. So tell me, tell me, how you started Neurovision and what your path to this space was.

Steven Verdooner
Right, so thanks again for having me with your program, very much appreciate it. So Neurovision was actually started a little bit over 10 years ago when I read a press release actually, out of Cedars-Sinai Medical Center in Los Angeles. And this was the very first discovery of amyloid beta plaque in the retina.And this was done out of the Koronyo Lab by work by Maya and Yosef Koronyo, and Dr. Gwen with Dr. Keith Black and Paul Schwartz. And that was the genesis of Neurovision. I read that press release And my background's in retinal imaging.

I was always fascinated with other diseases that manifest in the retina, whether they be neurodegenerative, cardiovascular risk factors, always had a fascination, was looking at other applications, built a company in retinal imaging previously, took it public. So this was like the next frontier for me, saw this press release, saw great potential, flew down two days later. And long story short, we formed a company licensed the IP from Cedars and off we went. At that time, it was just in transgenic mice and human cadaver tissue. So we had a very long path ahead of us to develop the technology into something that could ultimately be used in humans.

Dr. Heather Sandison, N.D.
Wow. So tell me exactly what is retinal imaging and what are you looking for?

Steven Verdooner
Right.So retinal imaging has existed for a very long time. My very first company back in 1985 was the first company to do digital imaging of the retina; effectively take pictures of the retina. So originally this was all done on photographic film.

And then with specialized instruments, a patient puts their head in a chin and forehead assembly. You dilate the pupil, in most instances, and you take pictures of the retina or the back of the eye. And it made sense, for example, in the Koronyo work that we would see amyloid in the retina in the back of the eye with imaging.
The retina is a developmental outgrowth of the central nervous system. So we, we expected to see the same kind of findings that you would see in brain almost like another brain region, but effectively retinal imaging has existed for a long time for retinal disease, macular degeneration, diabetic retinopathy, glaucoma, taking pictures of the back of the eye sometimes with dye sometimes with different wavelengths. And so where that ties in is

with different wavelengths. We do a procedure called auto fluorescence. So there are certain features in the, in the retina that actually fluoresce. And so when we look at that spec, those spectral characteristics, and in fact, a beta amyloid plaque, and other, other types of features in the retina, like Drusen for macular degeneration fluoresce. So it's, it's using these devices to image them and then ultimately process and analyze and segment them.

Dr. Heather Sandison, N.D.
So in the case of dementia, we're looking for a beta amyloid plaques. Now, how does that get from my brain into my eye?

Steven Verdooner
Yeah. So very good question. And we've asked a lot of scientists that question, in terms of how it does, so, as I said, that's not known, is the short answer, how it actually gets to the back of the eye. I think what we do understand is if you look at the retina, it acts like a brain region. And as I said, it's a developmental outgrowth of the central nervous system.

A lot of the same and the Koronyo lab at Cedars has shown this exquisitely, they've shown microglia, they've shown tau, they've shown amyloid; a lot of findings that you see in the brain and the, and the pathology associated with Alzheimer's disease, you also see in the retina, even the, the morphology of the plaques that you see in brain is mimicked in the retina and the, a very exquisite examples of this, where you can actually see punctate amyloid beta plaque artifacts in brain and in retina. And so we don't know how they get there, but they're there. And this has been proven and also work duplicated in other labs as well.

Dr. Heather Sandison, N.D.
Interesting. So how do you tell, you said you fluoresce different things. How can you tell what one thing is compared to another? So how do I know for sure it's a beta amyloid plaque and not macular degeneration?

Steven Verdooner
Right, it's an excellent question So in our earliest studies, we used something called Curcumin. So Curcumin actually has a, first, they did it in mice, they injected it and they demonstrated that Curcumin has a very, and this is known, has a very high binding affinity

to amyloid beta plaque. So it works a lot like the different amyloid pet probes where it binds, and it also has a fluorescent spectral characteristic and, and the Koronyos figured out what that spectrum looked like. And we translated that into devices that could be used in humans, but the Curcumin enhances the, the auto-fluorescence that we already see.And so it does provide some specificity, although there are different features that also fluoresce in the retina. But, but if, so, for example, in macular degeneration, someone may have something called Drusen, which are large, irregularly shaped, puffy looking things that also auto-fluoresce. What we're looking for in Alzheimer's is we know what to expect in the morphology of amyloid beta plaque.

There's small dot like punctate lesions. And in fact, in our most advanced studies, those are the things that correlate best with what we see in patients that are amyloid positive. So if you roll the story all the way ahead to the end, it's turning out that that's, what's driving the signal, these small punctate plaques. And that's what we detect from this fluorescence in the retina.

Dr. Heather Sandison, N.D.
So does someone's, Alzheimer's need to be pretty progressed in order to find these amyloid plaques in the eye and the retina?

Steven Verdooner
No, in fact, even before we existed in pathology studies, you see a buildup of plaque in the brain. As we know in cognitively normal test subjects. In fact, we did a very large study with a major pharmaceutical company in, in 100% cognitively normal population. That's what their drug target was. Yet they did PET scan on all these patients, and we did very well segmenting, amyloid positive from amyloid negative in retina. We actually currently are doing a study with David Bennett at Rush University, as part of the ROSMAP study. We're in fact, we are imaging in vivo, and then after patients pass, they've consented to autopsy. And so we'll have live imaging, blood biomarkers, and then ultimately we'll have the pathology from brain and retina, and we can make that direct connection.

And so we, we know that, that we see the buildup at the very earliest stages, both in brain and retina in mice, in human cadaver and eventually we'll make that direct correlation in, in live human test subjects all the way through post-mortem.

Dr. Heather Sandison, N.D.
What an exciting technology. I was mentioning to you before we started recording that, you know, clinically, I would love to be able to see something that we could show a patient. Look, we took a picture. We know this is developing in your brain before you even have any symptoms. If we could do that, that would give us all the power in the world to prevent that disease process from progressing.

Steven Verdooner
Right.

Dr. Heather Sandison, N.D.
So how far away from that are we? When can I offer this to my patients?

Steven Verdooner
Well it's a, it's a good question. So of course we have the FDA appropriately that we have to get clearance from. Our device, actually that we would utilize is cleared. It's 510 cleared, the actual retinal camera. So again, 10 years ago, it started in mice, but we now have a 510 cleared camera called Retia. So the camera's ready to go. And we use that in 24 different cameras and 15 different sites and clinical studies. And we also have a software as a medical device, called Afina, A F I N A, that's cleared by FDA that actually does the image processing and measurement.

That was no small task to get that cleared. However, to be clear, that's not associated with Alzheimer's disease that simply to do measurements in the retina, which can be applied eventually to a number of different disease states to help advise clinicians in their decision-making.

The final step of our strategy is to use those measurements and correlate it as a prediction to PET. And we actually are in the middle of those studies currently. Our validation studies in nine sites in the U.S. and UK. We of course had delays like many studies due to COVID. But actually right now I was on a call this morning talking about how those sites are starting back up. So that's good news.

And to answer your question though, It's going to take us probably about one more year to collect that data, and then we'll submit to FDA and there'll be a process beyond that. So hopefully sometime in 2022, 2023, we hope to obtain FDA clearance for that for that

Dr. Heather Sandison, N.D.
And so simultaneously you are working on some blood markers, not just the retinal imaging, but also other ways that we can start detecting Alzheimer's disease earlier through blood. Can you talk a bit about where you are in the process there and what exactly you're looking for?

Steven Verdooner
Sure. So, and to be clear, a lot of people have thought of us as a retinal imaging company, and that's what we're known for. If you look at the executives in the company and otherwise, and very quietly in the background, we've been building a blood biomarker business. So you said, why would you do that? And so part of that is the original vision of the company of Dr. Keith Black and myself, was to embrace a multi biomarker approach.

We live in the, in the industrial revolution of today's industrial revolution is data science, and that we should embrace that and we should be creating bio signatures and using all the data that we can. So our team at Neurovision is extremely experienced in data science. So we can take a data vector from retina and a data vector from blood and combine those together to improve the predictive power. So it was always our plan from the very beginning to embrace multiple biomarkers.

We thought that retina was very unique because we could directly image, essentially like directly imaging a brain region. In blood, t's a little bit different. We're looking at plasma. So it's sort of like, you're looking at the, by-product a lot of these, but we put the advancements in blood biomarkers in the last few years, few years has been tremendous. And so, and we have only recently have the pharmaceutical companies become aware of the work that we're doing. And so, and so that work consists of a partnership with a company that has a plan. And we have the exclusive rights to that platform. This, this company currently works in cancer, but they really had no expertise in neurology. So we combine our expertise in neurology. We put a blood biomarker team together and also our data science team works on that data. And, and basically together we're developing assays.

So we currently, and most people don't know about this, some are starting to learn because we're just, you know, in publication mode, but we have a proprietary test for amyloid beta. We've now, we have a multiplex that consists of amyloid beta, total tau, phosphorylated tau; three flavors of that. GFAP neurofilament light. What's special about this platform It has ultra high sensitivity, which you need for several of these markers, and you can multiplex many of them together from a very small volume of blood. So there's still work to be done, but the results are extremely promising. The work in progress. We're very pleased as are our pharmaceutical company partners.

So the reality is that that may make it to quote "market" before a retinal imaging tests in blood. There's something called laboratory developed tests, which again, have their own pathway with respect to how they are regulated or not. I should say by FDA, it's CLIA lab, basically designation and a laboratory developed tests, but we're finding other companies like C2N coming out with these blood tests.

And in our plan actually is to be in the market towards the end of this year with a blood test based on the work and the track that we're currently on. And this would be essentially to be looking at things like amyloid status.

Dr. Heather Sandison, N.D.
That's so exciting. As a clinician, seeing patients with dementia and then also their family members, right? Their children, who are concerned, there might be a genetic predisposition. If we can get multiple angles, right. If we can look at some imaging and if we can look at some blood testing and then they corroborate each other, I feel so much more confident suggesting a treatment plan.

When we, when we have a coup-, no test is perfect, right? Let's be real. So if we have, if we have no certainty, but some indication, right, we've got some data we're collecting, and then we have more data that supports that I feel so much more confident saying, yes, it's time to change your diet, do the, do the hard work. And I would imagine, you know, from a pharmaceutical perspective, you know, that isn't really my wheelhouse and there isn't a pharmaceutical that's been developed that really helps with dementia yet, but I certainly am not anti-drug. And from the perspective of a pharmaceutical company, I would imagine when we can get multiple biomarkers going in the same direction, again, there's so much more confidence.

All right, we're really gonna like go down this research path. We're really going to investigate this. Or we feel more confident sending it to the next round of FDA approval when we can see all those biomarkers going in the same direction. Right, When they're all telling the same story, there's so much more confidence that goes into any element of this, right? The treatment, the, the science, all of it.

Steven Verdooner
Yeah. I agree completely. And, you know, because of the world we live in, everyone becomes very pharmaceutical and drug focused, but you're a hundred percent, right. And there are many, many studies as you are, of course, at the center of this very well aware of the lifestyle interventions that can really push out the curve.

Yet, how well do we have feedback loops? You know, how well do we measure those? Are, is there a potential for blood biomarkers, for someone who knows they're at risk, maybe they're E4E4 and they're younger. Can you bend the curve? Can you understand if the lifestyle interventions, if sleep, if exercise and diet, isn't making an impact more than just the feedback loop of the sleep, the diet and the exercise. Can you look at things like neurofilament light and p-tau and see if they continue to go up, or if you're bending the curve a little, we think that this will play an essential role in that as well. Ultimately, you need to catch it early.

People are going to do lifestyle interventions and sometimes say, well, why do you need them to use people should do this anyway. But I think it's been proven when you have these feedback loops. And it's like, you know, it's like, you know, cholesterol, we take cholesterol test to see if, you know, our lifestyle interventions are working. Our drugs are working even though, you know, but we still are humans and we have these behaviors. So certainly having blood biomarkers to give that feedback loop, not just for drugs, but for lifestyle interventions, ultimately we think is essential.

Dr. Heather Sandison, N.D.
Well, it's challenging right? For someone to change from a standard American diet, to an organic ketogenic diet, like that's a big ask, and I know how challenging for someone who's not cognitively impaired, that is.

And then if you start to layer on top of it, cognitive impairment than asking someone to spend the money on maybe more expensive food or spend the money on the gym membership, or make the effort to go get that sleep study, all of those things we know, well, I know as a clinician, I watch it all every day.

I know that it changes people's cognitive function, but when we can then point to look, look at your labs, look at this image and look how it's changing. That gives everyone more confidence and more incentive. I think when there's a number to attach it to

Steven Verdooner
Right.
Dr. Heather Sandison, N.D.
And so sometimes the lifestyle changes are happening, but you're not experiencing the symptomatic benefit quite yet, particularly with later stage disease that can take months to turn around. So if we can track these changes at three months and then six months, and then nine months, and then twelve months and say, Hey, look, the data's shifting your symptoms are going to be right behind it. It can help people keep going.

Steven Verdooner
Yeah. And I think it provides motivation. And I think that, you know, it's look it's long and expensive for drug companies to do longitudinal trials, but for lifestyle intervention, I mean, longitudinal is going to tell the story because, you know, you're not going to have a silver bullet and say, your level is here. And your disease state is this. It's going to be relative to where you started and where you're going. And the reality is that people that are at risk, I mean, family members of mine and others and friends, they really ought to be getting, you know, markers measured, you know, as they get into their fifties and sixties to really understand what their trajectory is, what that looks like.

If they're bending the curve and then they ultimately become wonderful candidates, frankly, for, for drug trials and then ultimately for treatment having that background information. And it's also motivational for them to continue that behavior.

Dr. Heather Sandison, N.D.
Well, and I would imagine this would be something Dr. Bredesen, You've probably heard him say cognoscopy, that we should all be assessing where our cognitive function is at 40

and 50. And even if you're not experiencing any decline, there should be a ton of societal resources going into preventing this because it's so expensive, not just from a dollars and cents perspective to have Alzheimer's, of course it costs a lot for memory care. And when you can't take care of yourself, you're pulling somebody else out of the workforce to care for you, potentially in your family. I mean, you're, you're not giving to your friends and your community and your family. So it's extremely expensive to take our elders out of society with dementia. If we can prevent that, we keep so much value.

And so I would love to see a world where, you know, a test like this is covered by insurance early on with the benefit of getting that prevention started so that people don't develop dementia, right? Just the way we do for cancer screenings, right? He says cognoscopy like a colonoscopy. We, we check for colon cancer. Why not be checking for dementia?

Steven Verdooner
Right. I agree. And, you know, in screening, a prevention is extremely important. It's going to take time to get CMS to the point where they continue. I mean, we're seeing, seeing a little bit of advancement for screening and some very select areas, but we were more, you know, reflexive responsive to once we have symptoms. So certainly screening would be very important. And I think also whether it be blood biomarkers or retina allowing drug companies to do better targeting of patients who should be on our particular drug, I mean, we know there's something, a paper came out yesterday out of a group in Oscar Hanson's group that talk about four different types of Alzheimer's classifications based on tau pathology.

I mean, this is where we're going to end up. And the drug companies should be embracing biomarkers and targeting more. But certainly at the earliest stages, lifestyle intervention gets the same kind of advantages of looking at these same markers and starting to categorize, which are the even lifestyle interventions that benefit people the most, much less a particular targeted therapeutic.

Dr. Heather Sandison, N.D.
Right. It's so exciting. So what is your, you're doing a lot of testing prior to approval? Like, what is that process like? What what's kind of the standard before this goes to market?

Steven Verdooner
Right, so for retinal imaging, we have to show how we perform versus a PET scan. And so right now, and again, this is more of a therapeutic drug driven because of the regulatory implications of getting our tests done. You know, so all of the, all of the trials look at amyloid pet positive or negative, and then they're included in the trial or not.

And of course we know that the problems with PET being expensive, invasive, worldwide availability of PET scans, really in the U.S. in this country, we're okay. In many countries, even fully developed countries, PET scan is a problem and people don't love CSF. So our strategy is as a screen before PET. So we tune our algorithms to very high, negative, predictive value, meaning we want to identify normal people and let just those who are positive, go through to a PET scan. And that's part of our, from a regulatory perspective, that's part of our strategy.

So the test that we're currently doing in our validation trials is comparing our test versus amyloid PET. And that's what we've done. It's not our first trial. We have a lot of other studies and internal validation. That's giving us extremely promising information. on the blood side of the house, again, because of the agenda driven by pharmaceutical companies, looking at PET positive or PET negative screen to PET is what most of the world is focused on. Okay. That's very important, very helpful, but we're already looking over the horizon at all the things you just mentioned; of all of the multiple biomarkers, differential diagnosis. If your tau is high and your p-tau is low, you know, if your p-tau is high, you know, when your tau is low, there's so many; GFAP neurofilament light.

There's so many different things that we can understand in differential diagnosis, disease progression, response to therapy. So those are key elements of what we need to be focused on as we look forward.

Dr. Heather Sandison, N.D.
That's great. And so where do you see Neurovision kind of fitting into the entire Alzheimer's ecosystem today versus maybe five years from now?

Steven Verdooner
Yeah, well, today we've worked with drug companies and clinical trials. I mean, that's our role. We can't offer a test to practices like yours until we have regulatory clearance. So as we proceed forward with retinal imaging, that can become a reality. However, by the end of this year, we could potentially, if everything goes, according to plan, offer a blood test to you, that you could start to utilize with patients. And then over time, we're adding other elements to that blood test.

So we right now have about 12 biomarkers in a single blood test that we're developing. We won't come out with that initially, but that's where the goal is. And as a clinician that will give you the ability, you know, to look at that data and understand what that patient's trajectory is looking like. These blood tests are not going to draw conclusions. They're not going to say things like Alzheimer's yes or no. That's not what they're going to do. And the FDA won't let them us to do that. And we shouldn't be able to do that. It will augment your clinical decision-making.

You'll read the literature, you'll see the levels, you'll make your decisions. It's not unlike what happens in a lot of other laboratory developed tests today. It will rely on the clinician, but it will augment your clinical decision making, giving you valuable biomarker information. That is near-term. So you say, what do we look for today? It's clinical trials, but things get interesting as a laboratory developed tests, come on the market to potentially benefit even those that before, you know, that are being treated with lifestyle interventions before there's a drug.

Dr. Heather Sandison, N.D.
That's great. And so say five, ten years from now, how does that shift? I think you've mentioned a bit of it, right? That it will be available to clinicians pretty easily, but what's the future of Neurovision?

Steven Verdooner
It's really to be a dominant player in the biomarker space. We ultimately see that these patients will start at neurology with cognitive decline and symptoms. And, you know, there's about 10,000 neurologists in the U.S. you know, and have you ever tried to make an appointment with a neurologist? I mean, so, you know.

Dr. Heather Sandison, N.D.
They keep going on sabbatical.

Steven Verdooner
Yeah. So it's, it's a really long time. So ultimately these things, as you know, this is, I have a lot of lessons learned in ophthalmology. It'll start neurology very quickly. It'll likely migrate to primary care. Primary care is really where the education needs to be done. That's where tests will be ordered and they'll be the they'll screen things. And then appropriately referred to neurologists to monitor and administer treatment, you know, and, and I have a little bit of the benefit of coming from ophthalmology, where frankly, we've got wonderful tools.

We can measure things, we can image things, we can treat things, we can change the course of a disease. So I've seen what that success can look like and what those referral patterns look like. We've been very fortunate and retinal disease in Alzheimer's, you know, we've had many, many drug failures and retinal disease. I know what that looks like. And I know the role that imaging and biomarkers and tools can play, especially imaging for ophthalmology in really helping clinicians move the field forward and have have treatments. So I, you know, those of us who come from ophthalmology know what that looks like, know what that blueprint looks like and want to apply that to, to diseases like Alzheimer's.

Dr. Heather Sandison, N.D.
How exciting, well, I'm so grateful that you were doing this work to help us make Alzheimer's a rare disease. Hopefully that is on the horizon in our lifetimes. I think that we have a lot of the tools that are necessary. Certainly you mentioned the lifestyle pieces, but this tool from Neurovision, I think will really potentiate all of what we have in really, really meaningful ways. Steve it's been so a pleasure for me to learn from you about more about retinal imaging. And it's always been a curiosity of mine, but not available. And so I'm happy to hear what the timeline is. And so we hope it happens sooner than later. Again, thank you so much for sharing your passion and dedication to this field with us.

Steven Verdooner
Thanks Heather. Thanks for having me on.