REVERSE ALZHEIMER'S SUMMIT

Are We Ready For Disease-Modifying Therapies In Alzheimer's Disease? The Role Of MRI Biomarkers.

Dr. Heather Sandison, N.D. interviewing Dirk Smeets

Dr. Heather Sandison, N.D.
Welcome back to the Reverse Alzheimer's Summit. I'm your host, Dr. Heather Sandison and I'm so pleased to have Dirk Smeets here today of icometrix. Dirk Smeets is the current Chief Technology Officer at icometrix. Trained as a biomedical engineer, he obtained his PhD in medical image analysis in 2012, after joining icometrix, he took different roles covering responsibilities in research and development, quality management, information security management, marketing, sales management, and strategic partnerships.

Today, he is responsible for bringing new products to the market, demonstrating their clinical value and implementing them to be of value for the icometrix customers. Dirk, thanks so much for joining us today.

Dirk Smeets
It's a pleasure Heather.

Dr. Heather Sandison, N.D.
So as a clinician, I am really excited to learn more about what is on the cutting edge of imaging for Alzheimer's, as you and I both know, dementia, it's much easier to prevent it than to reverse it. And I think imaging has this really phenomenal ability to capture what

we don't see, maybe behaviorally before it's manifesting as symptoms, we can see it on a picture of our brains. So tell me a little bit about how you're doing that at icometrix.

Dirk Smeets
Yeah, that's really true. So with imaging, actually, we can look inside the brain so we can actually look what is happening there. And sometimes there are things visible there, already years, maybe sometimes decades before clinical symptoms are present. And what we actually do is at icometrix, we start from an MRI scan, an MRI scan that can be taken during the clinical routine practice. We analyze it with artificial intelligence and with the artificial intelligence, we are going to look at such subtle changes that are almost invisible with the human eye to pick up the earliest signs of change compared to the healthy aging. 'Cause in fact, that's what is important on imaging for dementia is to compare the MRI scan with MRI scans of unhealthy aging population and try to depict the earliest signs of differences that might lead us to an early diagnosis of, for example Alzheimer's disease.

Dr. Heather Sandison, N.D.
And so it also seems like it would make sense to have like a baseline for that individual where you're comparing not only to your, the image of your brain, to other people who are healthy, but the image of your brain to what it was previously so you could track change over time.

Dirk Smeets
Yes, absolutely. That's also very crucial as there is a wide variation of humans, as you know, but the same holds for brains, there's a wide variation of brains. Some people are born with a smaller brain, others are born with a larger brain and there is this congenital effect that is actually not related to the disease. So some people just have a low brain volume. And for those, we wanna know whether that's because of it's congenital or because it's due to a disease. And to get that answer, we need to follow up a patient over time and see how the brain is evolving, if the brain is shrinking faster than what we would expect for the same

age and gender in a normal aging, then we know that there might be a disease active and we might have some clue to get a diagnosis for a dementia.

Dr. Heather Sandison, N.D.
So then that brings up a good question that patients have asked me is, okay, it says here that my hypothalamus is a little bit small or my hippocampus is a little bit large, how confident can we be if we only have one image that it is related to a disease process?

Dirk Smeets
Yeah, that's again, something that we need to be very careful of because as I mentioned, some people have a congenitally small hippocampus or hypothalamus and others might have a bigger one. So there is this natural variation, same like with the length of people or the weight of people. So we need to be careful in doing the interpretation, but luckily there are some other signs. For example, if you look at the region around the hippocampus, the hippocampus, as you know is structured for the long-term memory, it is in a normal situation, there is not much surrounding cerebral spinal fluid, but in case of a pronounced Alzheimer's disease, we know that the CSF space, the cerebral spinal fluid space is increasing. And it's that ratio between the hippocampus and that CSF space that is around it, it is a quiet biomarker to indicate whether that patient has Alzheimer's disease or not. And that is less dependent on congenital factors like the hippocampus on its own.

So we have some tricks to cope with it, but still, we need to be careful in the interpretation, as mentioned earlier, it's always good to have a follow-up scan and look also at the evolution of the brain shrinkage over time.

Dr. Heather Sandison, N.D.
That makes a lot of sense. Okay, you're doing much more sophisticated analysis than just saying some brain region is this big, or there's this volume in your cerebral spinal fluid, you're going into ratios and comparisons and lots of other things that help you increase that confidence of saying there's something wrong, or you're in the clear.

Dirk Smeets
Absolutely, absolutely. We know that this is more sensitive and also more robust, so that's why we're doing those more complex ratios, but it also means that there is some additional education to be done for the interpretation of the software, because it's easier to interpret like, hey, the hippocampus is smaller, or hey, the whole brain is smaller, but if ratio start changing, it's not that intuitive anymore. So we need to do some education to get some adoption of these newer biomarkers, imaging biomarkers that are sensitive for the diagnosis of Alzheimer's disease.

Dr. Heather Sandison, N.D.
Let's jump into the tech then, because what we're doing is an MRI magnetic residence, and so there's no radiation, is that right?

Dirk Smeets
That's correct, yeah. MRI works with a very big magnet. It's either a one and a half Tesla or three Tesla. And this is an enormous magnetic field, if you compare that with the small magnets that are used in the household, these are huge magnets. And what they do is actually all the water molecules in your body are aligned in the direction of the magnetic field. And then what happens is there is some posts sent to the area of interest, for example the brain and that distorts these water molecules to be aligned with the magnetic field and how they relax back to their starting position that learns us a lot about the tissue properties.

This is called the magnetic properties of the tissue. For example, in the brain, there are different issues present, there's for example, fluid that brings nutritions to the brain, but there's also the actual brain tissue, basically from the actual brain tissue, we distinguish typically the white and the gray matter, and they each have different magnetic properties. And these intelligent devices and magnetic resonance imaging scan can distinguish those tissues, and based on that information, we learn a lot on how your brain is organized and whether some parts of the brain are changing compared to the last time, or are different

from a population, or whether there's some abnormalities there. So this is actually the principle of an MRI scan.

Dr. Heather Sandison, N.D.
And then with this particular MRI that we're talking about for detecting Alzheimer's and tracking the course of treatment or change over time is contrast involved in that?

Dirk Smeets
Yeah, it's an interesting topic actually, because if we inject contrast, it's basically a chemical substance that is injected in the blood vessels and it travels all around the body and it also comes into the brain. And what the contrast is chosen to be, to have different magnetic properties than the rest of the brain tissue, and that causes a different signal and therefore it can be easily distinguished. So the contrast typically travels through the blood vessels, so the blood vessels are easier to distinguish. But sometimes in certain neurological conditions, for example, in multiple sclerosis, there is a problem with the blood brain barrier.

And because of that problem, there's also contrast going from the blood vessels into the brain and causing some yeah, for example, inflammation, the case of multiple sclerosis. So that's the reason why contrast is used. In case of dementia, it is not frequently used because also there might be some safety concerns around contrast. I think today we are quite confident that if you have every now and then a little contrast, there might not be any health risks, but there are more and more concerns that if you have on a very regular basis, these contrast injections, there might be some accumulation of the contrast in the brain or in other organs. So we should always be careful with the admission of contrast in the blood to see more actually, because it has an advantage, but if you compare that risks and those benefits, you typically would use, not really contrast for patients with dementia, but it can be done. And for example, it is done to exclude reasons of dementia that are caused for example by a tumor, the contrast will help to find the tumor much easier, and also explain how active it is. So sometimes it's used, but it's less used on a frequent basis in dementia.

Dr. Heather Sandison, N.D.
Right, because balancing that risk benefit ratio of we want this information, this can be really helpful, and yet we don't wanna put the patient at risk by having these repeated exposures to the gadolinium or whatever else.

Dirk Smeets
Absolutely.

Dr. Heather Sandison, N.D.
Could be in that contrast agent. So with dementia, what you're saying is we can these kind of repeat scans, look to make sure we're on track with treatment, look to make sure disease isn't progressing, or, I guess determine that it is that we need to change our treatment plan. And we can do that without using contrast so that we're not accumulating that risk.

Dirk Smeets
Yeah, exactly. So here it is that the artificial intelligence comes into play. Basically such an image is like, I sometimes compare it with a bread where you scan slice the bread in multiple slices. And that's actually also how the brain is imaged. You image a brain in different slices and each slice is reviewed by a radiologist to look at it, whether is something wrong or not. The beauty of a computer is that it can look in more dimensions than a human can read it. So basically what the computer will do, it will take the whole bread, basically the whole brain as a three dimensional volume and it starts doing all kinds of analysis on it, and that can help us to depict smaller changes that is possible by the human eye.

For example, we know that for a human eye, it is quite challenging to see a difference of 5% between two structures. So if the patient is scanned and is scanned again after a certain period of time, if the change is smaller than 5%, the human eye will have challenges with it, just because it's so subtle to pick it up. But with the artificial intelligence, we are able to depict changes for, which are much, much smaller.

For example, for the total brain volume, every brain tissue that is inside the scope, we can see differences up to 0.1, 0.2%, which is small enough to distinguish between how a healthy a person, healthy subject is aging and compare that with the disease person. We know for example, unfortunately that all our brains are shrinking, at the age of 30, it is around 0.1% per year, at the age of 75, this is about 0.3% a year. So of course, when you want to see something meaningful in one year, you need to have a tool that can measure it with an accuracy that is lower than what the actual brain is shrinking. And therefore we need those AI tools to see that change because the human eye will not depict them, it will not be clear to them. So that's the reason why we are applying those AI tools on the imaging.

Dr. Heather Sandison, N.D.
And is the AI that developed already, or is this something that you were planning for in the future?

Dirk Smeets
No, yeah, the AI is available and this is also kind of the beauty of AI and software, it is quite rapid to build it and it can be put into like the clinical team help neuroradiologists, help neurologist, help PCPs all around the world. And because it sees so much new data, it can learn from it and it can become smarter and smarter, and this measurement error goes down and down and down. So that's the beauty about the system. So it is now for example, to take our system as an example, it's now in the US market since 2016, and it underwent several improvements over this time. Of course, there's luckily and I think this is a very good thing, there is a regulator, the food and drug administration, the FDA that looks whether every change is really an improvement before you can put it into like the clinical routine as a company. But the beauty is that it keeps on improving all of these tools, and at a certain moment, it will be able to maybe depict changes that are so relevant that it can also, have the necessary accuracy to be quite certain about a certain diagnosis.

Whereas now it's more of a support for diagnosis, I think decisions support tool, rather than a decision tool. And of course it will always be a help for the physician, but at some point it might be a bigger help. So interesting changes to come here as well.

Dr. Heather Sandison, N.D.
Very exciting. So if someone is looking at doing an MRI to measure these volume metrics for someone and they're considering a diagnosis of dementia, maybe they even already have that diagnosis, what would be required for the MRI? Like what things are necessary to be able to have more, and get the full benefit from this potential technology?

Dirk Smeets
Yeah. It's of course important that the MRI machine is used in a good way. We unfortunately see that in the real world, so in the data that are acquired everywhere in the United States, there is quite some variation in the quality of the data that is acquired by the MRI scan. Today's MRI scans typically have the ability to do good MRI scans for dementia. I told earlier that it needs to be a good, strong magnet. And if it's a strong magnet, it is typically able to get good images. And basically what we would like to see is what we call a 3D image. That means it should cover the full brain, and it's like the slices of bread that are acquired in such a way that the full bread is present inside the image. So sometimes it's like that, that half of the slices are thrown away and only a couple of slices are kept of the bread. And that's not good 'cause then we miss information, or the artificial intelligence information and algorithm misses information that is important to quantify certain smaller structures like the hippocampus. That's an important one.

The second important one is also that with the MRI scan, it is a magnificent device because the posters that you can send inside the brain to make the water molecules deviate from their standard position, there are multiple ways to do so, and that gives different types of images. We call them a T1 weighted image or a T2 weighted image, and that gives us other information, it gives us other magnetic properties.

And what we wanna know typically for a dementia patient is the T1 weighted scan, which is very good at distinguishing the different brain tissues, as I explained earlier, the white and the gray matter. So we need a T1 weighted three dimensional scan in order to be able to use these AI algorithms. We can also use T2 weighted imaging. These are other weighted imaging, and that's interesting to, for example, understand better whether there are some vascular lesions which can occur in case of vascular dementia. And this is one of the most common differential diagnostic questions, but whether a certain patient has Alzheimer's disease or vascular dementia, the two most common diseases causing dementia, and with the quantification and the assessment of the white matter, lesions that can be extracted from a T2 weighted scan, we can also extract that with the artificial intelligence. So a long, long explanation to explain that with the MRI, if the MRI machine is good, we can acquire the images that the AI needs, and we can help a lot with the differential diagnosis for patients with the dementia.

Dr. Heather Sandison, N.D.
So if a patient, say who's listening or watching this summit right now, or maybe a loved one of a patient who is suffering with dementia, if they were to go to a doctor and ask for this type of imaging, what would they ask for specifically?

Dirk Smeets
I would recommend them to ask for definitely a 3D T1 weighted image, which every MRI scan can do. And I would also recommend them to ask for a volumetric quantification because that is also sometimes how it's called, and because AI is a little bit of a hype, a trendy name of volumetric quantification. So most radiologists probably know it more under that term. And basically what it does is it asks the radiologist to quantify certain structures in the brain and basically also compare them with what is expected, and depict changes from that.

Dr. Heather Sandison, N.D.
And will this also be getting those ratios that we discussed, some of that more advanced analysis?

Dirk Smeets
Yes, I would say so. So there are different software packages on the market and some of them will do these ratios, others won't. But I would say the better packages do, and I think this is something that is very valuable, especially if it's the first scan. As I explained earlier, it can give already some clue on whether the patient is affected by a disease or whether it's just something that is part of the normal variation.

Dr. Heather Sandison, N.D.
So a traumatic brain injury is one of the big kind of risk factors as people age in terms of developing dementia. And you guys offer imaging for TBIs as well. How is that different from the type of imaging that you would get for dementia?

Dirk Smeets
Yeah, well, that's very interesting because the field of TBI is largely unexplored. There are so many things we need to learn. We know at the moment that TBI is not really, traumatic brain injury, is not really a one-time event. So obviously there is this event itself that causes damage to the brain, but it's actually the so the events that happened after that damage that are very interesting. Some patients recover quickly from the brain trauma and might not have real symptoms afterwards, but for others, there is a start of a neurodegenerative process. So a process where the brain is dying or parts of the brains are dying. And the interesting point is that, we are now starting to understand the relationship between what's happening shortly after the traumatic brain injury and dementia later on is important.

So for that reason, we are also investigating and spending a lot of efforts in trying to build artificial intelligence models that can better quantify, better assess patients with traumatic brain injury and preferably those with a mild traumatic brain injury, because they are at risk of developing dementia for a portion of the population, whereas it's unclear for a clinician at the moment that it happens, which portion it is.

Dr. Heather Sandison, N.D.
Hmm.

Dirk Smeets
And basically we look at something that is called the white matter bundles, which is the white matter consists of connections between the cortex of the brain, where all the functional areas are and everything else in the body. And these bundles, you can see them a little bit as ordered spaghetti bundles, in traumatic brain injury they might get damaged. And with a technique called diffusion, tensor imaging, or more general diffusion imaging, we can learn more about the damage of those bundles and what we are developing and have developed actually is an AI algorithm that can learn where the damage of those spaghetti bundles is occurring. And typically, if there is a certain amount of damage, it is the start of a neurodegenerative process and that can lead to dementia.

So what we try to do now is with patients with traumatic brain injury, try to measure what's happening in the brain, which of these spaghetti bundles are damaged. And based on that, having an understanding whether there is a risk of further neurodegeneration and whether we need to lookout for dementia. And this is an interesting population because we can do a lot of interventions there, we might do cognitive exercises or other therapies at this point, because this is typically very early in the process, it's only at the start of a neurodegenerative process. So this is pointing to the importance of imaging very, very early in a person.

Dr. Heather Sandison, N.D.
Oh, that's so exciting to me as well, because it means that you might be able to measure how well the treatment is going in the absence of symptoms, right, you don't have to go back to, okay, how fatigued are you? Are you nauseous, are your pupils, right, like you can say, let's take a picture of your brain and let's look at these spaghetti noodles and see how disorganized they are, and then apply some sort of treatment like exercises or oxygen therapy, hyperbaric treatments, the phosphatidylcholine and , and the laundry list of things that I think of right away when there's been a TBI. And if we do that when someone's 18 or 19, and having this TBI, then measure the changes on the pictures, maybe we skip that dementia when they're 60, 70, 80 years old.

Dirk Smeets
There is definitely a very, very big chance that that is working. And the beauty indeed is that what's happening inside the brain is typically so much earlier to the symptoms that will occur many years later. So even if a patient with mild TBI has not really that much symptoms, it might be very important to treat the patient early, because it's the brain that needs to be preserved because the brain that is preserved will keep this healthy life much longer later onwards. And to do so, we need endpoints, these are evaluation measures to define whether the therapy is working that are less related to long-term outcomes, because that is just way too long to wait for that and MRI, and the derived metrics that we can assess from it are an intelligent way to do so. So it's definitely worthwhile doing and worthwhile investigating like that.

Dr. Heather Sandison, N.D.
And as a clinician, I always wondered in the absence of symptoms, are we done? Have we completed this process? Like, did we fully treat it? Another time that imaging would be so helpful is sometimes we measure that people are getting better in some way, but they're not feeling it quite yet, but when we can point to the picture, when we can point to the measurement and say, no, no, hang in there, keep doing the work because it is about to pay off, even though you're not feeling it, we can watch this picture and we can see it

improving. That is such a motivator for people to do the hard work of changing their lifestyle, their diet, some of these other things that we know are very impactful, but sometimes just take a little while to reap the benefits.

Dirk Smeets
That's, from a scientific point of view, that's absolutely true, but I'm super happy to hear from you that yeah, that can also be a motivator for patients because actually it's so important that people can follow that therapy to get the end actually and there should be all kinds of like measures to keep them motivated. So I'm happy to hear that that might be one, and that's definitely good.

Dr. Heather Sandison, N.D.
So what about costs, a typical MRI, a typical image like this is, do you know in the US if it's typically covered by insurance, or if people are paying out of pocket, what that might look like?

Dirk Smeets
Yeah, so the MRI images is typically covered by insurance. There might be an out of pocket expense there, and the artificial intelligence analysis that comes on top of it is really nominal compared to the MRI price. So typically that's also part of the whole package. And that really depends on center by center, obviously the, or luminary centers might ask a little bit more for that than an imaging center. So there is some variation there, but it's a quite small cost compared to the MRI scan itself.

Dr. Heather Sandison, N.D.
Got it, got it. So applying the AI to the images that are gonna maybe be done anyways, it adds a ton of value, but not a ton of cost.

Dirk Smeets
Exactly, exactly. I truly believe that, but hopefully I'm not the only one convinced of that.

Dr. Heather Sandison, N.D.
So Dirk, if somebody wanted to learn more about what all you guys offer at icometrix, how could they learn?

Dirk Smeets
Well, we're doing so much in the moment, but I wanna maybe pick out one particular initiative, and that's a website that we have launched. It is called alzimaging.com, alzimaging.com. And it is a website that tries to summarize a lot on how imaging in Alzheimer's disease is happening. And it's completely unbranded, it's all factual, it's with a lot of the strong clinical evidence. And I would definitely recommend everyone to have a look there and learn more about Alzheimer's disease and imaging, because there is so much that we can learn from the imaging, especially in relation to therapies. It will help us understand much better the therapies in the future as well. It will also in case, at some point, some medication will come on the market as a compliment to the existing therapies. It might also be of value there, and all of that information can be found there.

I know, of course, from a commercial offering, as a company, I would also be happy to refer you our website, icometrix.com, where you can also find some nice blogs on the products and how they can help and there is also an opinion piece on how the world is evolving today on Alzheimer's disease and what the role of imaging could be. So there's definitely so much valuable information that is out there. Obviously that's all coming next to the great content that the patient organizations are putting online. Also the websites like the one you have Dr. Sandison is so valuable to have that content there, to have that dedication, because that's typically what we see as the main factor of good care, as a good education, good background, if patients are informed, the likelihood of having a good outcome is just better. So I would definitely recommend to all of this great content that is out there.

Dr. Heather Sandison, N.D.
Thank you Dirk, I really appreciate that. I told you before we started recording that I feel sometimes intimidated by the different imaging that is available and kind of unsure of how much it's going to influence my clinical course and the treatment. And so having access to this information, especially as it's changing so rapidly as the AI develops, and as these things really mature, I agree that they're going to take a much bigger role in the clinical sort of, the entire path, right in terms of diagnosis and treatment. And so I'm looking forward to that and having a little bit more confidence in all of these pieces as the imaging and the AI on top of that start to inform what we're doing.

Dirk Smeets
Okay, fantastic to hear that.

Dr. Heather Sandison, N.D.
Yeah, so thank you so much for all of your insights and wisdom and for just kind of nerding out with us on how MRIs and imaging can be helpful in diagnosing and then preventing and reversing Alzheimer's.

Dirk Smeets
It was super excited to speak with you, Dr. Sandison, it's fantastic, very great.