Buzzilia Video: Day 2

Video from day 2 of Buzzilia: nightly news, interviews and features from the HD World Congress 2013 in Brazil

By Professor Ed Wild | **October 19, 2013** | **Edited by Dr Jeff Carroll**

Here's Buzzilia, video 2: highlights and interviews from the World Congress on Huntington's disease 2013 in Rio de Janeiro. Jeff and Ed discuss biomarkers and talk to Dr Ralf Reilmann about quantitative motor assessment, and Dr Julie Stout about cognitive problems.

The full unedited video (31 minutes), including a special appearance from Charles Sabine, can be found on YouTube.

You can also watch videos of 33 World Congress sessions here, thanks to Gene Veritas.

[Samba music]

ED: Welcome back to day two of Buzzilia. We have started unexpectedly early. So welcome back, everyone. Which is to say on time. So, once again coming to you from Rio de Janeiro for the World Congress on Huntington's disease, I am Ed Wild.

JEFF: Thanks everybody for sticking around. I'm Jeff Carroll. Just to remind you, we're here at the end of the day to try and summarise some of what we saw at the meeting. Really importantly, hopefully, record it, and put it online and share it with families who couldn't

make it all the way to Rio, so they can still get a taste of the excitement in this meeting. First, we wanted to briefly reflect on some of today's highlights. So, Ed, you first. What struck you about the science, today?

ED: For me, my area of research interest is in biomarkers, so there was a session this morning on biomarkers which really caught me attention. It was kind of encouraging, actually.

JEFF: So this is the obvious question, what is a biomarker?

ED: There's a lot of debate about this, but the way I think about it is that a biomarker is anything that we can measure, that helps us to understand the disease, or to develop drugs for a disease. For instance, if you think about blood pressure, that could be considered to be a biomarker for the health of your heart, and your circulation. If your blood pressure is up, that can predict heart attacks and strokes, and if you treat to lower the blood pressure, that can reduce your risk of heart attack and stroke. So that's a really useful biomarker, and it's easy to measure. We're looking for biomarkers for Huntington's disease. We've been looking for a while, and actually we've found quite a few. What we heard today was that those biomarkers are likely to be helpful to support the next generation of clinical trials. We're not going to do away with clinical end points, and the crucial thing with any drug is, does it make people better? Does it slow down the progression? Do people feel better? Are their lives improved by this drug? These biomarkers will hopefully help us to accelerate that programme, understand how the drug and the disease are interacting. What we heard is that over the past decade, we've made huge strides, through things like Track HD and Predict HD, and a number of other efforts to developing really good biomarkers that will really help with that. So that was cool. What was your highlight?

JEFF: My word of the day was compensation.

ED: So what you need to know, Jeff, is that you cannot sue the hotel because you fell asleep by the pool, and got sunburnt.

JEFF: Leave my skin out of this. No, this is the idea that as brains are damaged in the course of HD, they remain capable of performing pretty normally. So, we heard today from Alexandra Durr, that even normal people's brains are shrinking, as they age.

ED: That sounds pretty scary.

JEFF: Yes actually, but Julie Stout from Monash University told us that even in the face of this ongoing shrinkage, the brains of HD patients are able to perform the tasks they need to work well, quite surprisingly effectively, through ways that we don't really understand, yet. It seems the brain has the ability to compensate in ways that are really surprising.

ED: Okay, so it's that kind of compensation. That sounds encouraging, because that's the sort of thing that, hopefully, we can work on helping the brain to do better, and that might make a difference?

JEFF: That's right. Stop the insult, and maybe we can make some room for more compensation.

ED: I will never stop the insult. Let us invite to the stage Herr Dr Ralf Reilmann from the University of Munster. I should say, "No more", from the University of Munster. Welcome, Ralf. Have a seat. In fact, Ralf has recently broken away from the University of Munster and formed the George Huntington Institute. Congratulations.

RALF: Yes, thank you very much. It's a very exciting step for us to be able to provide, I hope, better care for our patients, in a different infrastructure. We will still work with the University of Munster. There will be an affiliation, but due to certain circumstances, we had the opportunity to actually develop and work, build up an institute. Which gives us a lot more space for the people, for the physicians, for my team to work in. We are very excited to be able to do this. We also are very grateful for the support we got from different people to be able to make that step.

ED: Congratulations. So, I feel we have to address the elephant in the room, or rather the woolly mammoth. We need to talk about the monobrow.

RALF: That's a genetic compound, because I'm living in Munster in Germany, and that's a city which is famous for its rain. So eventually, over the generations, we had some protection developing.

ED: So kind of like Elena was saying yesterday, that maybe some expansion of the Huntington gene protects or maybe a helpful progression of the human being the monobrow is a genetic advantage if you live in Munster?

RALF: Yes, exactly. I think that's probably the point, but I've had some very well meaning friends from the HD scene. I think she is hiding somewhere, one of my good colleagues from Track, who has, I think, a lot of experience with fashion, because she comes from that kind of city. She praised it this morning, she actually told me, secretly a few times, that I should take better care of this. Actually, what's very frustrating is I did. So this is actually cut.

ED: This is one day's growth?

RALF: Yes.

ED: I'm sorry to say it has completely reunited, like Germany after WWII. I can make that disappear; I can make the mono brow disappear. Everyone please join me in thanking Dr Reilmann as he retakes his… No No No! He's not going to sit down after a two minute conversation about his monobrow! Come on, people!

RALF: I want to thank you still, because I think, while we had this nice yoga exercise, you started a new idea in me about a new motor assessment. So thank you very much.

ED: Okay, yogamotography. So, you are a gadget man? Right?

RALF: What's that?

ED: You like electronic gadgets?

RALF: Gadgets, yes.

ED: Basically, one of your main focuses and what you spoke about today was what we call quantitative motor assessment? To my mind, I'm a neurologist, and there are lots of family members in the audience, the movement problems in HD tend to be fairly obvious. We see unwanted movements, and we see people who have problems with balancing, or tripping over pavements. What you're doing is using electronic gadgets to measure those problems. Why do we need to do that, if the movements seem to be quite obvious?

RALF: As we have discussed this morning one of the big opportunities we have in Huntington's disease, actually, is that we could potentially find treatments to introduce so early on that we could delay the disease start. If we go to what we call today the premanifest cohort of gene carriers, which I think is the intention we all have. For that particular purpose, we would need to have very sensitive measurements to judge whether drugs do work, in this early stage of Huntington, actually not disease, but so early on. I think it's very important to realise that these motor measurements that we are taking, if you read the papers from Track, for instance, don't be worried if you're a gene carrier. Because, what we're measuring there doesn't mean - and that's what I wanted to point out this morning, I think it's very important - it's not a symptom. So it's not a deficit, it's not an illness, as was pointed out by Karl this morning. That's very important to know. What we're measuring is really a very sensitive fingerprint of something subtle happening, which doesn't affect you at all, but which allows us to potentially say whether a compound X, or Y, or some vector that is injected in the brain potentially slows down the disease. It's not really a biomarker if you wish, it's really the clinic that we look at, and I think that's the good close link. As we all know, the motor symptoms are not always the most disabling to our patients, but they can be a very nice hint for us to understand whether a drug works. That's what it is about.

ED: Can you give us some examples of the sorts of gadgets that you use to try and tease out these very subtle motor things that might help us to understand this?

RALF: I guess you were thinking of the tongue protrusion task, right?

ED: The tongue protrusion task?

RALF: We have very simple things, actually. It's very easy to do; it's like playing with a mouse. We have little force sensors, it's nothing with needles, it's not invasive. You just touch with your hand; you try to do a regular movement. We can see very fine, discreet differences between people in early stages of Huntington's disease, and controls. We can actually see how these very fine motor deficits in coordination do progress over time. So it's very easy. We actually have a little thing that looks like a bottle, if you wish. It has a force sensor attached to it, so we measure the grip forces that you apply. We have the sensor

attached to it that measures the position of the device. So if you would have chorea for instance, which would have some amplitude movement, we could quantify that. We could see whether a drug reduces this, or whether it progresses over time, as an example.

ED: The other thing you talked about today was the challenge of recruiting patients for Huntington's disease trials. Briefly, if you don't mind, roughly are we in terms of that? Are we good at recruiting or bad? What can we do as a community to improve recruitment?

RALF: I think it's quite exciting to review the history of Huntington's disease trials. If you look into trials in the '70s, or '80s, they usually had patient numbers of 'n' equals 7 to 10, or 20 maybe at the best. Due to the amazing efforts that were put up by people in the Huntington Study Group, and now in the European HD network, I think we have the amazing ability today to actually do clinical trials, in a large scale. Which means today, it's not even impossible to consider to do several trials, and parallel that may, theoretically, require 400 or more patients. I think this is something that 10, 15 years ago, wouldn't have been possible to even consider. I think it's great that the opportunity is here to do this, and it's the work of 30, 40 years of investigators, like I mentioned this morning, the Wexler family, that started the committee to combat Huntington's disease back in '68. It has been a couple of decades and I think it's great to see how it has all evolved. Of course, all the patients that we have and the relatives are so amazingly motivated to support this kind of research, which is understandable. I think it's an amazing pleasure for me, for my team, and I guess for all of us here to be part of this scientific, historic opportunity we have to maybe stop the first neuro degenerative disease, if we have the tools for it.

ED: So if we want to make sure that the forthcoming trials are recruited as quickly as possible, it sounds like people need to, in a sense, sign up in advance? So that the centres of excellence will know that they exist, when it comes to recruiting, right?

RALF: Yes. Fortunately, we do have the big cohort studies, which in Europe is REGISTRY, and then now, fortunately, we do have the opportunity to have a world wide recruiting study, ENROLL-HD. Which of course we would want to ask anyone who is affected by Huntington's disease, or is a family member, to add. Because we even need controls for part of the study. So please go and see the next centre in your vicinity, and if you don't have one, make Bernhard Landwehrmeyer or Joe Giuliano aware of it, and you may have one, soon. So I think it's a very exciting project that we have that opportunity to recruit people globally, and potentially go to clinical trial recruitment in a way which we have never seen in other diseases, before.

ED: Than you Ralf. Stay seated, but please thank Ralf for joining us on stage. [Music] Ladies and gentleman, please welcome Professor Julie Stout. I'm sorry that you were welcomed by another flash of Ralf's monobrow, but welcome to the stage. Please have a seat.

JEFF: So, Julie, thanks for joining us. I was thinking, as you talked today, that as a scientist and an HD family member, I was struck, and I was listening with two brains. Because you study cognition, so I kind of understand, as a scientist, what that means. As a family

member, to me the worst part of watching my mother get sick with Huntington's disease wasn't the movements and stuff, as bad as they can be, it was the cognition problems. I realised that patients at home, and family members, might not necessarily know precisely what we mean by cognition. So could you just briefly explain what cognition means? What different kinds of cognition you study in HD patients?

JULIE: Sure. Cognition is really our thinking skills; our ability to remember things and pay attention, our ability to make decisions. Our ability to respond quickly if somebody asks us a question. Those are the kinds of things that we think of, that are different types of cognition. One particular one that's quite interesting, and important in Huntington's disease, is something we call executive function. This is like a controller type of function that helps us to think ahead, do planning, strategy. To change what we're doing if the need arises for us to make a change. So executive function is something that is affected in Huntington's disease, that has an impact on lots of different parts of our lives, and that's something that's affected in Huntington's disease.

JEFF: So have you found that all these different aspects of thinking skills, of cognition, are equally affected in Huntington's disease? Or are there particular ones that, when you talk to patients, are the most damaging to their quality of life?

JULIE: An important thing to realise is that for different people, different patients with Huntington's disease, they have different courses. So for some people, they might have more problems with their memories, and for other people they might have more problems with just slowed thinking. Or not being able to be very strategic, or make a decision. So it really varies from person to person, but what we do know is that just by and large, for example, Huntington's disease looks different from Alzheimer's disease. The kind of memory problem that you have in Huntington's disease is the kind of memory problem where you know something, but you have a bit of trouble remembering and finding it right when you need it. Whereas in Alzheimer's disease what happens is people really lose their memory for something. That's not really the way it is in Huntington's, they just have trouble getting it back out when they need it. So, Huntington's disease has really some very specific effects, and it's going to have an impact in different people's lives, differently. I suppose one thing that's important to say is that a lot of times those difficulties manifest themselves when people have really challenging jobs to do. An everyday job that's challenging is cooking. When you have to make three or four things, and you have to get them all to be ready at the same time, so that your family can sit down together. It means you've got to manage the things on the stove, and there are other things in the microwave. You've got to get the salad going, between starting the microwave, and managing all those tasks at the same time, and getting things to come out even, at the same time, without burning something. This is something that's hard for everyone, but it's actually something that gets quite a lot harder in Huntington's disease, and it can really have an impact on the ability to function just normally, everyday.

JEFF: You talked about a new battery of questions you have for HD folks, and I'm struck that if we want to have drugs, or treatments, that make cognition better, which I think everyone would, you need to have the right questions to ask. For example, about cooking. So can you say a little bit about the new battery of tests you've developed?

JULIE: Yes. The battery of tests, what it does, is it tries to test people on all the different types of abilities that are affected in Huntington's disease. Then, it sums it all together. So, somebody might have a problem on function A and another person on function B, and another person on function C, plus D. If you sum all of that together, then you can get a good measure that shows us the impairment that anyone with Huntington's has, but not every person might have the same type of problem. So that's the kind of strategy we use in that test, and we've tried to take the approach of getting pretty broad coverage, of all the different types of cognition that are affected.

JEFF: And just as the last question, we've heard a couple of things today that have been about the idea of environmental enrichment, this is mostly the animal stuff, but I wondered if you could say a few words about what environmental enrichment is, and what it means for people who have an HD mutation?

JULIE: Well, we'd really like to know what it means for people who have the HD mutation, and we need to work on getting that answer. I think that's an answer we can come to in the next five to ten years. In animals, and that's what I talked about, we know that in, for example, the HD mice, that if you put them in a very enriched environment, you give them cute little mousey toys to play with, and they have mouse playmates, and they have mouse exercise wheels. These animals; it takes longer for their cognition to begin to show the deterioration, for it to begin to show problems. What we don't know is how that might pan out in humans. In the animals, one thing that's interesting is that some part of the brain seem to benefit more from, say, the physical exercise, and some parts of the brain from the cognitive exercise. So we don't actually know how this is going to pan out in humans. We don't know much of these enriching environments we need, and we don't know which types of enriching environments might be the most important. So far, in humans, the only evidence there is, is really just this small bit of evidence, I would say, about if a person lives a more passive lifestyle, that they may have an earlier age of onset. That doesn't tell us anything about cognition, at all. It just tells us something about the age of onset, so we really need to know more.

JEFF: So the best idea right now, and the best advice we can give, probably, is stay as active as you can, it can't hurt?

JULIE: Yes, I think that's probably a good lesson for everyone. I think a great thing about environmental enrichment is it's actually never going to have a bad side effect. So, what I think is a promising approach to think about in the future is, it could be environment enrichment may be the part that has the physical exercise might give you a 2% advantage. If you have the intellectual stimulation, that might give you 3%. Then, if you get a good drug

on top of that, might give you another 15%, maybe a little bit more, who knows? We don't know how all of these things might add up, but I think it's really interesting to think about the possibility of combining different strategies - especially some that don't have side effects - and seeing whether we can just get the most out of trying to make the brain work better, for a longer period of time.

JEFF: Sounds good. Thank you Julie and Ralf, for sharing your enthusiasm, and for putting up with Ed, incidentally. Please join us in thanking them.

ED: Thank you guys, thank you.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

manifest after HD diagnosis, or when symptoms are already showing

chorea Involuntary, irregular 'fidgety' movements that are common in HD

cohort a group of participants in a clinical research study
