00:00 Introducing the topic and guests

Hazel: Welcome to this special edition of the **Tinnitus Talk Podcast**, dedicated to **Tinnitus Week**. Tinnitus Week is held every year in the first week of February, and most of the tinnitus organisations around the world take part in it. The aim is simple, to raise more awareness for tinnitus.

Now, we've tried in the past to use Tinnitus Week for broad, general awareness raising where we tried to make the general public understand the plight of people suffering from tinnitus and the need for a cure. We've created, for instance, videos that describe what it's like to suffer from tinnitus ... and while we're proud of that work, we found it difficult to be honest, because to really pull off such a campaign and reach lots of people around the world and really make an impact, you need a large budget to buy ads and such, and you need a team of professional campaigners. Especially because there are so many causes out there that seem to generate public sympathy much more easily than tinnitus, whether it's cancer or animal welfare. We're just a tiny non-profit without any full-time staff. So, while we still stand behind this broad awareness raising goal, because clearly the suffering caused by tinnitus remains very under-recognised, and if there are any bigger organisations or philanthropists out there who can afford to set up the kind of large-scale campaign that is needed, we will gladly jump on board... But, as this is not the case yet, we decided for Tinnitus Week this year to promote something a bit more manageable and in scope for us, and more directly related to our daily work.

We do a lot of work with tinnitus researchers, so our theme for this week is related to a research project that we are working on, within a consortium, on the topic of biobanks. This might be a topic that you've never really considered in relation to tinnitus, but I can assure you biobanks are crucial to cracking the case of tinnitus. A biobank stores biological samples and other data from typically large populations, like 1000s, tens of 1000s or even hundreds of 1000s of people, and it's this kind of thorough and large-scale data collection that's currently lacking for tinnitus.

I talk about this with our two guests: Christopher Cederroth, a researcher who focuses on the genetic underpinnings of tinnitus, and David Stockdale, the CEO of the BTA. We talk a lot about the need for better definitions of tinnitus and obviously the need for more data; those two are closely related: lack of clear definitions and clear target patient groups often leads to collecting the wrong kind of data, and lack of big data is one of the reasons in the first place we don't have good definitions and clarity on sub-types of tinnitus. We also talk a bit, at the beginning, about COVID-19 and its relation to tinnitus and hearing loss, and Chris talks quite candidly about his personal experience with tinnitus.

As you might know, we are a small team of volunteers working on the Tinnitus Talk Podcast. We spend about 70h creating one episode. One of the extra things we do for our audience is we always create a transcript. This is especially important because we're dealing with a hearing impaired and hearing sensitive audience. You can find transcripts for all our episodes on tinnitustalk.com/podcast where next to each episode there's button marked CC to download the transcript.

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Now, without further ado, let's listen to **Christopher Cederroth** and **David Stockdale**.

Hazel: Today we're talking about biobanks. It might sound like not the most exciting topic to some of you, but I promise you it is an interesting topic and very important because if we truly want to understand tinnitus and perhaps cure it, we will need big data from biobanks, and that's what we're talking about today with two guests who are joining me. I will ask each of them to introduce themselves shortly, but just briefly, we have Christopher Cederroth with us, a researcher who has been focusing on tinnitus for many years, and has specifically been looking at the genetic underpinnings of tinnitus, and we have David Stockdale, a returning guest of the podcast, the CEO of the British Tinnitus Association, and a big advocate for biobanks for tinnitus research. David, can I ask you to start by briefly introducing yourself?

David: Yep, so thank you for the welcome and introduction, Hazel. As you said, I am David Stockdale, Chief Executive of the **British Tinnitus Association**, and I've been Chief Executive since

2010. A big passion of mine has been in following the tinnitus research, looking at how to engage with it effectively, how to support the research community, and ultimately how to encourage and steer the community towards looking at cure-focused tinnitus research.

Hazel: Thank you, David. Chris, do you want to do the same?

Chris: Yes, sure. Thanks a lot for the intro as well, I'm delighted to be here. Indeed, a very important topic. So, my name is Chris, and I'm a biologist by training. I've made my PhD degree in mouse biology and reproduction and metabolism, and it's only during my postdoc that I shifted towards tinnitus also because I experienced it and I found the same problems as many of your listeners. So, I went to the **Rockefeller University** for my first postdoc and started developing the mouse model for tinnitus, and then I moved to Sweden, the **Karolinska Institute**, where I joined the lab of **Barbara Canlon** and worked on her topic of circadian regulation of noise-induced hearing loss, but then also I started launching my own research arms on tinnitus in humans. So, after that experience, I moved to England. Very shortly, a period of COVID made it difficult, and I'm now back in Geneva with the family and still doing some research on tinnitus and hearing loss but at the small-scale level.

06:32 Chris' personal experience with tinnitus

Hazel: Right, so Chris, was it literally your own experience with tinnitus that caused you to pick that up as a research topic, or were there other factors involved?

Chris: Yes, I've been curious about it. Most of it was more on aspects of hearing, and that happened before my Master's, because I've been playing music for a long time and during my teenage years. Probably I've been exposing my ears to a lot of damaging sounds. At that time, we were not equally aware about auditory protection, and I made my Master's research in Montpellier with a team from **Jean-Luc Puel**, who's a brilliant researcher, and that's where I got introduced to people that were doing tinnitus research in animal models. That was interesting, but that was my first interaction, and I thought, well, that's fantastic, that you can ask an animal whether it has or not, tinnitus, and I thought this was really interesting, but then at that time, I had found a PhD position in Switzerland, so I went back there and learnt things from other fields too, and I think that this was beneficial and to bring back another approach to the area, and so that there was limited knowledge in molecular mechanisms and hearing as well, isolating RNA was difficult… So, I got exposed to that before, and I think this gave me a little chance to come back afterwards.

Hazel: If you're comfortable talking about it, can you tell us a little bit about the personal experience that you mentioned? How was it in the beginning and how is it now?

Chris: Sure. The initial experience, in February of 2002, I went to Spain and I went to visit some friends there during the period of New Year time, and Spanish people have this tradition of using fire crackers all the time, and this kind of thing is okay-ish. In the streets, there was a young guy that launched a dynamite stick that was equally long as my arm, and it exploded next to my ear, and that's where I got instantaneously tinnitus. And it lasted, very loud, over a lot of time, much more than the other occasions where I went to discotheques and parties where it was occasional, and then it would fade away after a day or two, but this one kept on ringing always. And, as I was saying, it has now kept on ringing for 20 years. And so, I went there to visit some doctors and they claimed as per usual — "Well, we see nothing wrong with your hearing. It must be stress." How can you say that?

Hazel: You had acoustic trauma!

Chris: Yeah, I just have trauma, what are you talking about?! My trauma was not visible on any of the tests that were performed at that time, so I was 20 years old, hearing is rather good at that age, and maybe the damages were not equally obvious. And then with time, it took four years before it went kind of down in intensity, the first two years, it was very loud, and my only way of going to bed and sleep was just to work like a madman during my thesis work. I would just crash into bed, not even listening to the loud noises that I had, but then I think that working intensively helped me focus on something else, and this has helped me a lot coping with it and had reduced my anxiety levels and reduce my stress, and I had a lot of funding for the research, so that was a very pleasant time of my life and coinciding with a lower degree of distress but also perceived loudness.

And I'd say that this has been rather stable until very recently, and now things have gone a little bit back up, but I've experienced a tremendous amount of changes in the last year. Now moving with the kids and the family to Nottingham, them not being super satisfied about the changes and the situation of COVID in England, I declined on this substantial position and brought back the family here. I lost my mum four months ago, and now my wife left me and I'm divorcing so you can feel that it's putting a little bit of pressure on top of it, and it seems it's coinciding with what everybody experiences with apex of stress, apex of anxiety, the level rises and I'm quite comfortable that with time when my personal situation will improve, that things will kind of fade away, I still have no problem sleeping and so I continue working equally.

Hazel: Wow! That's a lot of huge personal changes, Chris. Yeah, I can imagine that triggers your tinnitus more. That's of course, a recognizable story for many of us who suffer from tinnitus. I certainly notice when I'm very stressed, because I'm quite habituated, so I'm not, on a day-to-

day basis, usually not that bothered about my tinnitus, but it is really in those moments of stress, then suddenly I hear it very loudly. I'm like, “gee, where did that suddenly come from?” And I know it's because I'm really stressed that day.

12:05 Links between COVID-19 and tinnitus

Hazel: David, I think you've said before that you're getting a lot more calls to the BTA helpline these days because of the COVID pandemic. Is there a stress factor there involved as well, or what do you think is happening?

David: Yeah, we believe so. Sorry to hear your news as well, Chris. We spoke about it before, but... Yeah, sorry to hear all that. So, yeah, we believe there is a link between stress and anxiety and tinnitus, of course. It is well proven in the literature, I think, and we're certainly seeing that play out through our helpline and our web chat calls as well as we see numbers drastically increase, and especially when new lockdowns or new news appears or occurs with the COVID situation, then yeah, we certainly noticed that impact on our helpline and something else we’re seeing at the moment as well, is people really struggling to get help from the health services as well, so from primary care, from GPS and physicians, and then being able to go for onward referral. Also, we've certainly taken a lot of calls from people really frustrated because it’s just got harder to get through the healthcare system, as well, with other issues like tinnitus, because COVID is just dominating, and a lot of healthcare workers are off sick with COVID as well, putting further stresses and strains on the existing systems. So yeah, lots of issues mix together really, which is making a really unpleasant experience and quite traumatic for a number of people living with tinnitus.

Hazel: I can imagine. Yeah, are you getting a lot of questions about the vaccine, because we see a lot of discussion on the **Tinnitus Talk** forum about potential risks of the vaccine. My personal non-expert opinion is that probably getting COVID would be much more dangerous to your hearing than the, probably very, very low risks of side effects from the vaccine, but again, that's like I haven't read up on all this, if there is any scientific study on that. Are you getting a lot of questions on this?

David: Yes. Lots, and we have a page on our website as well at **tinnitus.org.uk** that's keeping up to date with the UK data on how many people are reporting tinnitus as a side effect of the vaccines. So, we've got a page, and we're following the advice from the **MHRA** and at the moment, it does look like tinnitus is a side effect of the vaccines, although it's a rare side effect. Much like you said there, Hazel, our advice and guidance, following the UK authorities, is still that the vaccine and the protection it gives far outweighs any of the risks of the side effects that we know about at the moment. And also, so we don't know what impact that is, if it's tinnitus, that

becomes permanent, if it's transient, all we know is the number of people that are reporting it through what's called the yellow card scheme within the MHRA in the UK.

Hazel: Chris, this is something you've looked into at all, potential links between COVID-19 and tinnitus?

Chris: Not personally, it was one of the purposes when I came to **Nottingham**, they wanted to start launching the project like that... Well, it's been a big... How to say? Engagement from the NIHR to motivate different labs to start focusing on COVID problems, but for the short time that I was there, it was extremely difficult to design a study with proper control people to make a very well design and really answer the questions with our doubts about the impact of that COVID onto tinnitus and some difficulties... Yeah, you want to say something, David?

David: No, I was just gonna agree with what you're saying. Sorry I was going to wait till you finished before coming in, but I think you're right, and we've been working with the University of Manchester as well, just trying to understand and unpick the picture of what's happening. So, in the UK, the **National Institute of Clinical Excellence** has recognized tinnitus as a symptom of both COVID and long COVID. And what we believe will happen is that when people have had COVID that you'll see this first wave of issues like respiratory issues and other things that people seek help for, and then once they're through that they naturally maybe they left with residual issues like tinnitus, and it then sees this second wave of help seeking as well, and we think that's what's happening at the moment, and that's certainly something that's coming out in the data is that tinnitus does seem to have some sort of link. But no one really understands what that is, and some research that's imminent from the **University of Manchester** as well, suggests that possibly it's something that's happening alongside COVID, and it may not be as linked as first believed, but... Yeah, we're really not sure, I think, on what's happening, and it'll take bigger and more data than is available at the moment, I think, to really unpick that picture.

Chris: Yeah, because you want to also distinguish whether the effects are due to stress related to the confinement... Stress related to the situation and employment from the virus infection itself, for those that have been infected. Some have been diagnosed with a test, but others have not, some have been diagnosed but been asymptomatic, some that are asymptomatic didn't know they had been infected, and so there is a lot of cloud of noisy data in there that had delayed the start of the project. Now, I'm not aware about the status of this within Nottingham, but I acknowledge the complexity in designing studies in this context, although I see a lot of work being published in other conditions, but they can be highly unreliable, and I guess the philosophy from Nottingham is that you don't press on the button until you're really sure what you have in hand and publish quality work.

David: And the early research as well, was based on people who had been admitted to hospital with COVID as well, and then following them at discharge, so again, it may be that those cases were much more serious, of course, have been hospitalized with COVID, and that did suggest, you know, much higher levels of tinnitus and hearing loss than maybe's being seen in more generalized data now, I think.

Chris: Yes, there you also have complex confounding factors, like in ICU care, you have a lot of hypoxia, the deprivation of oxygen, which is highly damaging for the ear, and this could impact on hearing loss and also on tinnitus, and in fact, generally, there is very little knowledge about the impact of ICU on those two disorders separately. That's maybe only now that people start to think about this as a possibility, maybe thanks to the COVID pandemic that this has awakened a new area of research, but still low activity there, too.

Hazel: Right, so let's move on to the topic of biobanks, as interesting as this is. This is probably worth a dedicated podcast episode, actually — links between COVID-19 and tinnitus — but probably once there is a bit more data and evidence available.

18:58 The function of biobanks

Hazel: So, on the topic of biobanks, Chris, not all our listeners might even know what a biobank is, how would you define it?

Chris: That's a big question in some ways, because I would say first that there are a lot of epidemiologists that have gathered data on questions on people to understand. That is quite typical now for tinnitus, we have a lot of epidemiology in the literature, but biobanking, maybe the difference is that you collect the same type of information, but on top of it you include samples from donors or people, individuals — that can be urine, that can be blood or plasma — that with the blood, you can extract DNA from saliva as well, from blood and saliva, you can extract different molecules, hormones, things like that, that can help you then go a little bit beyond just the simple abstract data that you collect with that can be questions, but also auditory measures, they stand into a computer or … MRI also a stands into a computer so that's not proper biobanking.

If we also want to go a little bit further, now it's something that could be very interesting for tinnitus research in the future. There are in the ICU system, and if the university has a relationship with those IC units in a hospital, sometimes they also do biobanking on material from people that have died, so necropsies happen and then you collect tissues and, in some countries, you can have history about the patient, information into a medical registry. That happens in Sweden, for

instance. So, you can relate a tissue with previous history of, in that case, we're interested in tinnitus and things like that, so brain tissue, cochlear tissue, the ear that's very seldom collected, unfortunately, because it's very difficult for accessing it, is really in the middle. If you have to break the temporal bone, most of the time, once you've achieved that, and it's a lot of drilling process in, the ear has been under quite a long time of oxygen deprivation and everything starts to degrade dramatically fast, so in that area, I'd say we've been a bit delayed versus other fields, so knowledge has been lagging there, but it's definitely something that has to be enforced in the future as well, so biobanking is really bio-material samples that are collected on top of informatical data that solely stands on a computer.

Hazel: David, how did this topic first come onto your radar? You can also add, of course, to Chris' definition if you want.

David: Yeah, thank you. So, I think that's a great overview of a biobank that Chris has given there, and I think it's just worth sort of reflecting there are also different types of biobanks as well. So you can have ones like the UK Biobank, which may be the most famous one, where you just collect lots and lots of data and then use it for very different studies, or you can have biobanks where you're targeting a specific disease or a condition like tinnitus and try and get studies off the ground that are much more focused and dedicated, and you try and collect a higher quality data in a specific area that will hopefully help you. Then use that data to access other sources or access wider sources like UK, biobank after collecting it as well.

In terms of why myself and the BTA have got interested in biobanking, it's really part of the journey we've been on through our research evolution really, so I'm sure everyone was aware of the drugs trials that happened around 2017-2018, and of course, really frustratingly for the community, they all failed, but what happened was that actually those companies were very vocal and open about why those trials failed, but also then started saying what was wrong or what would be needed to really see investment in tinnitus research from an industry, from Pharma, from Biotechs in the future, and they started talking about things like the need for a better way to objectively measure tinnitus, the need to better understand how to translate findings in animal studies to human studies and the need to potentially sub-type tinnitus and look at how to better define target audiences for recruitment into research.

So, we heard all of these messages and started developing what we called the cure map as well, which was just looking at trying to assimilate all the research that was happening around tinnitus and trying to plot it in terms of where did it fit, and where did it go. And we published that in a paper called "Why is There No Cure for Tinnitus," which really tried to go through these challenges the research community faces in terms of moving on, and whilst we were discussing

it and developing that with industry, with the charities, with Academia, what became clear was that actually, there were several questions that needed addressing ideally at once, things like what is the mechanism of tinnitus, how do we develop better ways to measure it, and actually through that thinking and discovery, what we really felt was one way that you could address this in a big bang, if you like, in a way that would move the field forward would be to develop a biobank and look at addressing as many of those questions as you could in one shot by getting as many people living with tinnitus through a research project, but trying to ask every question you could rather than what we have at the moment, which is lots of smaller scale studies looking at quite niche areas. If you could actually get the scale and the breadth that maybe we can successfully answer some of these questions in one go.

24:44 What have we learned about tinnitus from existing data?

Hazel: And so, both of you have already been involved in some studies using existing biobank data to glean new insights about tinnitus. I'd like to talk a little bit about some of those studies and see what can we already learn from data that already exists, and then later we'll talk about what more is needed, because I think it's clear we need a lot more data, and there's a lot more that needs to be done. Chris, can you start by giving us an example of a study where you used existing biobank data and you really learned something new about tinnitus?

Chris: Yeah, sure. I'd say that there are three different studies that I'd like to share because they were all very different, but all were very insightful into the struggles we've been facing and what we learn from that. The first one was part of a European Project called ESIT, the **European School of Interdisciplinary Tinnitus**, and there we got funding for a PhD student, **Natalia Trpchevska**, who's been working on GWAS, so genome-wide association studies. We got a donation to start genotyping people from the **Swedish Twin Registry**, which was a database we've been using in Sweden to evidence some first parts of the heritability of tinnitus in the Swedish population, and there we gathered efforts with other researchers at **Karolinska**, because this is still very costly to help genotyping the majority of the samples, the block samples available there, and thanks to that, Natalia started doing the work on about 20,000 people from the Twin Registry, but it came very obvious and rapidly obvious to us that this was not enough. So, we started collaborating with a lot of other people knocking on doors, simply existing bio banks that can be **FinnGen**, so that's in Helsinki, Finland, the **Estonian Biobank** who have registry data. It's not proper questionnaire answers, they just have been diagnosed by a doctor encoded with the 93.1 ICD code from the **WHO**, which is, one can say, quite reliable in some ways. And then of course, we expanded to, for instance, **HUNT** in Norway, the **UK Biobank** was interesting, and we found other people were also working on a topic that were completely complementary samples, so there was **Paul Nagtegaal** and **Frances Williams** from the UK Twins. So, we joined efforts, and now we have a sum of 700,000 people that is being analysed. During that time **Clifford et al.** from the

University of San Diego and **San Francisco** published the first GWAS on tinnitus and so we had hoped, and this has been published for schizophrenia typically, when you increase the number of samples, you have a linear increase in number of polymorphisms that you can identify in the population.

Hazel: Sorry, Chris, can you define polymorphisms?

Chris: Yes, very good. Yeah, tell me at any time if I have to stop there. A **polymorphism** would be variants in the genetic code that may be associated with a specific trait. So when you study genome-wide associations data, you're not focusing on the whole genome, you are interested in taking the surface of the iceberg by looking at about 10 million of those polymorphisms, and see whether they have a trend in associating themselves with a given trait, so that's kind of a more shallow, I'd say, analysis than the whole genome sequencing where you're looking at all the letters and the basis from the entire sequences from a human being, but GWAS is still very powerful to guide you on potential genes that could be involved in tinnitus. It doesn't tell you which one, but it tells you which region within the genomic landscape there could be some important things to dig in further. So, what we found with this is that we didn't really increase our knowledge for tinnitus and what had been published before, and we were quite disappointed. This work is not published yet but we're trying to.

Hazel: Meaning you didn't find a clear link between a specific polymorphism or genotype and and tinnitus?

29:41 Tinnitus for 5 minutes is NOT tinnitus!

Chris: Some of the things that they have found in the past, we replicated, but we didn't have an incremental knowledge in the finding, so we increased the sample by three-fold, but we didn't increase the knowledge by three-fold. And what we believe is the issue is that we have a big heterogeneity and how tinnitus is defined in those different cohorts, because if you take the same data for the UK Biobank and what Clifford had published for tinnitus, the number of hits that you find for hearing loss is much higher. You get three regions for tinnitus, but you get about 40 for hearing loss, and now that we expanded also this number to 700,000 people, we also increase the knowledge for hearing loss, but we didn't for tinnitus, and what we believe is the issue is that how it's defined in the different courts is causing a lot of noise. And that's why we need better definitions. Sometimes cohorts ask the question: *Have you ever had tinnitus in your life that lasted more than five minutes?* But this doesn't tell you if you have tinnitus now, if it's constant, if you suffer from it, and so on. Others just focused on severity, but not knowing if you have it continuously, permanently. Let's take the example of the UK Biobank. The most stringent definition you have there is whether you have tinnitus most of the time or always, but it's within

the same definition, and the prevalence for that group is 7% out of the whole UK Biobank. But we know severe tinnitus is rarer, it's about 1-2% of the population, so even the UK Biobank is missing that type of information.

Hazel: Right, so you've got all this detailed information about people's genes, but you don't have the details needed about their tinnitus.

Chris: That's correct. In contacting back people, re-asking that specific question is not really do-able, it's a huge effort for all the different participating biobanks to do that just for the sake of tinnitus, and that's where there is a big need for investing funds and efforts into developing maybe our own biobanking system.

So in fact, in other projects that we had from the EU, so that's TIGER (**Tinnitus Interactions between Genetic and Environmental Risks**) tinnitus interactions between genes and environments, and the other one is **UNITI**, which is currently ongoing as well, we received funding to do some of those more detailed genetic analysis to soldier sequence, either the whole **exome**, so exome is the region of the genome that encodes for protein, that's about 1% of the genome, and then we also had money to perform whole genome sequencing, so to get the entire length of the individual sequences.

And here we did a different thing. We've seen in our own studies that with greater severity, it appears that there is also a greater likelihood for tinnitus to be shared within a family, so we believe that with greater severity comes also greater genetic viability, and that's why we started thinking. That was work with **Jose Antonio Lopez-Escamez** from Granada to focus on extreme cases of tinnitus, so highly severe. And there we managed to obtain about 100 samples that were fully sequenced, so we went for very homogenous populations, but very detailed analysis as well, and there we managed to find some variants in genes that are encoding synaptic plasticity in different regions in the brain, but we were able to replicate these in an independent cohort, so it shows also the value of having greater details in the data that you collect, because then you don't need 700,000 people to find something new. You need smaller numbers, but now, of course, the question is maybe how much, how much effort should we spend on that?

For sure, with 100 people that we have been sequencing, we don't have the Holy Grail in there. Other studies that have been performed, for instance with schizophrenia, have shown that they needed 1,000 participants, patients, I would say, to replicate many of the findings that were obtained with the GWAS, so that gives us a little bit of a sense about the size of the need, but tinnitus is also a bit more complex, that's quite heterogeneous. Some people have pulsatile tinnitus, and that cannot be considered the same. Others have it constant, but buzzing, like a

tone maybe because of a trauma. Others have a hissing or creaking or even pulsatile but against body rhythms. So, in anticipation of such heterogeneity, we have to think about collecting even more samples than that.

Hazel: So, I want to get back to that topic in a moment of sub-typing or whether sub-types exist or not, and I will ask David in a moment to talk about some of the studies he has been involved in, but Chris, if you would have to summarize, what is the status quo of our knowledge at the moment about the link between genetics and tinnitus? How would you summarize that? To me, okay, let me try my own sort of lay interpretation. It sounds like you're saying we're fairly certain that there is some kind of genetic predisposition to tinnitus, that could be one of the factors that causes someone to develop tinnitus, but we don't really know yet which genes are involved or maybe only have a vague idea.

Chris: Yeah. And not to be a bit negative here, I'd say that recently people have found that any trait has a genetic component. On average it is 50%. So it's not a surprise to see that even tinnitus falls into that region, but we needed to gather that evidence anyway. Now, differences that we see, that the greater the severity and the greater the involvement of genes in there, but now the status of knowledge, I'd say that the existing biobanks don't offer the resolution to gather the data that's there. I'll give you other examples for those definition issues. We've been working with other data, not biobanks, but data from epidemiology that has been the **Swedish Longitudinal Occupational Survey of Health**, that's 20,000 people, and the prevalence of those severe cases is 1%. Same with the **Swedish Twin Registry Stockholm Public Health Cohort**, so when you have 70,000 people and you scroll down to those that you want to study, the prevalence or the abundance of that material is low. Or to work with populational data, you need very big amounts to finally identify the target population you want to study, and this is the limitation we have currently.

We've designed our own project called STOP, the **Swedish Tinnitus Outreach Project**. This has been our first type of biobanking effort. We're trying to work it a bit wisely because recruiting people from outside is quite difficult. So instead, we collaborated with other biobanks that were in the neighboring side of Karolinska. I think that Sweden is known for a lot of their biobanking efforts, so we collaborated with **LifeGene** and LifeGene said, no problem, we can invite the people — our participants — to join STOP and to contribute in what way they can, so we invited 60,000 people; 6,000 were registered, half of them had tinnitus, the other half did not, but this was a populational scale, and then when you look at those that were of interest for us, then we had 100 for whom we had DNA collected. So out of 6,000 people, even if we have a nice design, because we also have controls, this is something that's difficult to get. The target population,

what we've figured out after all these years of analyzing the data is that that's a very small portion of what we gathered.

Hazel: Yeah, so this demonstrates the struggle with getting the sample sizes you need.

38:11 How tinnitus develops over time

Hazel: David, do you have anything to add in terms of studies that you've been involved in that you think are interesting to share?

David: Sure, so The British Tinnitus Association supports research in two ways, one is that we fund research and we have funded research looking at biobanks. So, one of the projects that Chris is working on, they mentioned they're looking at the UK Twins Registry with **Frances Williams** at **King's College London** is a project that the BTA's funding, and Chris is writing up I'm assured at the moment for publication. But another way we do it is encouraging and then working alongside researchers as well to try and find key questions and look at how to publicize and publish those. So, we've been looking a lot at **UK Biobank** data in particular, and we found some longitudinal data in there as well, and some longitudinal data about tinnitus, so whilst a lot of basic epidemiology studies have been done and published on tinnitus, one of the studies that hasn't been done is just looking at our longitudinal data and seeing if it tells anything as well. So, I looked at that along with **Piers Dawes**, **David Baguley** and **John Newall**, and just tried to understand if that told us anything interesting. And it did, looking at prevalence of tinnitus, we saw that actually tinnitus remained broadly static in those groups and broadly static in terms of how people perceive the troublesome-ness of it as well, and severity.

Hazel: So, you mean if they were asked a point 'A' in time, do you have tinnitus; how badly do you suffer from it? And you ask them at point 'B', I guess a couple of years later, I don't know what time difference we're talking about, then it's mostly the same answers that you're getting.

David: Yeah, broadly static. And this was one of the issues with the paper was that you didn't know if all the research and the data, you don't know if those people have sought help or treatment in that time. You don't know if anything else has deteriorated and on average, well, there wasn't an average, the time gap between people going in at the first point and then going in at the second time was between two and seven years, so a huge variability in the data.

But yes, what we saw was that there was a fairly large percentage of people who said they had tinnitus at timepoint 1 and then said at timepoint 2 later on that they'd *never* had tinnitus, so actually that leads to some fundamental questions to ask about how we're defining tinnitus and

how we're asking those questions. But also, then we saw once you discounted that group, we saw 9% of people improving, 9% getting worse, and the rest staying broadly static.

40:44 The need to focus on chronic, severe tinnitus

David: And so, to Chris's point, then what was really interesting was understanding more about what's happening to those with severe tinnitus, but actually once you got down to this level of data and you tried to analyze it again, you're down to numbers which were fairly meaningless. So again, we wanted and were more ambitious with what we thought we may be able to get out of that paper than actually ended up being the case.

But I still think there were stories left in the UK by other biobanks that can really help us. As Chris was saying, if we can develop some sort of meaningful 'severe type of tinnitus' and actually then go back on the data at a large level and interrogate it, we may well find something more interesting, and that was a study that I was working on that sadly fell apart due to a few colleagues moving on in key positions. But again, I think our research, if you like, it's a little more superficial than some of the great work that Chris has been involved with, but we're coming up with the same issues. It's how do you define tinnitus in an adequate way that's going to be meaningful and allows you to potentially separate people with long-standing tinnitus with permanent tinnitus from those who may have experienced it in a more transitional way, and how do you get the number and quality of data that's really going to be able to take you forward with that characterization of tinnitus as well to give you truly meaningful results?

And I'll just give you one more example before finishing, so we're looking at, could we actually understand some of it and use some of the imaging data within the UK Biobank study with a team a while ago, and you're looking at it going, *this would be great*, but actually we need to understand laterality, if we're going to use the imaging data in this way, so we need to understand does someone hear tinnitus in the left ear and the right or in both ears, and even data, at that basic level, isn't there, which just hampers so many studies from moving forward that it becomes almost irrelevant to use that and you have to then start thinking about, *we need to go and do it from scratch*.

Another criticism might be, well, why don't you go back to the UK Biobank and ask everyone in there much more detailed questions about tinnitus? — which you certainly could do, but then you've got data about someone's tinnitus, possibly a decade later from when an imaging study was done, and how useful or how comparable is that? So, lots of challenges, I think, in terms of using existing data that is well published now and well understood, that means that actually, I believe we have to look at our own community resource.

Hazel: So, you've both clearly run into the limitations here with the existing data. What is really needed now to take a big leap forward?

Chris: I'd say even the studies that David is describing here, they've been very important. We've been replicating many of those findings, about the dynamic and transition of people with occasional tinnitus, and we had little chance because the data that we had included a better definition for constant tinnitus, and there we could show that when you have occasional tinnitus, which is what is defined now with the questions in the UK Biobank, people shift from one condition to another, and that's every two years; we got samples collected over a 10-year period, every two years. So, five follow-ups, and there the transition in the groups is really big. But once you get to constant tinnitus, the likelihood you have it constant afterwards increases dramatically. So there, we were able to see something that was not possible with the UK Biobank, is that with increasing frequency of occasional tinnitus, the risk for getting tinnitus constantly raises a lot, and if you already have constant tinnitus, the likelihood of it to persist in time also increases dramatically.

So, this guided us to ask the question. We had data collected over these four years' time, did those 1000 people that I mentioned before, we recruited a thousand of them to measure **auditory brainstem responses**, so that's a non-invasive measure for hearing, usually hearing could be tested with pure tone audiometry where we asked people if they hear consciously a sound and they press on a button and acknowledge that they have heard something, but ABRs, so the brainstem response is a bit more objective, and there you stimulate the auditory pathway from the ear to the auditory cortex, and you can merge its activity, the amplitude of those nerve responses, and then we ask the question, can we see something different between non-tinnitus people, people with occasional tinnitus and those with constant. And what we saw is that the wave forms are different than those that have constant tinnitus when compared to those that have it occasionally, so this hasn't been published yet. That's pending an evaluation still. But we're comfortable in saying that we see that the epidemiology on one side shows the transition to constant tinnitus, and we see that the nervous system also has altered in this group of people, which is suggesting that already there we have a sub-type that can be defined with some form of biomarker. So an electrophysiological change that's objective, and that could be a first evidence that this group is at least the minimum required for being studied in tinnitus.

We shouldn't be focusing on occasional tinnitus. To give you more arguments on this with seeing examples also for schizophrenia. Schizophrenia is very hard to diagnose. You agree? People complain always that tinnitus cannot be objectively diagnosed, but people have been focusing on schizophrenia research for 40 years without being able to put a diagnostic marker on it, so sometimes I feel frustrated that there is so much rigour in tinnitus, but... So, it's the case. But in

their genetic analysis, the best way to ensure a high-quality phenotype was to say we only consider patients that have been to the hospital as in-patients at least two times. That's very interesting, because in the case of tinnitus, for instance, people that come to the clinic because of a tinnitus complaint are directly labeled with the IC code and get them stuck into the medical registry data with this 93.1 coding. But we don't know there also, if it's something chronic, if it's something constant, and sometimes people are curious about it. They have experienced it maybe one night after a concert or a party, they go to the clinic site, *well, I heard this beeping sound*, what is it, and finally they go back home because it's faded away, and then still they're in the registry system.

So, I think even the prevalence of those that have severe tinnitus that is chronic, constant, and severe is even lower than what we think now it is, and that should be the target population. And that's aspects of new definitions that we need to consider. The problem is that we use the same word for everything. Tinnitus is occasional, tinnitus is constant, tinnitus is severe.

I'll give the example, for instance of blood pressure, there have been guidelines now for hypertension, and they say you cannot diagnose someone with hypertension if he comes once to the clinic and has high blood pressure; you have to have at least four rounds of sequential visits, spaced with three to four weeks before you say "alright, now you do have hypertension", and I think our limitation is that we have a word for a condition where it might be a meaningless condition, like some of that experience is just overnight, that can be a symptom of noise exposure or maybe stress, but those that have it constant, severe and chronic, there, there is something that's wrong and that's different from the other ones, and we cannot say they have a symptom at the moment that the symptomatology came over and dominates everything, then that becomes a condition worthy of digging, warranting details.

The other problem is that sometimes when you go to the clinic because of hearing loss, you mentioned you have tinnitus, but it might be non-bothersome, still you're tagged with it, so you have a lot of noise even in medical registry data, and there is a great need for improving those definitions, such that first those that have something that's symptomatic or classified as such but those that have a disorder are recognized also as having a problem that deserves clinical care. So, I think that's where the future is needed; to have optimized definitions for a better classification there.

David: I think, again, Chris is making some really valid points in terms of what's our definition of tinnitus, and I sometimes wonder when you see those big general epidemiology studies as well, if they're really helping or hindering us a little bit. So, there's one out recently which again put the number of people with tinnitus at an order of magnitude from where it was previously. A

paper from the **ESIT** cohort that Chris referenced earlier. And actually, if you look at the question that was asked, it was, *have you heard sounds such as ringing, hissing, or buzzing in your ears lasting longer than five minutes in the last year?* My surprise is that's not everyone! It almost seems like, surely, that's a greater population than even reports it within the paper. So, I think there is a question like Chris says about, *do we really need to think about how we're narrowing down and defining tinnitus?* — especially for some of these studies where we really want to fundamentally understand and help those who are really, really struggling and actually, there are the recruitment profiles and everything else we're using at the moment, actually, is that, is that a barrier to really effective research and looking at how we do move forward with some of these studies.

Hazel: Yeah, makes a lot of sense. And I really like what you're both bringing forward here in terms of focusing specifically on that group of chronic, severe sufferers. Clearly that's a different beast than someone who just intermittently hears tinnitus. Also, it's interesting to hear you explain, Chris, that once you have chronic tinnitus, the likelihood that it persists is quite great, it's probably not what people with chronic tinnitus want to hear, but the data shows this, right? And so, I think zooming in on that group and particularly the severe sufferers that I would agree. That's what's needed. So, I think you've both clearly highlighted that in order to move forward, we need clear definitions of tinnitus and which groups of people with tinnitus we're actually focusing on. Are there other things that are needed?

Chris: Yeah, maybe I can bounce back on that, mentioning to answer back on your comment about the fact that chronic tinnitus might persist, we still see that people that have constant tinnitus might come back to an occasional stage, so it's not that it's completely resistant to any remission, that there are events happening, so we shouldn't emphasize it.

Hazel: Do you have a percentage on that?

Chris: Not yet, but if it gets published, I'll keep you posted and then you can share this with the Tinnitus Hub observers. Hopefully soon.

52:07 Missing links: patient recruitment, funding, and politics

Chris: But then, when you say what's missing, I think that we're in two different scenarios. When we started working in Nottingham and wanted to think about biobanking, because that was one of the reasons why I got recruited there, the big question was, again, how do we also collect the controls that come to the clinic? The majority of them have hearing loss, so we would get also people with hearing loss, without tinnitus. And that becomes tricky because then you fall into a configure, which is also a pure clinical environment, that's another aspect, people have shown

that there is already a genetic difference for those that go and seek help to the doctor and those that don't. So just by looking at a clinical population, you might get differences in the gene from what you would have got from the population. Now we see also that not everybody with severe tinnitus goes and seeks help, and not everybody that has been seeking help has severe tinnitus, so there are things like that, that one has to consider. And this is why we not only have to work with clinics and start to gather data there, but we also have to work within the population, and these have been aspects that maybe David wants to talk about, is how to reach out to the population in an effective manner, this is quite a tricky aspect, but I think his ideas are brilliant and he should share those here. But I believe that it's dual efforts that are needed.

Then biobanks shouldn't be restricted to a country. We need other countries to do the same, because you need validation. There's been outstanding work, performed for instance within Sweden for diabetes. They've managed to identify sub-types, five sub-types of diabetes, when we thought there were only two, type 1 type 2 and that's it, and then thanks to additional blood collection by markers and genetic data, they were really comfortable in saying, when we identify a group of patients that is responsive to Metformin treatment and we can help them getting a cure for diabetes, but they had sample sizes about 7,000 replicated in another cohort in Sweden with 3,000 to 4,000. Well, all that information available. That's really outstanding. And I think that because of the rare condition we have, we're not at the scale of diabetes, we need a lot of material, but we need other countries to join that effort. And here, I would say that the work that the BTA is doing in England is outstanding.

The fact that there are many of the institutions working on hearing is fantastic. That's not the case everywhere in Europe. I've always wondered why there was such a difference between the UK and the rest of Europe, and I would say even USA and UK are, both of them, quite investing financial resources towards hearing and tinnitus, and I think I understood that they have a better definition for what are auditory problems considered like a disability. So, in the US, hearing problems are within the **Disability Act**, so the government has the responsibility, the liability to favor research, to give them proper care, to train audiologists to measure the hearing, to give them care, to give them the ability to attend courses at the university to be able to find a job and attend this, and the same as in the UK, there are also such big definitions. But in Europe, Europe has delegated that definition to each country, and each country has its proper thought about whether hearing loss should be considered a disability or not

There is also a lot of that, I would say, lobbying of the deaf community that doesn't want to be considered a disability group because they can communicate, they can work on their own, but there is not enough emphasis on that difference between someone that has acquired hearing in their life and loses it suddenly and then cannot communicate anymore, and within that group

comes also those with tinnitus. So, I would say that at a political level, we need something, and that's where maybe the involvement of patients, and that's an important point also, is that patients in other countries and already in the UK, and also should raise their voices about the importance of tinnitus. Now, COVID is a fantastic opportunity for them to be heard and emphasizing the need for research in that area. Also, 'long COVID' now is becoming more and more focused in research as well. Tinnitus is a part of that too, so I think that that's part of some of the needs we have there.

And the biobanking efforts, we should learn from all of these great cohorts. Like the psychiatric genomic consortium has now published GWAS studies on … more than a million people. It's outstanding, and that's not the result of one UK Biobank thing, it's individual clinicians that we're sending samples directly to Chapel Hill where things got sequenced. And what we need is something centralized where individual doctors, wherever in the world would agree to have their ethics approved in their own country, and ship the samples to the same area, have it centralized by an organism, and there you sequence it with everybody in the same way for the same tools, same technology, same batches, this is very important for the homogeneity of the analysis as well. And there you can get information that's outstandingly valuable, but if everybody is working on their side, that will not work, so here we need a change also in the attitude from the ENT clinics and the researchers, we need to join forces, we need to join hands. And this is a spirit that is not…. I would say I've been working in metabolism and reproduction before and I've seen different attitudes in that area of research, this has been a bit lagging in the ENT field. Hopefully, when that happens, then we can really raise the things altogether and give a solution, because that's the ultimate aim.

58:20 Creating a tinnitus biobank & mobile data collection

Hazel: So, David, I'm sure you have some things to add to this and then we'd like to hear also, about any specific plans that you have in this area, and also maybe you could respond to some of the comments Chris made about political environment and, specifically in the UK. I assume this is something you're working on as well.

David: Sure. Yeah, there was a lot to go out there, Chris, thank you. So yes, starting from, what's missing or what else would we need? Chris covered it really well. I think in terms of patient data and everything else, a big challenge will be funding. If we do manage to produce the Tinnitus Biobank, it will probably be the largest, most expensive study of tinnitus that happened outside of Pharma. That's for sure. So again, we would need funding of a magnitude beyond what's ever been invested in tinnitus research in the past, so that's a certain challenge I think that we'd face in terms of development.

Hazel: Could you give us an idea of what we're talking about here? I think people would find it hard to imagine, I mean, 100,000 sounds like a lot to some people, but I assume it's more than that.

David: Yeah, we've priced it within the BTA at the moment, it's about 4 million. So, the only project that's come close to that would be **UNITI**, which is a EUR 6 million EU-funded project, but one that is quite diverse and a number of different partners and a number of different research projects within it as well, so I think it would be of magnitude bigger than anything else I've seen for a single project, so funding is certainly an issue, and then we have talked a lot about the data as well and that really deep characterization of tinnitus was, of course what's missing in a lot of biobanks at the moment, but also, the other thing that's missing is high quality audiometry, and actually the data that would once and for all allow us to answer that question of what comes first, tinnitus or hearing loss. Also, what is the true interaction between the two, which will really, again, help us push forward in our understanding of tinnitus, so in terms of the data that's going to be a key issue for us to resolve, and another, which is always surprising, but it's sadly a bit of a fact is that tinnitus research trials are tricky to recruit to. So, actually, can we get enough people who would turn up and be part of a Tinnitus Biobank, and not only people with Tinnitus, but as Chris and I have said, people with chronic tinnitus, ideally young people with chronic tinnitus, to try and get us as fewer co-morbidities as possible.

David: So, can we get the right people to turn up and be part of this as well as obviously wanting to then recruit Control Studies, so people who do not have tinnitus to be part of it, so we can compare and, really importantly, can we get controls that have similar levels of hearing loss to those with tinnitus as well, so we can really start to unpick things. So, lots and lots of challenges. My big hope is that people with tinnitus would form an orderly queue and be part of a study this big that has this much potential to be a game changer, but it's not being tried. So, until someone does go out there and put the sign above the door we don't know.

Hazel: Yeah, we'd love to help with that. Where we can, if we hopefully do get to that point where you're actually ready to recruit patients, then we will certainly do what we can to help out, but... Sorry, go ahead with what you were saying.

David: No, absolutely, and we'll be relying on any and every mechanism we have really, to really try and push up those numbers, and the way we're thinking of collecting the data at the moment is through having a mobile data collection unit, so it's something that other Biobanks have done in the past, but we'd want one that was sort of custom-built for a Tinnitus Biobank. So, one with a sound booth built into it so that we could do all the audiometry and, basically, we'd tour the UK and go around different towns and cities and do a huge PR campaign as we went to each town

and just recruit locally and try and target populations whilst we're in each of those settings as well, and really try and activate people with tinnitus to come along and ideally bring a control with them. Someone who doesn't have tinnitus to be part of it, and we feel that that's probably got the best shot of doing what we want to do in collecting the type of data that would be needed, and at the same time, hopefully, we'd publish all our protocol and everything else and how we design the Bank and encourage other organizations around the world to do the same and hopefully collect the same level of quality of data as well, which would respond to many of the points we've seen, but also hopefully respond to the point that Chris was making that actually you have to have quite a small population in reality, while you want to cover the spectrum of tinnitus, you want everyone in there, actually the people you really want, you want to overweight it in terms of who you're recruiting to those who have severe tinnitus who, ideally, are a little bit younger as well.

Hazel: I assume the mobile data collection, there are limitations to that. I mean, would you be able to collect samples?

David: Yes, so, we are designing it with a hope of, well, with the expectation of collecting blood as well. That is do-able, we've spoken about that and got a good idea of how we could do that and administer it in the same place. There are challenges with everything else, you've gotta be careful where you park it. You can't park it next to a railway line or anything else because the sound would be too great in the soundproof room, but yeah, we've looked at it and there is a pioneer in this area as well as the University of Manchester does conduct studies in hearing loss in this way at the moment. So, they do have this specification out there on the road, so we've got something that we can learn from as well in terms of something else that's been successful in terms of recruiting and being used in studies like this. Our big challenge will be trying to do as many tests as possible within a short amount of time, because the other thing we've got is how much will people put up with, if you like. How many tests can you run and how much time will people be willing to give to something like this. So, we're trying to limit it to two hours at the moment, and there's quite a discussion between myself, Chris and other colleagues about if that's the case, then what test do you do and what tests don't you do? But the reality is, the time limit is going to be another factor, I think, in terms of how much you can collect, because of course, the other thing is the longer time it takes, then the less numbers you get or the longer the time period is to collect the data as well.

Hazel: Yeah, and in the end, you are kind of stuck with the fact that you have to meet the patients face-to-face for a few hours, one way or other, unless you've thought about collecting other … collecting data somehow remotely. I don't know if that would be possible in a way where people all over the world could take part. Is that possible?

David: Yeah, and again, that's something that already exists, so there are some of those top projects already out there, but yeah, we will be looking at how to collect some of the data ahead of people coming to the centre as well.

What we haven't figured out yet and is still an active discussion is if you ask someone to do the TFI, for instance, the Tinnitus Functional Index or other tinnitus questionnaire, and they do it a couple of days before they then turn up and you do the rest of it. Are their numbers from that test still valid, two days later? Don't know. No one's done that study to really find out, so you know there are challenges with that with how far in advance you collect some of the data, but, yeah, we would certainly hope to look at doing a lot of it before people turn up. In terms of collecting, like I say, the greater volume of data is certainly something we'll consider. We haven't quite got to a stage where we know what to do with that yet because again, and it's my view rather than necessarily the community's view, is that it's available, I think it's that quality of audiometry and that quality of the bio-samples that's missing at the moment so that would certainly be our focus within this. I don't know, I think Chris might have more to add on that. He's got his hand up!

1:06:17 Why are trials failing? Let's get the right data

Chris: We've been reflecting on that aspect of that also in UNITI because one of the complications at some stage was, you know, should we collect saliva, which is easier for non-experienced ENT staff to collect versus blood, which requires a nurse to come and do that, and then came up some publications that revealed that If you do saliva and perform genome sequencing on it, you get a lot of contamination from the bacteria you have in your mouth. This does not happen if you perform genome sequencing because then you only focus on the products that will be produced in the human body, so you can distinguish what comes from a bacteria and what comes from the human body, but not if you have all genomes, so saliva is not appropriate, if you want to have that deep level of sequencing that you can achieve when you collect blood samples instead, so that's one detail that one has to know you can reach out for broader than the mobile unit, but then you might be restricted in not being able to collect the blood, but instead collect some saliva, but then have a limited amount of information and that can be critical too.

Chris: Then we've also performed this analysis that David has been talking about, about checking biomarkers in the blood, and this is also not published now, but we've screened for 190 different inflammatory molecules, we made the hypothesis that tinnitus was related to that because there is emerging data from animal work suggesting there is inflammation in the cortex, and if those markers are detectable in the blood, that can be a nice biomarker to use in the future as well, but we did that analysis or 1,000 people, so 500 cases, 500 controls with constant tinnitus. That's

for which we have evidence that they have electrophysiological changes, but we don't see anything in the blood, so some aspects there, we haven't searched for everything, but maybe the plasma or the blood for those molecules might not be the most needed. In fact, collecting the information for DNA and genetics, so that's one aspect there that having the DNA can help in doing that sub-typing that is really key for identifying groups that can be better responders to a specific treatment. So, getting DNA is not only for sub-typing, you can have greater knowledge in the fundamental mechanisms of tinnitus, and that's also what's lacking now.

People have worked on animal models, but there is a lot of scepticism and how can you measure tinnitus in a mouse? We don't believe that. And there again, people have been working on schizophrenia for 40 years and not asking those questions. They just went ahead and acquired a lot of information and now they have a great understanding of it.

Hazel: Just get the data first!

Chris: Having the genes in humans can help in designing better animal models that can then make the bridge between pre-clinical work and clinical work too, and this will increase the confidence into what has been generated in the past and what will be generated in the future. At some stage, one will have to test a drug on an animal before testing in a human, so we need that. I call it back translation, so from human to animals to validate what is found in humans. That's important. And in fact, what I'm talking about is, is part of the key things that **AstraZeneca** has been evaluating seven years ago, they were asking themselves the question: 'why are so many of our phase three clinical trials failing'? and they went back to their data and started digging into it, and they made their five 'R's. So, we need the right commercial potential. We read that for tinnitus, we have that, that's not an issue. You need the right patient, and that means the sub-type, which we don't have yet, we need the right tissue, so delivery in the brain or in ear, maybe that's also the type of information that now we don't really know. There is evidence that things happen in the brain but what if you cure the ear, would you also get rid of tinnitus right away. The right safety, so that's no side effects and so on. You don't want to target something else in the body, and then the right target, that means the good protein that you want to aim.

And this is important because genome studies or genetic studies, they can help validating in humans what your drug is. Is it a good target or not? So they figured out that when they have a protein target, if there is no GWAS data that shows that there is a link between that protein and the disease, then there is a greater likelihood of failure in the phase three trials, but if you have a genetic validation of your target, then the success is really increased. And based on that, they started getting rid of all the projects that had bad animal models, bad genetic connection with human diseases, and included in that was also a tinnitus project that was run in Stockholm, where

they were trying to redefine **Lidocaine**. So, Lidocaine has been for long, also known to transcend the suppressed tinnitus, but you cannot give it chronic because it has a lot of side effects. So, Lidocaine is really the first proof that tinnitus can fade away with a drug. That happened because people went to the dentist and got the injection in the jaw, and suddenly figured out, “oh my tinnitus is gone”, so something can be done there and AstraZeneca made a lot of efforts to try to make it with less side effects, they had a team working with animal models to try to develop that too, but they never achieved that. So that is part of the things that went into trash because they were not reliable animal models. There was not reliable genetic data to suggest it would be really a good disease to start focusing on, and biobanks will help bring that confidence there.

1:12:36 Are there sub-types of tinnitus?

Hazel: Yeah, yeah, those are all very interesting point points, especially those five criteria that you mentioned, can we zoom in on one of them, which is sub-typing because you've both mentioned it sort of in passing several times? I do think it's worth spending a few more minutes talking about sub-types, because it's one of those things where most people sort of intuit there must be sub-types because people have different causes for their tinnitus. They hear different things, but I don't think we have the real evidence or know exactly what the sub-types are, but then again, like you said a lot of trials are failing, and possibly one of the reasons is that if you test a new treatment on 500 people with tinnitus, but they're just 500 people with tinnitus then they could have all kinds of different tinnitus, then maybe you're just focusing on the wrong group there. Your group is too broad. And you can't figure out why what works for some people, doesn't work for others. So, what's your sense here... Well, do you guys... Are you strong believers in that there must be sub-types and how can we identify them?

David: Yeah, so I think there are. Again, as you say, Hazel, when you look at some of the data and you look at some of those data within papers and they publish individual patients, sometimes you see individual patients absolutely fly and get miraculously better almost to a level where you could say they're cured. You see others who flatline and others who get worse, so you do start to think there's got to be something in that that is beyond placebo or other reasons as to why some of these interventions are having such profound effect on some and no effect on others or are worsening as well. So, I do think there's something in sub-typing. As you presented in your question, how you go about sub-typing is still very much an open debate, do you go by cause, do you go by the sound someone hears, do you go by the frequency that sound is heard at or something else that we haven't yet discovered or looked at? And I think it is an emerging field, and I think we're seeing papers start to think about this and start to look at sub-typing in a way that's developing and opening the area. I know **Eleni Genitsaridi** published a paper last year looking at a potential way to sub-type tinnitus, which was interesting and looking at using big data to try and do that.

I have seen other data presented, which looks at using hearing loss and looking at where different types of hearing loss and maybe, hypothesizing that the different types of hearing loss that exist could be a way to sub-type and we see it within the research produced by **Neuromod** which actually looked at linking tinnitus to hyperacusis or not as well, and seeing if there were different results in populations of people who have tinnitus and hyperacusis or just tinnitus or hyperacusis. So again, I think we're seeing the emergence of the debate, but again, I don't think there's a clear direction of travel or a clear view from the research community as to what the right way to sub-type is.

Hazel: Chris?

Chris: Yeah, I think what David has explained is really, really good and clear. In fact, yeah, the study you're mentioning about hyperacusis was a work published by **Hofmeier**, **Knipper**, and **Rüttiger** in Germany, and they could see that the **auditory brainstem response** would differ depending on whether you had hyperacusis or not, but if you didn't make that distinction you wouldn't have seen any effect and it's only when you exclude those that have hyperacusis you start to see effects, and in fact, we recalculated part of these findings but with other approaches, so already here we can say, tinnitus with or without hyperacusis, these two groups are different.

And we see with our data that people that have constant tinnitus are different from those that are occasional. Maybe here, we're not talking about sub-typing, yet we're talking about how to optimize the target group we want to study. Those with severe, chronic constant tinnitus could be. And within there, that's where we don't know what will define them as a sub-type, and this is what is going to be the challenge of recruiting a sufficient amount of people, because even if you get 7,000 cases like that, the prevalence of those that have pulsatile tinnitus are so little that to just make that little subgroup critical, you need big samples.

People have been trying to focus on gender aspects in our group, we are looking into males and females, they behave differently, we see, for instance, and this has been published in the research topic on sex and gender differences in tinnitus, people have shown that women are more responsive to some of the treatments that happen nowadays than men, so there are things to consider there, and sex when people have already been including this as a variable in their data, not so many people have segregated that data to look at men and women separately and understand how they respond to the biology. But that already cuts your data by two, and so sub-typing is like a very big funnel and suddenly you end up with very little numbers that might have an impact on what you're going to study

So, because of that, and because that particular group of tinnitus people, constant, chronic, severe are rarely studied, we need as much as possible, and then we can ask the question. So, we're going a bit blindly in that data collection, but hopefully, this will be big enough, so then answers can be gathered in a very secure manner.

Hazel: Yeah, makes sense. So again, just get the data first, then you get the answers.

Chris: It's funny that you say that because when we started building up our staff cohort, and this is from an ethical aspect, it's quite difficult just to tell the Ethics Committee you just gather data for the sake of data gathering and they don't want that. You need a specific question. At that time, we had another one, but while we get our data, we figured out what we initially asked ourselves was wrong, and then we used the data for other purposes, but when we mentioned that to some of the patient organizations in Sweden, they were laughing and said, but what are you financed with, and we said, we have no financing. How many are you? We're two, me and an audiologist, 'and you're going to become the biggest cohort ever'? Well, that's what we hoped and we have an ambition to. And we never got support for that because you don't get money support for the data acquisition. We got the money then, once acquired, to do genetic studies with UNITI and ESIT and TIGER, but the whole data collection was something we had to do on our own, and it was extremely challenging to convince people to do it, and that's why we relied on collaborations with people that already had gathered participants and motivate them to illustrate the relevance for our disease topic, and this is something I've tried to do in Nottingham. But I noticed that there are very few large cohorts of the kind where people could be sent out to a sub-study, if one may call it that, and to try to do deeper research, so these aspects one one will have to consider too.

1:20:06 Overcoming challenges through activism

Hazel: I think this is a good bridge, just sort of our last topic and we can start wrapping up, so we've talked a lot about what's needed from a scientific perspective, but you've both also mentioned some of the challenges with funding, etc. so can we talk about what's needed, I don't know, socially, politically, economically, to get these tinnitus biobank initiatives off the ground, and if there's anything that, let's say, the tinnitus community can do to help.

Chris: I think, from my perspective, I mean, this is tricky because for instance, where I came from in Sweden, tinnitus has not been a priority disorder, and the evaluation system in the funding schemes was not in favor of that stuff, they were focusing on **Parkinson's** disease, **Alzheimer's**, and so on and within the neurological field, that was not a top priority.

But one thing that we're good at in Sweden is philanthropism and there one had to ask larger private foundations that would sponsor big and ambitious projects. I never got that type of funding, but I think that if I would have stayed in Sweden longer, that would have been probably a strategy to have. Now, England was different because they have institutions that fund for auditory research. There is a very active BTA going on there. Patients are raising their voices, so there could be other means. Now, one thing that I'm not aware of is whether philanthropism exists to a level that we can really make a change there too. Maybe David can talk about it?

David: Sure. So again, speaking from a UK perspective, and even more focused on an England perspective, the BTA initiated a round table discussion at the **House of Commons** three years ago now, and from that we had a question asked on the Floor of the Commons of the **Health Secretary** who then promised to investigate funding into tinnitus research. That led to the **Department of Health and Social Care** in the UK looking at tinnitus research. They did their own round table event a year later, and there is now a group that's looking at how to invest greater funds in both tinnitus and hearing loss research and what the priorities are. Biobank is one of those that, of course, is being pushed within that group.

So that type of work and activity did work and did get us somewhere, but it's slow, to be honest. It's having those impacts and those effects on Government does take time, but certainly what people with lived experience of tinnitus can do is write to their MP in the UK, get their MPs' mailbags and inboxes full of information and experience of what it's like to live with tinnitus. That makes a huge difference. We've done that with a couple of support groups here in England as well, where we've invited the local MP to come along and speak to the Tinnitus Support Group and just learn what it's like to live with tinnitus and hearing that first-hand from their constituents does make a huge difference and does have an impact on MPs and politicians in the UK, and I'm sure elsewhere as well. It is that real life story that does have an impact and does make a difference.

We do get letters fairly regularly from MP's offices saying: "We've had this letter, can you help us answer it?" and things like that, so it does make a difference and people having that type of activism and knocking on the door and saying: "This is my experience. Having tinnitus is awful. What are you doing about it as a government?". That does really have impact and MPs do respond to that.

Hazel: Yeah, I do think that the UK is probably a bit ahead of the curve compared to many other countries when it comes to patient activism, involvement, etc. but it's a good example, I would say that hopefully other countries can follow.

David: I think so, and just more broadly, of course, we will be asking for people to sign up, during Tinnitus Week and say that they're interested in a Biobank and would participate, again, that's going to be important intelligence gathering for us to look at. You know, could we really recruit at the level at which we would need to be effective. Do you believe that they would participate in and would be a part, and please sign up whether to demonstrate that there is that interest as well. At some point, we are going to need fundraising, we are going to need advocacy for this to really make it work. It is going to be a community project that sees this to be a success and to really take us forward.

Hazel: I think that's a great call to action that we can end on, but I will ask both of you if you have any sort of concluding remarks or anything that you still want to mention. Chris?

Chris: Yeah, I'd like to compliment David on what he just said here. So yesterday, I had a very interesting session with the **WHO**, because they are planning on a **World Hearing Day** on the 3rd March, and I was really surprised about the global investment in people, the activity that they have there, all concerted into a single day. They just raise the voice about hearing problems, the importance of it, and the activities are impressively large, and depending on every country's resources – these go to screening hearing in schools… **Italy** is doing large conferences where they invite the **Ministry of Health** and all the other people to join, and they have big doctors presenting. They have several groups talking about the different priorities that are needed in the country for change and for tinnitus maybe this is kind of missing.

So, when we had the Tinnitus Week, I was telling the patient organizations in Sweden, maybe we should centralise all the activities within the same period of time. "Oh, we have our own there"… and that doesn't make the system work a lot, so maybe if one day we get the WHO to acknowledge that tinnitus can be within their systems of definition of disorders that need to be assessed on a global scale, that can be fantastic. I guess we might reach a step like that once we have the proper definition of tinnitus, and then we are able to gather the optimal data as well.

I worked with the **Global Health Burden of Disease** study, which is funded by Bill Gates. So, I'm not a primary researcher in this, but I've been helping and checking the data that's been collected on hearing in different countries. And I'm surprised to see how much information is even lacking for hearing at the population level. There are, you know, isolated studies here and there like that, but the summary of this is that we need really large-scale population data to check on those prevalences, and for that we need the proper definitions of tinnitus as well.

When we started with nothing, we were limited in space and how much information we could ask the people. We were not solely focusing on tinnitus as a biobanking effort, but also different

types of auditory disorders, vestibular disorders, and we were only able to put one question on tinnitus. And how do you do that? Do you ask for severity? Or do you ask for constant versus occasional? So, I think that we cannot answer tinnitus with one single question. It's multi-dimensional. We need aspects of chronicity, the temporal aspects, whether it's intermittent or constant, and then the third dimension is severity. So, all of this needs to be taken into account for a proper definition, and it makes the conditions harder to pick up in our studies like that, but I think it's doable. I think it's do-able.

So, I have good hopes that in the near future, we can have those efforts synchronized with everybody. Ourselves now with this large GWAS consortium that's called **G-EAR**, hopefully we can get a bit of funding as well just to start financing some infrastructure, maybe. Maybe in the future, we can centralize all biobanking efforts to the Karolinska where samples can be stored there for a long time, and if everybody was to ship them there, if someone else has the power to do it now elsewhere, please stand up and do so, because at some point one will have to do it, and hopefully then people can gather efforts and working together, have shared productivity and large papers. And this is the way to go for the future.

Hazel: Great, it's good to end on an optimistic note. David, do you have any concluding remarks?

David: Yes, I'd say I'm excited. I think there is some real consensus coming together about how we do move forward from where we are, and that's been lacking for a while, and I think that consensus, that move towards doing something on a scale of a **Tinnitus Biobank** with ambition would truly transform our area and our knowledge on tinnitus and really push us forward, and so whilst, you know, the road ahead is incredibly challenging, and we've spoken about a lot of the challenges we will face in trying to get there, I think it's a goal that the community will hopefully get behind and understand the potential, if you like, of where this could take us. I genuinely do think it's exciting to see so many people come together with the aligned aims of doing something on this scale that will really, hopefully, push forward our knowledge and get to a stage where we can open those floodgates for Pharma and Industry and others to really invest in tinnitus research and take it seriously, and hopefully get Chris's paper in Nature or something as well.

Hazel: Alright, I would like to thank you both very much for your time and sharing your insights and for this informative discussion, thank you, Chris and David.

Chris: Thanks Hazel to you. I think it's a fantastic event. An opportunity for everybody to disseminate this. It's important for the community and it's important for researchers also to get that connection, so thanks to you for giving us that chance.

David: Yes. Absolutely, thank you Hazel and **Tinnitus Hub** for inviting me back and yes, good luck with all your other work and... yes, thank you for everything you do to support the tinnitus community.