SPECIAL INQUIRY

THE HONOURABLE THOMAS BATHURST AC KC

FOURTH DAY: TUESDAY 14 FEBRUARY 2023

INQUIRY INTO THE CONVICTIONS OF KATHLEEN MEGAN FOLBIGG

AUDIO VISUAL LINK COMMENCED AT 10.06AM

JUDICIAL OFFICER: Yes, Ms Callan.

CALLAN: Your Honour, I call Professor Todor Arsov, and I note that he is already in the witness box.

<TODOR ARSOV, AFFIRMED(10.07AM)

<EXAMINATION BY MS CALLAN

Q. Could you confirm for the record your full name?
A. Todor Arsov, T-O-D-O-R A-R-S-O-V.

Q. And it's the case, Professor Arsov, that you're a Professor of Genetics.
A. That's correct.

Q. The Inquiry has received a version of your curriculum vitae attached to a report that you provided on 25 October of last year.
A. Yeah.

Q. It was a joint report with your colleagues Professor Vinuesa and Professor Cook. You recall including a copy of your curriculum vitae in that report.
A. That's correct.

Q. And is that up-to-date?
A. It is not. I have changed my affiliation with the University back home in Macedonia a couple of days ago actually.

Q. I see. And what's your present affiliation?
A. University Goce Delchev, G-O-C-E, last name D-E-L-C-H-E-V, so just another university in the country.

Q. But what is the role?
A. Professor of Genetics, yeah.

CALLAN: Your Honour, for the record, the CV I'm referring to is Annexure D to the report of 25 October 2022 which appears at Exhibit 5-06, commencing at red p 169.

Q. Professor Arsov, I'll come in a moment to the reports that you have provided which have come into evidence before this Inquiry, but can I just ask you, in your own words to explain what are the areas of specialised knowledge and expertise that you draw upon to express the opinions that you have.
A. Right. So I'm a geneticist. I identify professionally as a geneticist both in a research capacity and in a clinical capacity. So in the research capacity, I have a background both in animal genetics using animal, mouse models to elucidate mechanisms, novel genes as cause of human disease, and then also human genetics by way of using human pedigrees or patients to either discovering new genes or expands of the clinical spectrum of known genes. I think in my clinical capacity, I have a bit of a varied role in medical genetics in general so I'm a licensed physician in Macedonia. So I see patients with various genetic problems, you know starting from prenatal paediatrics to adult onset conditions and also do genetic counselling, so it's my training as well in Australia. I think I do engage a bit in genetic diagnosis as well, both in my research over again in the clinical work. So yeah.

Q. Prior to the work that you've undertaken in relation to this matter, have you undertaken research or any other work in the field of electrophysiology?
A. No, I haven't.

Q. What about calmodulin or calmodulinopathies.
A. I haven't.

Q. What about more generally the field of cardiac genetics?
A. No, I haven't.

Q. There's just one preliminary matter I wanted to take you – by way of, in a sense, overview in terms of the approach you've taken to this matter and your ultimate views before we get into some of the detail. First of all, in your approach to, and the contribution you've made in this case, do you consider it's outside your terrain to form or express a view about what Kathleen Folbigg may or may not have done?
A. Look, yes and no. I think you know, yes in that I don't have a formal training in electrophysiology or cardiology as such but I'm a trained physician so I have, you know, studied around this areas that we are talking about, and I think, you know, no, because my expertise is in genetics and you know, I guess in the world today, I mean you find that this is a very collaborative area I suppose. You know, it's often times even in clinics today running in a multi disciplinary way where two physicians sit next to each other, the geneticist running the genetics business and the clinician say for example, cardiologist, the clinical part of the - of the story. So yes, I think from a genetics perspective I feel I've done what I've always done and would feel quite confident I have expertise in. When it comes to the cardiac area or calmodulinopathies specifically, it's been new for me, but yes, it's been a while now since I think we have read the therapy.

Q. Sure. Perhaps I wasn't sufficiently precise in my question. Do you regard it as beyond your terrain, your area to form a view or comment on the question as to whether Kathleen Folbigg did or did not murder her children?

A. I don't think it's beyond my ability to make that assessment or comment.

Q. I understand you've just said you don't think that's beyond your--
A. Yeah.

Q. --ability to assess or comment on?
A. Well, yeah.

Q. Well, Professor, do you accept that there is evidence and information relevant to that ultimate question which is beyond the fields of cardiac and genetics.
A. All right. I mean, you know--

Q. Sorry, do you accept that?
A. I'm not sure it's yes or no. I sort of think it's - you know, it depends on, you know, the way the question is asked I suppose. I mean, if you're talking about pathogenicity of this variant--

Q. I'm not asking that question, Professor. I'm asking--
A. They're linked in a way, you know, because if you're--

Q. Okay. Can I take it in that respect, having formed the view that you have, as you've expressed about the pathogenicity of the variant G114R, have you formed your own view as to whether Kathleen Folbigg did or did not murder her children?
A. Well, I mean I can talk around, you know, the likelihoods that this pathogenic variant may have resulted in, you know, sudden cardiac death in the female children.

Q. Certainly. Beyond that though--
A. And by extension I suppose, I mean these are linked, I mean if I - you know, if I'm of the view which I am of that this is very likely you know the cause of the death, then you know, you're kind of making - kind of in a way the other call as well, I mean what you're asking for, right, because it's - there's the alternative hypothesis.

JUDICIAL OFFICER

Q. Professor, can I ask you this because it just puzzles me a little bit. I understand that if concluded this variant is pathogenic.
A. Yeah.

Q. And you've concluded that at least two of her children have this pathogenic variant. And you have concluded that that could cause the children to have some condition which led to their death; is that right? You have to answer because of the reporting.
A. Right. I mean, it is in the spectrum of what this specific gene does and what this variant we believe does as well, yes.

Q. But what you can't do, is this right, is identify a precise clinical cause of

death. You don't know, is that right?
A. Well, I mean - I mean, it's really how you--

Q. Let me put it to you this way. They had a missense to a variant which could give rise to particular conditions such as LQTS or CVPT or one of the other ones, but you can't specify I don't think that these children died from any particular condition as distinct from saying they had a gene which could have caused some condition which killed them?
A. Well, I mean, we can't say anything categorically in this life I don't think but we can talk about probabilities or likelihoods, you know, that one or another thing happened.

CALLAN

Q. We might move on, Professor Arsov. I understand that you've prepared some slides that you wish to refer to to provide some evidence of a more general nature--
A. Yes.

Q. --which by reference to an example, not this variant, a different variant--
A. Yep, yep.

Q. --and you draw on that example to seek to explain some concepts which have arisen for consideration in this Inquiry, for instance in respect of incomplete penetrants and variable expressivity?
A. Yeah. Yes, that is correct.

Q. I'm conscious of making good use of the Inquiry's time, could I ask you to commence with that but to the extent that - please proceed on the basis that we have read and carefully considered all that has been included in the various reports on these topics?
A. Sure. Yes. So, look, you know, I think that - I mean when you ask about the expertise, I mean we can't just - to think about these things as cardiology and genetics, but I think, you know, what this really is about or how I look at this is from a perspective of a rare disease, you know, so this is not something that's common, it's not something that we see or any clinician sees every day. Rare diseases are a problem in clinical medicine because they are rare. I mean if they're rare we don't see many of these cases and if we don't see many of these cases then of course we don't know much and if we approach these situations, you know, with a mind that we kind of know, then we kind of bring a lot of bias I think to it. Now, just to put numbers to it, when we talk about rare disease, I mean there are different legal definitions around the planet, but it's one in 2,500 somewhere, maybe up to one in 10,000 people general population would have a certain condition. So just, your Honour, to put this in a perspective, you know, when we get down to one in 100,000, for example, people which would translate to 20 or 25 people in Australia with the specific condition, we are talking about ultra-rare conditions now. This is something that most physicians will probably not see in their lifetime.

Now if we consider that for calmodulinopathy, you know, we have only around

maybe 200 cases described on the planet and if we divide, you know, seven billion people, we can kind of come out with this number of around one in 30 million-35 million people, so you understand this is super-rare and I think, you know, we just have to be mindful I suppose of that is how I approach these things, you know, when they do research and when we're asked these questions, I mean we just can't know that much and we just can't be too sure and we can't be too dogmatic and try to apply what your Honour has just said, you know, the current dogma of CPVT or, you know, Long QTS or IVF as separate entities and try and, you know, think that it will ever fit into those specific bins. So what I believe is that this is an unusual scenario where, you know, we have a blunted, and blunted I suppose phenotype in a way which presents the way it does. But just to kind of illustrate that and to put a little bit of context with this so we don't think that this is specific to this variant or this gene, I'm going to give you some examples of my prior work so you know we can kind of get a little bit of understanding that these things that we are bringing up, they're not specific to calmodulinopathies. All they mean, this is genetics 101, you know, wherein it affects, you know, lots of conditions, particularly super-rare conditions. So the first example is with the Kufs disease, so this is slide number one I guess for the record, and I will talk about the CLN6 spectrum. So also touch on this idea of a clinical versus genetic classification of disease and specifically touch on this age of presentation, you know, issue because - of relates to a--

JUDICIAL OFFICER

Q. Professor, I know it's difficult, but if you could speak just a little bit more slowly.
A. Yeah, slowly yes. I will.

Q. There's a lot of people down the back I think are starting to get restive.
A. Yeah. Okay, so I'm not going to say much - to the next slide please.

CALLAN

Q. So it's slide two?
A. Yep. Yes, I'm not going to go too much into too many details around the condition, but this is a neurological condition, it's a metabolic brain disease which is presented, you know, as neurodegeneration due to accumulation of certain substances in the nerve cells. Usually affects the eye as well, so, you know, we have this neurological impairment which is progressive, it leads to both motor and intellectual deteriorations, seizures, visual failure and early death. So in the past these so called neuronal ceroid lipofuscinoses, they have been classified based on the clinical presentation and particularly based on the age of onset. Is infantile, late infantile, juvenile and adult, and these adult forms specifically Kufs disease, is while it's been known to have this unusual presentation with onset in late adulthood, usually the retina is not involved, and you know, they - it was even given a specific made-up I suppose gene name or a specific locus for this gene in the 1990s. So the gene remained elusive for many years just because of the application of this phenotypic I suppose classification. If we can go to the next slide please.

Q. Slide three?
A. Until we engaged in this research which you have involved a large international cohort to be able to collect some of these families so we can see one, two, three, four, five, six pedigrees here--

Q. Pausing there, Professor, when you say we engage in this research, is that research that you undertook and was the subject of the article that is referenced on slide two?
A. Yes, yes, that is correct.

Q. Go on?
A. So, you know, many of these cases would have been current decades before that, so most of these, you know, people this we can see on the pedigree were not alive, so not alive is a symbol that's crossed with a diagonal line. So what we are looking in any pedigree are, you know, the squares are boys and circles are girls. Whoever comes from the same line, it's a sibsheet so these are brothers and sisters, and if we go one line up, these are the parents. And so when we did our research we actually were able to find that you know although the thinking for almost 20 years due to the clinical presentation was that this is a different gene, to actually find that it was - that these were mutations in the CLN6 specifically gene which was until then known to be the - of variant late infantile CLN6 disease. So this is this classically presents between 18 months and five years of age, so quite early in the childhood, with seizures and visual loss usually present, a visual loss characteristic.

Now when we compare to the Kufs disease which now became part of the CLN6 spectrum, I mean although already we have what are manifestations much later on in life and you can see through the individuals here, anywhere between 17, 35, 43, even 51 years of age when the condition was diagnosed, you know. The seizures and the visual loss, seizures are late in Kufs disease and the visual loss is not present. So think is just an example, you know, to show how this age of onset which ruled I suppose this thinking, you know, hindered research and understanding of what this disease was, I mean all of these patients needed to go very painful rectal biopsies in order to be diagnosed, now we have the gene they don't need to do that anymore, we can by genetic diagnosis. If we can go to - and I mean the most important thing here probably is that now when you go through this literature around the neuronal ceroid lipofuscinoses, there is no more early onset late infantile, you know, classification based on age but it's CLN1-related diseases, CLN2-related disease, and I think there is a big move in genetics to kind of step away from these classical phenotypes based on classifications based on the phenotype but moving to a gene-based classification of conditions and so they're extending the spectrum--

JUDICIAL OFFICER

Q. Professor, on this slide, did all the people have the same variant?
A. No, they all have different variants.

Q. They're all different variants, yes?
A. Different variants and this is, I suppose if you're comparing, your Honour, to the calmodulinopathies, the mode of inheritance here is recessive which means you need to get one variant for both parents, and there usually the very ability of the clinical presentation is meant to be much less, classically, for recessive conditions, but still I mean genetics is weird in a way and we see that as well. For every of one of these family would have different mutation. Sometimes they're homozygous which means they can carry the same mutation from both parents, sometimes they can mean sharing two different variants in the same gene, different variants, yes.

JUDICIAL OFFICER: Thank you.

CALLAN

Q. Moving onto slide four?
A. Next slide please. Yes. So this is the other example of the so called GLUT1 deficiency. So we are again going to talk about this spectrum and expanding the spectrum. Initially we know that this gene does miss something, but over time we learn that the story is much bigger actually. I mean we think it affects 100 people on the planet, but then we realise that it may be actually 100,000 or more.

Q. Are we in that category with the G114R variant?
A. Well, we don't know.

Q. Okay, sorry, back to your?
A. Yeah, and so going to the next slide please, initially this condition was, you know, described by Professor DeVivo from Columbia University in the 90s, we - it's a big encephalopathy metabolic brain disease with early onset seizures, small head, developmental delays and some biochemical problems, usually responding in terms of controlling the seizures with ketogenic diet, I mean this is just from his - you know, the first publication, and if we can go next slide.

Q. That was slide five, we're moving to slide six.
A. You know, until ten or more years later when we kind of - well not we, but the group of holder of the literature - coming to these family which cosegregated a movement disorder, so little to do with the encephalopathy, and this is a condition where, you know, if you exercise you start to get these muscle cramps and pains or women wearing high heels getting the calf pains, and so they tried to mark this gene and actually came to GLUT1 as the cause where they found a mutation in GLUT1 and this is inherited like calmodulinopathies, your Honour, so it only comes from the one side of the family, you only need one of the two genes to be affected in order for the condition to manifest. Now what was quite interesting in this condition was that in this family specifically that in addition to the movement problem, the exertion of dyskinesia which is shown with this grey little square to the bottom left of the individuals, they also cosegregated some type of epilepsies or seizures and very interestingly haemolytic anaemia. Now haemolytic anaemia

is when your red blood cells start to crush a little bit earlier than they should and a little bit excessively, and so you get anaemic, you may also get jaundice. And so it was quite unusual that these would one mutation presented in this way, so they did a lot of work to kind of show that what actually happened is that this specific variant in this specific family changed the GLUT1 channel and so this is a channel that allows glucose to enter through the cell membrane in the cell to actually change within to an ion channel, and so all of a sudden, you know, there was too much potassium inside the cell and too little sodium, or the other way around, so that made the - sides of the red blood cells unstable and breaking. This is an amazing example that sometimes the specificities in the phenotype can be very, very unspecific, so you know, this is not something that's common for any other GLUT1 mutation and it doesn't happen, it which happens for a specific mutation with just by way of how it is happens to change the GLUT1 transporter to an ion transporter. If we can go to the next slide.

Q. Just pausing there, do I understand your evidence correctly that this is an example where by observation as to phenotype, and consideration of functional features of this particular variant, certain conclusions were arrived at in relation to the mutation?
A. Well, that is correct, but I guess my point is that the same gene which was known to cause this massive encephalopathic problem and the brain development problem was all of a sudden found to cause something very different, a movement disorder accompanied by epilepsy and accompanied by hemolytic anemia just because this specific variant does something different to - does what other variants do probably but does something different as well.

Q. I see.
A. And so then if we can go to the next slide, this was interesting for us.

Q. So this is slide 7 and this is some work that you undertook?
A. That's right, and so because there were, you know, cases here that they sort of presented like generalised epilepsy, idiopathic generalised epilepsy which is a fairly common condition in the general population, we have the question well, could these variants or some of the variants in this gene actually be involved or responsible for this specific phenotype and so we then screen patients with idiopathic generalised epilepsy to find that a proportion of them, around one per cent, actually have mutations in this specific gene we did functional studies in collaboration with the living group at the time in Australia that did these kind of studies to show that, you know, in every case where there was penetrance in the family where most of the patients that actually had the mutation had experienced seizures or epilepsy, had significantly reduced function of this glucose transporter. And if we move this if we move towards the right from pedigree A to pedigree D we kind of see that, you know, the phenotype tends to dilute a little bit and this is because - well, I mean, there is a less reduction in the function of this transporter.

And so this is again expanding the phenotype and in something which was initially, you know - small number of people, very big disease, early onset, born with microcephaly, born with these biochemical features, never developing

properly the links physically and so forth, all of a sudden - I mean, these are people that are going to the university, you know, have high-functioning jobs and you know, have had history or still have history of epilepsy for which they're being treated. If you can go to the next slide.

Q. Slide 8.
A. And it's obviously, then, you know, we come to families like this where even within the family where you have this same variant, you know, in family A or in family B. I mean, you know, you don't see two symbols that are coloured with the same colour, and I'm not going to go through what each colour means but just to illustrate, you know, no two people can if you know can be expected necessarily to you know present in the same way. And so if we go to the next slide.

Q. Slide 9.
A. And then just to bring it home I think, the main message here is that what was GLUT1 encephalopathy to start with in the 90s, discovered by Professor DeVivo and this is the circle with the black in the bottom of this flower, you know, it actually ended up being quite small, you know the - you know, the surface of this is meant to represent maybe the number of patients, and you know, then we have on the right one petal of this flower, or it looks to me like tulip maybe, you know is the epilepsy condition. The left petal of the tulip would be, you know, the movement disorder, I mean this getting pains in the muscles when the muscles are used too much, and then there is the spectrum in the middle you know, which is kind of incorporates both, and then if you go to these other things that came on board, and you know, ataxia, problems with walking. And if we can go to the next slide. And - I think--

Q. Slide 10.
A. If we go back last slide.

Q. Sorry. Back to slide 9?
A. Okay. So anyway - and so just to - to finish on this, and so again you see how there's something that was just, you know, very small number of people that had the very big disease now became lots of people that actually have something very different to what we initially knew.

JUDICIAL OFFICER

Q. All of whom had different variants to this particular gene; is that right?
A. Well, I mean it's sometimes interesting. Even if you can go back to the previous slide, I mean these people in family A - if you can - all of this, you know, people I mean they have the same variant, they inherit the same variant in this family but they all get something different in the way they present phenotypically. If we can go to the next slide.

CALLAN

Q. So we're up to slide 10.
A. Yeah. Next. And so this is again another example of - so this is the

literature example which I haven't been involved in but it's - I've been involved in testing this gene SCN1A specifically, and I just want to touch a little bit on this binary expanding to a spectrum in terms of this *de novo* versus inherited. Now, inherently this is linguistics and semantics. I mean with everything genetics inherited, it's always inherited, so genetics is always inherited, though not all genetics is inherited. Some genetics is *de novo* which means happen for the first time in this individual, you know, who inherited just one sperm cell or one - one egg where this mutation may have happened, the parents don't have it but the person has it. And so we kind of tend to seeing that, you know, in this specific case, but in other rare diseases particularly that *de novo* mutations are probably more severe. They can be tolerated if they're inherited, and you know, they're - they're causing bigger phenotypes, and in this case this is the Dravet Syndrome, another catastrophic neurological condition. Versus say, for example, inherited forms of this SCN1A mutations where you know, the phenotype is, you know, milder for example presenting as febrile seizures. And so if we can go to the next slide.

Q. Slide 11.

A. And so until a family like this - and there are others - other examples of the same story, so where you know, all of a sudden there was this big family where obviously the syndrome is being inherited, starting from this patient that's here in 4(1), so fourth generation, the first individual which is designated with the red arrow, which had the big condition which is meant usually to be *de novo* and so he had the Dravet Syndrome, so big encephalopathy, developmental delays, some regressions and so forth, you know, and then you have this other individuals in the family which also have inherited the very same variant, your Honour, which you know, present in a very different way. So everybody in the orange, so the brother of this little girl, only has febrile seizures plus - I mean, it's kind of in a way minimal, you know, disease. Then if you go one generation up in the third generation in the in the sibship 10 – 15, you have 10, 11, 15 who have the, you know, the plus means they have the mutation, also presenting, you know, with febrile seizures.

And then you know, if we go to you know, green and blue also have some additional problems like myoclonic seizures and what have you. And then very interestingly, Ms Callan and your Honour, I mean we come to this sibship here, for example, between individuals 2 to 9 who inherited the variant from their father, for example, and you see that individuals 3, 4 and 9 who are designated with the green arrows. I mean, they have the mutation but they don't have any phenotypes. So this is an example that kind of brings in one family everything that we're talking about so there is this variable clinical expressivity. There is something that was always meant to be *de novo* but it's now not *de novo*; it's inherited. And then we have the non penetrant cases in the - in the middle. I mean, this is not a single family. There are a few families like this, for example, in this condition but of course, I mean if you go through other conditions there are many examples of similar scenarios. So if you go to the next slide.

Q. Just pausing there on slide 11, using this as the example. As you said, there was this growing knowledge that progressed over time to get to the

position where it was ultimately observed that this was not necessarily always a *de novo* presentation.
A. Yes, yes.

Q. And that there was variable clinical expressivity. What does that, in this instance, mean in terms of predicting in a particular individual how the variant might present in clinical terms?
A. Well, I mean, you can't always predict and this is a problem, you know, in genetic counselling. I mean, this is the bread and butter with these problems with the dominant conditions where you can't be sure and sometimes the question is about prenatal diagnosis, so you know, you have to tread very carefully about these things and I think it goes along the same lines for you know, doing research work where you just cannot be too sure, and you cannot be too dramatic about these things. You have to be careful. You have to have open mind. You don't miss any - don't discard any - disregard any piece of information. It is important because it may do just that, it may allow you to predict.

Q. I see. Can we move to slide 12. Is that where you were at?
A. And then there is the spectrum. You know, so this is this idea of expanding the spectrum like we saw before in the GLUT1 case. So here there is expansion of this SCN1 spectrum, you know, something that was, you know, *de novo* inherited - *de novo* Dravet Syndrome inherited, you know, forms of epilepsies. Other things came on board even, you know, on the milder end of the spectrum we have this familial headaches; for example, hemiplegic migraines and so forth. So next slide.

Q. Slide 13.
A. And so coming to another condition which you know is illustrative I think for some of the things that we are talking about, and this is a case of a family where immune deficiency presented much earlier than what was usually described in a phenotype. If we can go to the next slide, so this is a Macedonian family which had this condition which had been described only a couple of years before it was found by Professor Vinuesa in her lab, so I think it's, you know, condition which presents with immune deficiencies so lots of infections early on in life, some bleeding tendencies as well and various forms of immune dysfunctions from some inflammatory involvements and so forth. I mean, at the time when we go to this mutation there were, you know, maybe around 12 or 14 cases described around the world and there are not that much more at this stage. So mega, ultra, ultra rare condition where you know, all you have to go by is the information of 12 people. And this is what we are trying to do, you know, in rare disease. I mean, you approach, you know, people who have the expertise, people who hold, you know, the - that have written the papers, people who hold, you know, databases to be able to build on their expertise because if we can go just a few ticks into just - go to the summary of the phenotype, as we knew it. If we can go further and further again and again.

And so - so as I say there were around 12 - 12 cases, and I think, you know, they mostly at the time were around lesser. There have been fatalities but you

know, maybe about age of ten years. And so if we can go to the next slide, and then we were presented with this Macedonian family which is a tragic story of a family with four dead male children, you know, because they inherited, you know, variants from their parents which were the cause of this condition. So that quite usually you know, these four children died much much younger to what it would have been expected that we knew from the previous cases. I mean, anywhere between 20 days of age and three months of age. And you know, they had some of the features more prominently than the other described cases but presented much earlier. So if we can go to the next slide.

And so obviously we did - we did some work to identify this mutation and then we again approached the experts to kind of consult around the fractional aspects of it and in the end of the day we were able to diagnose this condition in the family which has now opened reproductive options for the - for them because I mean, for quite a few years after the last - this twin pregnancy, the last pregnancy, they actually felt you know, insecure to start another pregnancy because they didn't know, and so now I mean they're able to go through prenatal testing and secure a healthy healthy family. If we can go the next slide. Yeah, next.

Yes. I think this is kind of the setting the stage, to kind of - just to give you some examples I think around some of the issues that we're talking about, and they're pretty - pretty common in - in the field of variation disease, and I think you know when I think about the things that I've done, it is variant disease, so you know, whether it's, you know, cardiology or neurology or immunology, immune deficiencies, there are common themes, and I think, you know, some of the things that are important here is that, you know, it starts in one way, and as Professor Schwartz says in his report, you know, initially it's more severe, it's *de novo*, but as we learn more, as we test more, as we get more patients, I mean the phenotypes invariably become, you know, more varied, less severe, more inherited, we start seeing this inherited cases and so forth.

JUDICIAL OFFICER

Q. One critical difference in this slide to the others, if you go down to the bottom right-hand corner.
A. Yes.

CALLAN: Just to be clear, your Honour, we're looking at slide 16 which is the pedigree document made by Professor Arsov of 8 October 2018 and that's Exhibit 2-AE.

JUDICIAL OFFICER

Q. If you go down to the bottom right-hand corner, alongside what I might - right at the end, alongside the cause of death you've got a question mark alongside each one, and what I want to ask you is, isn't that a real difference between the examples you've given and this case? Because whilst you're able to show that a series of identified clinical conditions causing death or causing brain damage occurred in people who had that variant which you're

referring, in this case there is, as you point out, still a question mark as to what I might describe as the ultimate cause of death, is that right?
A. Well, I mean, you know, it comes down to how much you believe SIDS for example is a, you know, what does it actually mean, you know what I mean?

Q. I understand.
A. It's not a - it's not--

Q. SIDS is generally considered--
A. --I mean it's something we find but I--

Q. --a diagnosis of exclusion, isn't it?
A. No. So, your Honour, I think the question mark here specifically, well you know when I was drawing this pedigree, for me it meant, you know, the way Ms Folbigg would've conveyed that information to me, because, you know, you know we went through the pedigree and the taking the history, the interview, you know, and I was you know obviously taking notes of it - or drawing the pedigree, taking notes, and I think you know she was telling me about what she knew or remembered were the medical - I mean this was the first time I ever heard of this was, you know, a few days before that, so I had no idea, and you know she said, well, I know I think they all have been diagnosed, you know, with SIDS at one stage or another. She thought Patrick was - formally diagnosed as asphyxia as the cause of death, so you know, I guess the question mark is just noting the uncertainty that I felt she had around how she conveyed the information to me.

CALLAN

Q. Professor Arsov, in evidence you've given that's before this Inquiry you've said, "...the starting point is that the phenotype which caused death in each child remains ambiguous." Do you stand by that?
A. Can you repeat that?

Q. "...the starting point is that the phenotype which caused death in each child remains ambiguous."
A. Where - can you provide me with the reference for this?

Q. Certainly. Could the witness be shown Exhibit 2-BW, page 1? Do you recognise this as a letter drafted by Professor Vinuesa and yourself endorsed by Peter Schwartz, Matthew Cook and Michael Toft Overgaard?
A. I mean I'll - I--

Q. Do you see that at paragraph 7.1?
A. Yes. I mean can you just ask me--

Q. Sorry, just pausing there, you recognise this is a document that you were an author of?
A. Yeah.

Q. Could I take you to paragraph 2.2? The first sentence refers to a quote

from something that had come from the so called Sydney team. There's a reference to segregation in the second sentence. In the middle of that paragraph it says:

> "Contrary to the Sydney team, we do not consider death a phenotype. Instead our starting point is that the phenotype that caused death in each child remains ambiguous."

A. Look, I think, you know, in--

Q. Sorry, do you stand by that statement?
A. I do think that, you know, the phenotype in this family includes sudden cardiac death, yes. The sudden unexplained death, sudden cardiac death, yes.

Q. So you don't regard it as ambiguous anymore, the cause of death of the children?
A. Well, the, you know, the word ambiguous is, you know, I think we don't have the mutation in all four I suppose children.

Q. No, you--
A. So, yeah, I guess--

Q. Professor, when you wrote that - sorry, did you write any part of that letter?
A. I would've - I would've been involved, yes.

Q. What did you mean when the word ambiguous was presented there?
A. Well, probably what I just said, you know, it's that it's not a single course, you know, that you could - because I mean the mutation is only in the female children.

Q. Why did you not write that?
A. I could've. I just want to make clear that to me I believe that these unexplained death is part of the phenotype, now whether you want to call it phenotype or a phenotypic outcome, because the--

JUDICIAL OFFICER

Q. Do you say that death, is it death is a phenotype itself?
A. Well it's part of the clinical spectrum because, your Honour, some of these things, particularly in Idiopathic Ventricular Fibrillation, and there is literature around this, I mean the first and only manifestations of the electrical instability of the heart can be death, and so you have to consider that as part of the clinical spectrum. So, I mean if we - I mean in this stems at the heart of this phenotype issue, I mean if we were to say that we need to specifically identify one of these electrophysiological beams of what calmodulinopathy may or may not present as, then it is ambiguous, because we don't know at the moment, so Ms Callan so this is probably the answer to your question is that, you know, we don't know because it doesn't fall in any of these beams and we don't have ECGs. I mean here we are faced with double whammy in a way, in

it's an ultra-rare condition but then we also have incomplete information, we don't have the luxury of the clinical situation to be able to do all the testing in the province of the children, to have all the like ECGs and stuff, so it is ambiguous in that you know we don't know really where that kind of falls. I mean - is that I believe it is a blended phenotype in the family, you know. So there is the ambiguity, so then if we say that the phenotypic outcome is the death or that is part of the phenotypic spectrum if you like, I firmly believe that death - that is the case and now there are examples in the literature, you know, where, you know, sequencing in families has been done based on only this phenotype sudden unexplained death or aborted, you know, cardiac death because there was a defibrillator in place to, you know, prevent, you know, the - so - but yes, I believe a death outcome to be part of the phenotype.

CALLAN

Q. Are you using the death of the girls in your assessment of the pathogenicity of the CALM2 variant?
A. Well, not in the assessment because I think the assessment assumes, you know, a phenotype, so that would be - that's a, you know, starting point in a way. I don't think that that would play - yes, I may need to come back to that if - if - yeah, I may explain it a little bit more if there are further questions around that.

Q. I see. Right. Could we focus on this pedigree that you took?
A. Yes.

CALLAN: As I've said for the record, your Honour, it's Exhibit 2-AE.

Q. In one of your answers to a question from his Honour you, as I understood it, were seeking to describe the circumstance in which you created this document by reference to, is this the case, visiting Ms Folbigg in custody and taking a history from her?
A. Yes. This is noted in the pedigree, the pedigree was taken in the Silverwater correctional facility on 8 October 20. Yes, I was visiting her there.

Q. Just to be clear, did you create this document on 8 October 2018?
A. Yes. I mean it would've been transcribed from notes.

Q. You took notes when you visited her?
A. The pedigree was drawn with a pencil.

Q. I see, and then you--
A. Transferred it in an electronic form.

Q. Is everything on this pedigree document information that Ms Folbigg gave to you?
A. It would be all the information that she gave to me - well, I mean obviously when it comes to pedigree, pedigree contains information that is necessary for a quick orientation about what the phenotype may be, what are the relationships, who's affected, who's not affected, and then she's told me more

that's not necessarily written here I think, although I believe that most of what was said is captured.

Q. Not suggesting that this document reflects everything she told you--
A. Exactly, okay, just making sure.

Q. --but have you relied on any other sources of information?
A. No. So, as I said, you know, when I went to visit Ms Folbigg, I mean I knew almost nothing about - about any of this.

Q. When you attended to take that pedigree--
A. Yes.

Q. --was that a very standard first step when it comes to undertaking a genetic analysis of a family to seek from an individual comprehensive information about the affected person and their family?
A. Yes.

Q. Have you ever spoken directly with Ms Folbigg aside from the instance you attended at the correctional facility on 8 October 2018?
A. Never before or never - well, once again, because I visited two days or something later, I'm sure there are records in the prison, and this was to take the biological samples for the DNA analysis. I can just say, you know, just in reference to what you asked before, I guess it's a standard procedure and that's actually reflected in the guidelines for some of these - conditions, say for example you know these Long QT or whatever stating that the detailed family history looks for a history of syncope or sudden unexplained death at a young age and close relatives, directed questioning is essential with a family tree being drawn, so I mean this is just standard procedure, yes. I just wanted to--

Q. What are the guidelines that you're referring to there?
A. The guidelines are the guidelines for - I mean this would be in any guidelines, I have this just because of what we're talking about today, but this specific guideline is the guideline, "Update on the Diagnosis and Management of Familial Long QT Syndrome". Authored by Kathryn E Waddell-Smith and Jonathan R Skinner from 2016 in Heart, Lung and Circulation.

CALLAN: Your Honour, I'll get a reference, I'm fairly confident that's already in the--

WITNESS: Yeah, I'm sure it is, yes.

JUDICIAL OFFICER: Yes.

CALLAN: Thank you. Exhibit 15-10.

Q. That's a specific guideline that is in relation to the cardiac - well more specifically Long QT Syndrome--
A. Right.

Q. --and you mentioned that you amongst other things are looking for a history of syncope. When you attended on Ms Folbigg on 8 October, did you have in your mind a particular interest in the question of syncope?
A. Look not really, but I think, you know, when you're presented with this scenario, I mean it comes to mind because I mean there is, you know, it's - I'm sure you and your Honour would know from this proceedings, if not otherwise, you know, it's that I mean there is growing literature that some of these SIDS, CUDA, I mean all of these acronyms that we use, when you actually go and try to find and find the genetic codes, there is actually a certain proportion fall into an identifiable gene-related. And I mean, you know, and they--

Q. Sorry Professor, I think we're getting a little off track.
A. Yeah.

Q. My question was when you went to see Ms Folbigg on 8 October 2018--
A. I mean it was a consideration, yes.

Q. --and you asked her questions about a history of syncope, did you?
A. Look, I think I didn't necessarily need to ask because that came in the conversations, you know, when I - when we went through the history of the children, then we went one step up, one generation up, herself, and I think she volunteered that information.

Q. Okay. Other than the two occasions you've described, 8 October and--
A. Yes, yes, maybe tens, yeah.

Q. --a few days later to get the samples, have you ever spoken to her directly, that is Ms Folbigg?
A. No.

Q. You and Professor Vinuesa issued a report for the 2019 Inquiry, which is Exhibit 2-AF, which at that stage, amongst other things, referred to your finding of the presence of the G114R variant?
A. Yes.

Q. And based on information then available, and by reference to the ACMG criteria, you - the conclusion was likely pathogenic. Now, I recognise there's been quite a lot by way of development of the evidence and information since that time. I understand by reference to the most recent report you furnished to this Inquiry of the 22 January 2023, your view, again by reference to the ACMG criteria, is that the G114R variant satisfies the criteria of pathogenic, is that correct?
A. Yes.

Q. Now, when you gave oral evidence in the 2019 Inquiry, do you recall that one topic which came up was what you had been told by Ms Folbigg about fainting during the swimming carnival?
A. That is correct.

Q. And we might have a copy of that transcript up on the screen for you,

Professor Arsov. Your Honour, it's 16 April 2019, transcript page 506. All right, are you able to read that? We can enlarge it if you'd like, Professor. But do you see about the middle of the page, Counsel Assisting, so this is around line 23, says, "Dr Arsov, you visited Kathleen Folbigg and created the tree which is Exhibit 2-AE", do you have a copy of that?
A. Yes. I can - sorry, sorry, I'm reading. Yes, yes.

JUDICIAL OFFICER: Page 506?

CALLAN: Yes.

Q. And you're asked about the portion of Exhibit 2-AE which has 11- to 12-year-old fainted in swim race?
A. Yes.

Q. Your Honour asked, "Did she tell you - what did she tell you about that?" You said, "She was in a swimming competition", and then line 40, "After swimming for a while, she felt unwell and fainted." You were asked, "In the water or out of the water?", and you said, "I don't remember we went into that much detail", and Counsel Assisting's solicitors asked, "It didn't matter to you in terms of what you were seeking to achieve through the clinical review?", and you say, "So, I wasn't seeking to establish any specific diagnosis, it was just kind of asking about her health issues - what her health issues may have been", and you go on and Counsel Assisting asks, "So, you can't tell us anymore other than what you've just told us, and your answer was no?", do you see that?
A. Yeah.

Q. So, when you recorded in this pedigree, fainted in swim race, was that meant to convey that it was a faint which occurred either in or out of the water?
A. Can you just go to the next page, please?

Q. No, I'm just asking you about your evidence, Professor Arsov.
A. Yes, can you ask the question again.

Q. When you recorded in this pedigree that Ms Folbigg had fainted in swim race, were you meaning to convey that it might have been in or out of the water, you couldn't say?
A. Right. So, I mean, you know, you have to - I mean to answer that I'll just have to give a little bit of a context about the first hearing. I mean--

Q. No, Professor Arsov, we've seen what you said in the first hearing.
A. Yes.

Q. And you gave to that hearing in April, so this is some six months after your meeting with Ms Folbigg.
A. Right.

Q. Your recollection of what she told you in that meeting.
A. Right.

Q. And when you gave your recollection to the 2019 Inquiry, you were asked whether she was in or out of the water, and you said, "I don't remember that we went into that much detail"?
A. Right.

Q. Was that true evidence?
A. Yeah.

Q. And as at April 2019, you couldn't remember if she had told you whether it was in or out of the water?
A. I mean, I know that she lost consciousness, I mean that's what she said, that she kind of woke up on the side of the pool, is what I remember. But I think the question - again, this is why I wanted to kind of go through the questions, if I can have the next page again just so I can finish, you know, my statement, because I think there is something important there.

Q. Yes, 507, please.
A. Yes, please. Right, and so because, you know, for me at the time, I didn't go into this interview assuming - I mean to me this was all a surprise. I mean I had no idea that, you know, there was syncope, that there could have been a cardiac symptomatology in Ms Folbigg. So, my assumption, I suppose, then would, you know, have been that there would be some formal cardiac review, either done or about to be done, or I mean I can't imagine that somebody would lose four children like that and not have had, you know, a cardiac evaluation done, I mean that would be a standard procedure, I mean if you have such a family history, and so also you have to understand that you know when - you know when you are in these counselling sessions or interview sessions, you talk to a person, a human being, and these are very unusual circumstances that they went in, it's not standard practice, and you know, I had to also be careful, you're talking to somebody that's going through that loss and grieving and all of these things, and I - I mean in order to perhaps even get to that information, you have to build a relationship.

So, you have to know how far you go and push with these things. To me at the time, it really wasn't very important the exact circumstances of whether she fainted in or out of the pool. I mean all of this I learned afterwards about CPVT or other conditions that, you know, you need to swim and stuff like that, and so I don't know that she - that you know that she fainted - now, if I can just finish on that - while she was swimming or not. What I remember, and it wasn't asked like that, what I remember is that she woke up on the side of the pool.

Q. And she told you that?
A. Yes, and I think, you know--

Q. Sorry, just pausing there, you recall she told you she--
A. That's what I remember, you know.

Q. And you don't know, and please, it's no criticism, as I understand, you have explained you're seeking to build a rapport?
A. Yes.

Q. It's a delicate subject matter?
A. Yes.

Q. And you had an expectation or an assumption that there would or had been a formal cardiac review?
A. Exactly.

Q. So, you don't know whether she fainted in or out of the pool, but what you recall her telling you is that she woke up on the side of the pool?
A. That's right.

JUDICIAL OFFICER

Q. So, if you go back to Exhibit 2-AE, where you say 11 to 12 year old fainted in swim race, you can't say whether it was actually in the race, after the race?
A. Well, exactly. I mean, you know, as I said, these are - I didn't go into that much detail.

Q. No, I'm not criticising, I'm just asking to make it clear. Now, was Exhibit 2-AE, that's the pedigree document, was that prepared in discussion with Professor Vinuesa?
A. No, this is - you know, after I came home from the visit, I would have, you know, put it in a slide and shared it, yes. But I mean this would have been done by me.

JUDICIAL OFFICER: Thank you.

CALLAN

Q. Could I ask you, in your report - in the report that I took you to, or the letter of 11 July 2019, which is Exhibit 2-BW, that's the letter that - the letter that you provided to the 2019 Inquiry after giving your evidence?
A. What would the reference number be?

Q. BW. Your Honour, I'm referring to red page 7866, and it's paragraph 4.3, Professor. You see there's reference to what Dr Raju has reported of a longstanding history of recurrent transient loss of consciousness and syncope, including, "As a teenage she recorded multiple episodes of sudden post-exertion or syncope, some of them witnessed (one while swimming required her to be dragged out of the pool)", do you see that there?
A. Yes.

Q. She hadn't told you that, to be clear?
A. I mean, swimming race, and woke up at the side of the pool. So, I mean that would have been my inference, I suppose, but as I said, I didn't ask all that much.

Q. So, the words dragged out of the pool, that was an inference you'd made from what she told you?
A. Well, yes, I guess it sounds - I mean to me it sounds plausible, I mean this

would have been the interpretation a bit, I suppose, because you know, I mean if she was in a swim race, fainted, woke up on the side of the pool, as I said, I mean I didn't go through the details and sequences, but I mean it would have - yeah, I mean, it would have been--

Q. That's your interpretation of what may have happened, based on what she told you?
A. Yes.

Q. Being that she woke up on the side of the pool?
A. Yes.

Q. That paragraph refers to what Dr Raju had reported, I just wanted to take you to that to make sure that there's no unfairness. Professor Raju's report is Exhibit 2-BL, so it's still in that folder, just go back half a dozen tabs.
A. BL, yes.

Q. And do you see, using the red pagination, 7707?
A. Which paragraph?

Q. The third paragraph, second full paragraph, commencing with the words, "I also took the opportunity", do you see that?
A. Yes.

Q. "To discuss a further episode of syncope with her", you write:

> "In her youth, around age 12, she describes losing consciousness after a swimming event. She believes she swam 25 metres, completed the race, and her next recollection is recovering consciousness on the side of the pool. She does not recall any other event, but it is clear she was helped out of the pool on that occasion."

A. Yes.

Q. Were you relying on that account as recorded by Dr Raju when you included the words, "Syncope while swimming, requiring her to be dragged out of the pool"?
A. I mean, look, it would have been a while ago, so I can't be 100% sure, but I mean it makes sense.

Q. So doing the best you can, and I think you might be aware in, for instance, the report that you provided to this Inquiry of 25 October 2022 there's again a description of this swimming event which was that there was a syncope while swimming requiring Ms Folbigg to be dragged out of the pool. As an author of reports which make that statement, was that based on, first, an inference you drew based on what Ms Folbigg had in fact told you?
A. Well, I think it also has to do with - you know, I mean there's been subsequently, I suppose - I mean, as I say, I can't - I can't be 100% sure where it came from but helped out of the pool, dragged out of the pool, I mean I'm not

sure even "helped out of the pool" - I mean - I mean, she could have said something. I mean, at this stage at this moment I don't remember specifically. What I remember is having fainted in a swimming pool, waking up on the side of the pool like Professor Hari Raju is saying. You know, "helped out of the pool", would she have said, "dragged out of the pool", I don't know. I mean, if that was the case I would have probably recorded it in the pedigree but--

Q. No, I'm sorry. You may be misunderstanding me. Again, it's no criticism of the information that--
A. Yeah, yeah.

Q. --you obtained when you got the pedigree.
A. Right. I'm just trying to be volunteering--

Q. I'm just trying to give you an opportunity to explain to the Inquiry the sources of information you used in order to make this statement which has been made several times in your reports that this syncope was while swimming and required her to be dragged out of the pool. Now, you've told the Inquiry about the - that you didn't seek a great level of detail from Ms Folbigg when you saw her in October 2018.
A. Yes, yes.

Q. I've taken you to Dr Raju's description of what Ms Folbigg told Dr Raju. Is there any other source of information? For instance, Professor Vinuesa and her conversations with Ms Folbigg that has affected what is - that has caused you to describe it this way?
A. I don't believe so. I can't - I don't think so but I guess there was something else that I would have read, and this is an affidavit from Billy Joanne Buckley from 19 October 202.. I don't know what are the dates here - whether it was after or before.

Q. I can tell you that that affidavit of Ms Buckley was well after the report you provided in the--
A. I know but now--

Q. No. In the 2019 Inquiry.
A. But at this stage I have this information as well so that I'm trying to make this recollection, I kind of already know this, and I can't - it's difficult for me to kind of separate exactly what I heard from - you know, from - going back to the conversations with Ms Folbigg, I think what I recorded is what it is, but now I can't be sure. I guess to me this kind of also speaks to the fact that she was left behind so you know probably helped out of the pool is also I think something that can be - I could have inferred from here, yeah. So there's another source of probably information that may judge my - cloud my recollections.

Q. The choice of words "dragged out of the pool"--
A. Yes.

Q. --why did you not use Dr Raju's words which were "helped out"?
A. I mean, was this after the conversation that Professor Vinuesa had, I mean because I can't be sure exactly when we were - I mean, when this letter was written--

Q. I see.
A. --I mean we would have - you know, so she may have contributed and you know something from those conversations, I don't know.

Q. I see. Could I take you to the report you provided for this Inquiry of 25 October 2022, which is Exhibit 5-06 at red pagination 143.
A. What pages of my report, sorry?

Q. It's page 28 of the report, page 143 using the red pagination. Do you see in the second paragraph there is first the assertion that "Ms Folbigg suffered a complete loss of consciousness". Then is the statement that, "Ms Folbigg was dragged out of the pool and found herself by the side of the pool when she regained consciousness". It then says, "This was how the event was described to Professor Arsov when collecting a patient history from Ms Folbigg in 2018." Pausing there, that's not correct, is it? That wasn't what she told you?
A. Yeah - no.

Q. And then it says, "And to Professor Vinuesa when she spoke to Ms Folbigg on the phone to explain the results of genetic testing in December 2018", were you party to that phone call?
A. (No verbal reply)

Q. Now, it goes on to say, "It was also how the event was described to Professor Raju when collecting a patient history" and there's reference to that Exhibit I just took you to, BL. You accept it's described in slightly different terms by Professor Raju, "helped out" versus "dragged out", for instance. You accept it's described differently by Professor Raju?
A. I mean, you would have to - I mean, it's a different word, yes.

Q. Has the use of the word "dragged out of the pool", was that used to exaggerate what was known about Ms Folbigg's syncope in the pool?
A. Not - not really.

Q. From your perspective, was an event which involved fainting while swimming relevant to views about Ms Folbigg's phenotype?
A. I mean, in a swim race relating to a swimming pool, is one of the things that is mentioned in the papers, so it would be, yes. Associated with physical exertion is the extension of it so whether I think in the swimming pool or out of the pool you may need to, you know, ask you know the experts in the field about that, but I think you know for me it's exertion kind of related to ..(not transcribable)..

Q. What would you say to the suggestion that there's been an exaggeration of the description of that swimming event in order to put Ms Folbigg closer to a

phenotype.
A. Not really, no. I mean, she did faint in the swimming race so that to me it doesn't - I mean, it doesn't really - yeah. She fainted in a swimming pool.

JUDICIAL OFFICER: Didn't Professor Raju say, and correct me if I'm wrong, in Exhibit 2-BL that she fainted after she completed the swimming race.

CALLAN: Yes.

Q. Professor Arsov, that's the observation that his Honour--

JUDICIAL OFFICER

Q. Do you agree with that?
A. Sorry, sorry, I missed that. Yes, sorry, I missed that.

Q. Sorry, Professor. Professor Raju said she had completed the swimming race and then she fainted and was helped from the pool.
A. Right, but - well, I mean there are - yes, yes.

Q. That is, of course, somewhat different to fainting during the course of the swimming race and being dragged out of the pool.
A. Right. Well, I mean, she - it wasn't said to me, I don't think, that the race was completed. I will say that she was in a swimming race, she fainted, and then she woke up at the side of the pool. Now, again, when I read for example through this affidavit from Billy Joanne Buckley she said that she was anxious about--

CALLAN

Q. No, sorry, excuse me Professor Arsov. I think the focus is what you - information you had available to you--
A. That's right.

Q. --at the time you wrote the report in July 2019 and the report in October 2022.
A. Right.

Q. And his Honour was asking about the difference between what Dr Raju had recorded and what was written there.
A. Well, I mean, it's - yes, it's "helped out of the pool", you know "dragged out of the pool". I mean, you know, English is a second language and you know, these words are - I mean, whether you're helped, dragged, I mean it's - it's probably unfortunate choice of word but I mean, yeah.

Q. I see. But just to be clear, she didn't tell you whether it was in or out of the pool?
A. In a swim race. So I mean to me, I would have - the assumption is in the water, and I guess that's corroborated with this affidavit here which says that she had left behind:

> "Kathy and I started the race together but I got ahead of her in the pool. I swam the length of the pool, which I recall was 25 metres. The race was only one lap and when I completed the lap and got out of the pool I saw people were with Kathy on the left-hand side of the pool."

So I don't know.

JUDICIAL OFFICER

Q. What are you reading from, Professor?

CALLAN: I think the Professor's reading from an affidavit of Billy Jo Buckley and I'll get a reference for you, your Honour, in a moment.

WITNESS: Affidavit, yes.

CALLAN: It's Exhibit 14-05.

Q. Can I turn to one more topic before we take morning tea, subject to his Honour's convenience. Can I move to the article which was published in Euro-CASE. It's generally described as the Brohus article. Now, you're listed as a co-author of that article.
A. Yeah.

Q. What contribution did you make to the contents of that article?
A. Well, I provided the information around the pedigree, the variant specification, interpretation, some of the history and yeah, participated in writing, reviewing the content.

Q. Were you here when Professor Toft Overgaard gave evidence yesterday.
A. Yes.

Q. He described, from his perspective, that the primary authors of that article who took the lead were himself, Professor Vinuesa and Professor Schwartz?
A. Yes, a shared senior authorship of the paper.

Q. And was that your observation or experience of the process of the article coming together, that they were the shared senior authors.
A. Yeah.

Q. Your Honour, this is Exhibit 15-02. Do you have a copy of that article there. It's on the screen.
A. It's on the screen.

Q. Thank you. Over the page under the word "introduction", the first sentence refers to, "a diagnostic odyssey". Do you see that first sentence?
A. Yes.

Q. Do you recall if those are words you contributed to the article?

A. I mean it's words I use and know so I may have. I'm not 100% sure.

Q. Is that how you conceived of your task in terms of the work that you've done in relation to Ms Folbigg's case, a diagnostic odyssey involving such high stakes as the quest to determine whether recurring sudden unexplained deaths of children in a single family are the result of natural causes or infanticide? Is that what you were doing - have you been doing?
A. Well, no, I means is the diagnostic odyssey is trying to resolve the diagnostic odyssey. Trying to provide diagnosis.

Q. The particular contribution that you've made in terms of that bid to try to find a diagnosis has been, as it's developed, focussing on predicting the pathogenicity of the G114R variant?
A. That's correct.

Q. Then you have arrived at the conclusions and view, for instance, as expressed in this article, as to the likelihood that that is an explanation for the death of Sarah and Laura Folbigg?
A. Right.

Q. Can I take you to the conclusion which is at page 449? The final sentence reads:

> "The genomic revolution heralds a new era for the assessment of recurring familial sudden deaths of infants and children, an era that reasserts the presumption of innocence for tragically unlucky families."

Do you see that there?
A. I don't, can you just?

Q. Yes, under the heading "Conclusion", it's the final sentence? It's red page 19, your Honour.
A. Yeah.

JUDICIAL OFFICER: Yes, I've got it.

CALLAN

Q. Did you contribute those words to the article?
A. I don't believe so.

Q. Do you regard this situation involving Ms Folbigg as being that of a tragically unlucky family?
A. I think so.

Q. Is that because you formed a view as to the question of her guilt of murdering the children?
A. Not really. I mean I don't think ever I did that.

Q. You see it refers to reasserting the presumption of innocence?
A. No, I mean if you find a natural cause of death, then I suppose the alternative doesn't stand, does it.

CALLAN: Is that a convenient time, your Honour?

JUDICIAL OFFICER: Yes.

SHORT ADJOURNMENT

Yes, Ms Callan.

CALLAN

Q. Professor Arsov, I want to move to the reports you provided for this Inquiry. They are, as I understand it, a report that you prepared of 25 October 2022 with Professor Vinuesa and Professor Cook, and your Honour, for the record that's at Exhibit 5-06. There's a lot of paper you've unfortunately found yourself surrounded by there, Professor Arsov. Do you have a copy of that report?
A. Yeah, I think I do - I'm just going to find it.

Q. Sure. And we can put any part of it on the screen. But also just in terms of identifying your reports, in addition to that you were part of a joint report, again with Professor Vinuesa and Professor Cook dated 23 January 2023 which, in part, was responsive to the further evidence that the Inquiry had received from Professors Toft Overgaard and Nyegaard.
A. Yes.

Q. And your Honour, for the record, that's at Exhibit 5-08. Can I ask you this, Professor Arsov.

Sorry, 5-08 is the report of 1 February 2023.

CALLAN: It must be 5-07.

JUDICIAL OFFICER: 5-07 is 23 January.

CALLAN: Sorry, that's my error, your Honour, thank you.

Q. Professor Arsov, can I ask you this. When you approach an assessment of the pathogenicity of any variant, is it the case that you're engaging in what might be described as a probabilistic exercise.
A. Yes.

Q. And you're having regard to different considerations and types of evidence which you weigh and combine.
A. That's right.

Q. To assess the probability that a particular variant is disease-causing.

A. That's right.

Q. And as we referenced earlier in your evidence, your present view is that the G114 variant satisfies the ACMG criteria of pathogenic.
A. Yes.

Q. And according to the use of that criteria, that denotes a very high degree of confidence that the variant is associated with a Mendelian disease. Is that a yes?
A. Yes.

Q. Just I'm afraid nodding doesn't get picked up on the transcript.
A. Yes, sorry. Yeah.

Q. Now, in relation to the use of the ACMG criteria in the circumstances of this case, first, you have used that criteria and it's by reference to that criteria that you've classified the G114 variant as pathogenic.
A. Yeah.

Q. But you've also in material in evidence before the Inquiry described those guidelines as conservative and to some degree rigid.
A. Yes.

Q. And do I understand this correctly. You've suggested that those guidelines may not be particularly apt for the present case because for instance, those guidelines were not intended to be applied in a research context.
A. Right.

Q. They were specifically designed for a clinical setting.
A. Yes.

Q. And is it the case that you consider that there is also a difficulty applying ACMG criteria in a case such as this where you're classifying a novel variant.
A. Yes, it makes it more difficult, yeah.

Q. Now, would you accept that a benefit of guidelines such as the ACMG is that it is an internationally accepted framework which allows for a unified or harmonised interpretation of genetic variants.
A. In a diagnostic setting.

Q. Yes, of course. And as I've already adverted to, notwithstanding the concerns that you've expressed about the use of those guidelines in this case, you have nevertheless used them and by reference to your use of those guidelines, you've arrived at the conclusion of pathogenic.
A. Yes.

Q. I wanted to ask you about two of the considerations which have arisen, in particular in the task which has been undertaken by you and many others of assessing the pathogenicity of G114R, and those categories are, first, the functional assays and the relevance of those functional assays to the

prediction of pathogenicity. And then I'd like to ask you about the relevance of phenotype. In terms of the functional assays which have been performed, which are described in the Brohus article, and then there are further assays which Professor Toft Overgaard has given evidence about before this Inquiry. As I understand it, you regard that or you treat that as strong evidence of pathogenicity of the variant; is that the position?
A. Yes.

Q. Now, Professor Schwartz has in his evidence commented upon the limitations of functional assays emphasising the complexity of the clinical setting; do you agree with that observation?
A. There are always complexities, yes.

Q. And for instance, he's observed that bio-physical knowledge, that is the functional characteristics of a variant, may fail to fully explain the clinical consequences of a variant. Do you agree with that?
A. Yeah.

Q. Now, in the most recent report--

WOODS: I'm sorry, I missed the answer.

CALLAN: I think he said yes.

WITNESS: Yes.

CALLAN

Q. In the most recent report you provided to this Inquiry of 22 January 2023, you have amongst other things made reference--

JUDICIAL OFFICER: That's the penultimate report because there's a further one of 1 February.

CALLAN: Professor Arsov was not an author of that one, your Honour.

JUDICIAL OFFICER: I'm so sorry. Thank you.

CALLAN: Of course.

Q. Professor, in your report of 22 January 2023, amongst other things you make reference to some articles which describe the results of some variant effect mapped studies.
A. Yes.

Q. And do you recall Professor Toft Overgaard was asked in his evidence yesterday--
A. Yes.

Q. --about some of the features of that work, both in terms of the type of assay

and the process that was involved, but also the limitations on what conclusions could be drawn.
A. Correct, yes.

Q. And do you disagree with Professor Toft Overgaard's evidence on that topic.
A. There are limitations, yes.

Q. The Inquiry has received, amongst other things, a report from Professor Abrams. Your Honour, for the record that's at Exhibit 34-04. Have you read that report?
A. Yep.

Q. And in that report, Professor Abrams emphasises, to use his words, "the need to robustly link genetic findings with concorded phenotype to infer the causality". Do you recall reading that in his report?
A. Yes.

Q. And do you agree as to taking that approach?
A. Yes.

Q. That is, as to the importance that any in vitro data is concorded with clinical findings.
A. Well, I mean concorded is interpretational I suppose but in general, yes.

Q. Can I move then to the challenging phenotype situation that you were presented with in relation to Ms Folbigg and Sarah and Laura Folbigg.
A. Yes.

Q. I think you've already made reference to the fact that from the outset, a challenge has been incomplete information about phenotype.
A. Mmm-hmm.

Q. Is that "yes"?
A. Yes.

Q. In a report that was provided to the 2019 Inquiry, this was described as an exceptional clinical scenario. Would you describe it that way?
A. In what context?

Q. I'll take you to it because I want to make sure that I do understand what was meant by that.
A. Sure.

Q. So if we go back again to the letter of July 2019 that you prepared with Professor Vinuesa. It's Exhibit 2-BW. Your Honour, it's red page 7868. It's paragraph 6.5 of that report. Do you see on the third line it reads, "There is still general agreement that we are dealing with an exceptional clinical scenario. Rare genetic variants are by definition responsible for exceptional clinical scenarios." Does it remain your view that we are dealing with an

exceptional clinical scenario here?
A. Yeah.

Q. And what do you mean by "exceptional clinical scenario"?
A. Well, it's - as we said before, I mean it's a rare condition.

Q. Ultra rare?
A. Ultra rare.

Q. And in terms of the phenotypic information available to you about Sarah and Laura Folbigg, that phenotypic data is incomplete. In fact, there's no sound clinical data available, is there?
A. Apart from the sudden unexplained death. I mean, the myocarditis in Laura, right myocarditis in Laura, respiratory infections in both girls, so there is that, but nothing you know substantial of the cardiac end.

Q. Just in relation to Laura's myocarditis, in your report of 25 October to this Inquiry, Exhibit 5-06, you make reference for instance in answer to question 1.4 - I'll take you to that. It's red page 136. It's the report page 21. Do you see there in answer to question 1.4 the report refers to a number of propositions which emerge from the literature about myocarditis?
A. Yep.

Q. Do you see that there?
A. Yep.

Q. On this topic of the relevance of myocarditis, including the interplay between that and the CALM variant G114R, would you defer to the views of a cardiogeneticist?
A. Sure.

Q. In your further report of 23 January 2023 - which your Honour is at Exhibit 5-07 - at red page 203, which is your page 21, you have included some observations and comments by reference to some video footage of Laura Folbigg on 28 February 1999, do you see that there?
A. Mm-hmm.

Q. As I understand it, you recognised that as you're not a paediatrician it's beyond your particular specialised expertise to comment on that video, is that the case?
A. Yeah.

Q. But what you do is refer to evidence which has been given by other experts in the Inquiry?
A. Yes.

Q. Can I also ask you in developing the phenotypic picture of this family and your views about the pathogenicity of G114R, did you take into account the fact of the death of Caleb and Patrick Folbigg?
A. Yes.

Q. In what way did you take their death into account?
A. Well, I mean it's the views here have been expressed by some of the experts, that reduces the probability of the variant being pathogenic.

Q. Yes?
A. In my view that's not the case, because I think it doesn't require the interpretation of the variant necessarily a unified genetic explanation for the condition. So, I think, you know, we know from literature that conditions can cosegregate, so there could be two conditions that are running in the family. There are so called phenocopies in the pedigrees, so these are people that present in similarly - in seemingly the same way but for different unrelated reasons. So I think that to me was the consideration I suppose when that it's actually not reducing the likelihood of the pathogenicity.

Q. When you originally undertook the whole genome sequencing analysis and furnished that to the 2019 Inquiry, your task broadly was to seek to identify whether there was a possible genetic explanation for the death of all four of the children?
A. Or any?

Q. Yes?
A. I mean there are two possibilities. I mean you could have a unified or not unified - scenario.

Q. Certainly and you've just explained the various reasons why in your view it's not valid - I don't want to put words in your mouth -is what I understood you to be saying, to assume or proceed on the basis there must be a unified cause?
A. That's right.

Q. Separate from the two girl children, you have also undertaken some work to seek to identify whether there is any genetic variant which presents a plausible cause of the boys' death?
A. I haven't been involved, you know, very closely in that work. I think it's mostly done by Professor Vinuesa.

Q. Your report of 25 October 2022, Exhibit 5-06, deals with at red page 130, page 15, deals with the death of the Folbigg boys and you refer to some clinical features and then on page 16, red page 131, make this point, "...that it is unreasonable to expect a single unifying cause of death". As I understand the position you've reached in relation to the Folbigg boys is that no genetic variant has been identified which presents a plausible cause of their death?
A. Well, I mean it depends on what you mean by plausible. So I think there are some variants that are - candidates if you like, that warrant further work potentially. I mean, as you know, we're a little bit limited I think, that work is a bit limited by lack of, you know, paternal DNA in the case, so we - I mean you know it's not easy to assess, you know, whether variants, some of them are unitary to the *de novo*, but.

Q. As you presently sit here today you've not identified a genetic variant as a

plausible--
A. That we would say is pathogenic, yes.

Q. --cause of - that you would say is pathogenic?
A. Yes.

Q. There's reference in the Brohus article in respect of the two boys to the BSN L1898M variant?
A. Yes.

Q. Have you been involved in any of the work that's been undertaken to consider that variant, including the functional testing?
A. Not - not directly.

Q. Can I take you, still in your report of 25 October at Exhibit 5-06, to red page 153 and 154, and it's the report page 38 and 39?
A. Yes.

Q. You there set out some information, clinical information which you've identified in the evidence in relation to Caleb Folbigg. Do you see that?
A. Yeah.

Q. Do you accept that if we're not in the terrain of a pathogenic genetic variant that consideration as to the possible cause of death of Caleb Folbigg is beyond your area of specialised expertise?
A. Yes.

Q. Does the same apply to Patrick Folbigg and the information contained at page 39 and 40 of the report, red page 154 and 155?
A. Yes.

Q. Can I then turn to Ms Folbigg's phenotype? As I read your report of 23 January 2023 which is Exhibit 5-07, I take you to page 19 which is red page 201?
A. Yes.

Q. Do you see there under the blue heading BS2--
A. Yes.

Q. --which is the ACMG criteria of observed in a healthy adult individual, your position is you have not applied that criteria and you say it should not be applied?
A. Yes.

Q. That criteria is a category of strong evidence that a variant is benign?
A. Yes.

Q. And if you turn over the page, page 20, red page 202, you refer to the views which have been expressed by Professor Wilde and Professor Schwartz, you say they both indicate Ms Folbigg may have CPVT? Do you

see it's the paragraph just above question 2?
A. Yes.

Q. From your perspective that rules out the application of BS2?
A. Well not just that, I guess I mean there are other considerations.

Q. What are they?
A. So in the - if we can go maybe to - okay, no. So, I guess, all right, so just from - and I'm going from what she's volunteered as information, if we can go to the transcript you provided of the full conversation that happened between Ms Folbigg and Professor Vinuesa, so I think, you know, there is a little bit more information given in regards to her history of syncopes, so in addition to what was recorded in the pedigree and said to me or what was I aware of. So on page--

Q. I'll pause there. You're referring to a telephone call--
A. Yeah, a transcript, yeah.

Q. -- a transcript of a telephone call between Professor Vinuesa and Ms Folbigg--
A. Yes, page 2.

Q. I'll come to Professor Vinuesa's evidence, but just looking at what you've recorded in your report of 23 January 2023 as to why you have not applied the BS2 criteria, on page 20, red page 202, at paragraph above the heading "Question 2" refers to the reports of Professor Wilde and Professor Schwartz. You say that both indicate that Kathleen Folbigg may have CPVT which rules out the application of BS2?
A. Right.

Q. My question was whether you have ruled out the application of BS2 solely on the basis of the views of those experts--
A. Well I mean there are other experts--

Q. --or are there other reasons?
A. I mean those are valid but I think there are other plus those two, and if I can just maybe--

Q. Okay?
A. --make that stronger?

Q. You began to speak about a telephone call between Professor Vinuesa--
A. That's right.

Q. --and Ms Folbigg. In referring to that, is it the case that in ruling out the application of BS2 you were also having regard to the information or understanding you have from Ms Folbigg of her cardiac history?
A. Well, I mean this has to be read from the guidelines, family history and personal history is a big part of establishing a diagnosis, I mean that's where it all starts; in the conversation and what the person describes happens. So--

Q. Professor?
A. Yes. I mean it would add, I think. Look, none of this on its own is, you know, but I guess, you know, evidence stuck and I mean there are other experts that we may not have mentioned in that paragraph which are quite of the view that this is the case.

Q. On the question of whether Ms Folbigg presents with any phenotype of calmodulinopathy?
A. Yes.

Q. Would you defer to the views of Professor Wilde and Professor Schwartz?
A. Also, the report from Guicheney.

Q. Yes.
A. The report from the Oxford professor.

Q. Watkins?
A. Watkins.

Q. Okay.
A. So--

Q. Do you defer to the views expressed by Professor MacRae on the question of Ms Folbigg's phenotype?
A. No, I'll have to go through the report.

Q. Do you take issue with his expertise to express a view on the question of her phenotype?
A. No, but I mean I agree or disagree, I suppose, to some extent, I mean, because, you know, yes, I mean we spoke in the beginning, that, you know, this is not the standard condition, it's not - it's not fitting perfectly in the bins, in that I don't believe when I applied those - made those considerations, that it need necessarily to be that way. But--

Q. Sorry, I'm just asking - I'm trying to focus on the very specific question of the experts who - cardiac genetic experts who've given evidence in this Inquiry, and the views that they've expressed about Ms Folbigg's phenotype.
A. Yes.

Q. So, you've referred to the views of Professor Wilde and Professor Schwartz?
A. Yes.

Q. And you've said you also defer to the views of Professor Guicheney?
A. Yes.

Q. But you've said you don't defer to the views of Professor MacRae on the question of Kathleen Folbigg's phenotype, is that the position?
A. Yes.

Q. And you suggest that he doesn't have specialised expertise on the question?
A. Well, I mean, what I may say is that I don't necessarily agree.

Q. I see. But you recognise his expertise?
A. Yeah, yeah, yeah.

Q. And is the same - what about Professor Abrams, do you defer to his view on the question of Ms Folbigg's phenotype?
A. What does defer mean?

Q. Do you recognise that he has more specialised qualifications and expertise to arrive at an opinion about Ms Folbigg's phenotype?
A. Sure.

Q. As I read your report and hear your evidence, your position to rule out the application of BS2 is based on more than what these cardiac geneticists have said, you're also taking into account - you're also including your own view about Ms Folbigg's cardiac history?
A. Well, BS2 is not just about the phenotype. So, first of all there is discrepancy between these views from the cardiologists, and that's not well documented scenario. So, BS2 requires a well documented..(not transcribable)..phenotype, which I don't think is what we are dealing with here.

Q. I see.
A. So, that's number one, and number two is the application of BS2 also asks for a fully..(not transcribable)..condition in early life, which I don't believe is what the case here is.

Q. Okay. As I read your report to this Inquiry, for instance, of 25 October, you emphasise that Ms Folbigg's symptomatology has, you say, little bearing on whether the G114R variant is pathogenic, by reference to concepts including variable expressivity and incomplete penetrance. Have I understood your view correctly?
A. Sorry, can you - I just need to read that specific part, where is it?

Q. Sure. If you've got the report of 25 October, Exhibit 5-06, can we start with red page 130.
A. Yep, page which?

Q. 130, page 15.
A. Yes.

Q. Do you see in the first paragraph, you refer to some aspects of Ms Folbigg's history of syncope?
A. Sorry, which page is this?

Q. Page 15, it's red page 130.
A. From 23 January?

Q. No, 25 October. I apologise, Professor.
A. Yes.

Q. You describe Ms Folbigg's history of syncope?
A. Yes.

Q. You say this indicates she is likely symptomatic and may suffer from CPVT. You then go on to refer to variable expressivity and incomplete penetrance?
A. Yes.

Q. And then immediately above the heading about the death of the Folbigg boys, you say regardless of whether Ms Folbigg is symptomatic or not, or mosaic or not, and I think the position is that that's not under consideration here, as the functional studies of the G114R variant described in the Brohus article indicate the variant is pathogenic and arrhythmogenic. Coupled with the findings of the recent Kato article, you say, "Ms Folbigg's limited symptomatology has, in our opinion, little bearing on whether the Folbigg girls died as a result of the G114R variant"?
A. Yes.

Q. So, as I read it, your view is that Ms Folbigg's symptomatology has little bearing on whether the variant is pathogenic, is that right?
A. Well, I mean is this in regards to BS2?

Q. No, it's in relation to the G114R variant.
A. Yeah, in regards to which criteria?

Q. Sorry, I misunderstood. I'm asking you the general question by reference to that part of your report as to the relevance you place on Ms Folbigg's symptomatology, on the question as to whether the variant is pathogenic?
A. I - yes, I mean, yes.

Q. Is it your evidence that carrying a variant which is classified as pathogenic doesn't automatically mean it has or will cause a clinically manifest disease?
A. Yes. It's non-penetrance, right?

Q. Yes.
A. Or reduced penetrance.

Q. Do you take issue with the ACMG criteria of BS2 insofar as it is described as providing strong evidence a variant is benign if it is in a well-documented form presents in a healthy adult?
A. Well documented healthy adult, for a condition which is fully penetrant at a young age.

Q. So, you don't disagree with that, that being strong evidence of a variant is benign?
A. I don't apply BS2, because the penetrance, we know it's not complete.

Q. How do we know it's not complete?
A. There are published pedigrees, if I can go through the slides, maybe I can put up a couple.

Q. Just to be clear, is this in relation to this variant?
A. To the condition. You know, I mean other variants--

JUDICIAL OFFICER: What condition?

CALLAN

Q. What condition?
A. Calmodulinopathy. Other cases of calmodulinopathy where the variant has not been fully penetrant. So, it's possible, within this genome to have a variant which is not fully penetrant.

Q. And drawing on what has been observed as to other variants within--
A. Well, we don't have other people that have this variant so that we can ascertain that.

Q. The inference that it is not fully penetrant, is that your evidence?
A. In calmodulinopathy, it's possible to carry a pathogenic variant in one of the genes and not manifest a condition. So, in other words, we cannot expect that it's a fully penetrant condition and apply BS2.

Q. In your - still on your report of 25 October, page 33, which is at red page 148, do you see there you are answering a question as to the relevance, if any, of potential triggers?
A. Yes.

Q. You - it commences, "That the study of environment of triggers in genetic conditions is a relatively nascent field"?
A. Yes.

Q. "Particularly in the context of the phenomena of incomplete penetrance and variable clinical expressivity"?
A. Yes.

Q. Professor Wilde has observed that the relevance, if any, of potential triggers is all highly speculative. Do you accept that that's the position?
A. It's a nascent field, it's new. It is difficult to study.

JUDICIAL OFFICER

Q. Sorry, I didn't catch that answer?
A. Sorry?

Q. I didn't hear that answer. I'm sorry, Professor.
A. It's difficult to study. It's a nascent field. So, it's not--

Q. Thank you.
A. Yes. I think he's saying similar things in a different way, I mean if I understand his position correctly.

CALLAN

Q. I want to take the step that you've taken beyond the question of pathogenicity of the variant G114R to the question about whether the variant is - there is a reasonable possibility that the variant caused the death in Sarah and Laura Folbigg, and you expressed your view about this in slightly different ways as expressed in the Brohus article and in your report of 25 October. The Brohus article conclusion is that this variant provides a reasonable explanation for the girls' death. You're an author, you're content with that description?
A. Yes.

Q. And the report of 25 October, if we turn over to page 34, red page 149, in answer to question 3.4, you expressed a view there's a reasonable possibility that the deaths of Sarah and Laura were caused by fatal cardiac arrhythmias attributable to the G114R variant, and earlier in your report, page 14, at red page 129, you observe that the death of both Folbigg girls are consistent with calmodulinopathy?
A. Yes.

Q. When you say, "consistent with calmodulinopathy", are you referring to a group of conditions that lead to the electrical instability of the heart and fatal arrhythmias.
A. Yes.

Q. For which the first and only symptom may be sudden death.
A. Yes.

Q. Now, the Inquiry has received expert evidence in the form of reports, for instance, by Professor Wilde and Professor Abrams that the functional assays which would predict clinical CPVT phenotype mean there is a mis-match having regard to the circumstance of the death of the two girls, and in particular reference is made to the fact that they were under two years and asleep, and they observe that CPVT has not been observed as a cause of death in, first of all, a child as young as that, or asleep.
A. Mmm-hmm.

Q. Now, do you generally defer to the views that have been expressed, not only by Professor Wilde and Professor Abrams but also Professor Schwartz.
A. Yes.

Q. And Professor Guicheney on the question of whether the - what the functional studies predict and the phenotype of the girls.
A. I'm sorry, you will have to repeat that. I lost you somewhere.
Q. Sure.

WOODS: Your Honour, that's a little broad.

CALLAN: I understand. My friend is quite right.

Q. Do you defer to the views, first which have been expressed by Professor Schwartz as to whether it's a reasonable possibility that this variant caused the death of Sarah and Laura Folbigg.
A. Yes.

Q. Do you defer to the views of Professor Wilde on that topic.
A. What does "defer" mean?

Q. Do you recognise that he has more specialised expertise?
A. Yes.

Q. And does the same go in relation to Professor Abrams.
A. Yes.

Q. And Professor Guicheney.
A. Yeah, and Professor - from Oxford.

Q. Watkins.
A. Watkins. Sorry, Watkins.

Q. So in terms of exploring the precise observed features of CPVT.
A. Yes.

Q. And aligning that with the variant, you recognise that it's that group of Professors who have the more specialised expertise to comment on the topic.
A. Sure.

Q. Finally, Professor Arsov, in your report of 25 October, Exhibit 5-06 at - it's your page 42, red page 157.
A. Could you repeat the page?

Q. 42, red page 157. Do you see there's a heading "opinion of Professor Todor Arsov".
A. Yeah.

Q. Do you see there you say, "I remain of the view that the Folbigg children died of natural causes." Can I just pause there. Do you express a view on your expertise as to the cause of death of Patrick or Caleb?
A. Yeah, I'm meaning - what I'm saying is - you know, it's yeah the girls.

Q. Okay. So that's limited to Sarah and Laura, is it?
A. Yes.

Q. So your view is that Sarah and Laura died of natural causes and the cause of death was a lethal arrhythmia due to pathogenic CALM2-G114R with a possible contribution from their infections.
A. I mean, there is also genetic that's under way so you know, something - but yes, yes.

Q. When you say there's genetics that's under way, you mean in relation to the boys?
A. Yes.

Q. I see. But focusing on the girls.
A. Yes.

Q. Your view is that they died of natural causes.
A. Yes.

Q. And you consider that the cause of death was lethal arrhythmia due to the pathogenic CALM2-G114R variant.
A. Yes.

Q. Now, elsewhere in the report, and I've taken you to it, the way it's expressed is that there is a reasonable possibility that their deaths are attributable to the variant. Do you accept that you can't express the view more highly than the fact that it's a reasonable possibility.
A. Sure.

Q. That you can't sitting there today--
A. Yes.

Q. --say whether in fact they died of natural causes but you say there's a reasonable possibility that they did.
A. I mean, is probabilistic, yes.

Q. Thank you, Professor, those are my questions.
A. No worries, thanks.

<EXAMINATION BY DR WOODS

Q. Professor Arsov, you've been taken to the various reports which you've either written or partly written. Do you continue to express the views written therein?
A. Yes.

Q. You've had the advantage of reading various reports additional to the material from the first Inquiry, reports by Dr Abrams, Dr Wilde, Dr MacRae, Dr Guicheney and so on. Have you taken that material into account in confirming your adherence to your earlier positions?
A. Yes.

Q. Thank you. I won't be very long with you, Professor. Just on your expertise about which you've been asked some questions, you're a Professor of Genetics. You worked earlier at Melbourne University; is that correct?
A. Yes.

Q. Then as your CV indicates, you worked at the Australian National University.

A. Yes.

Q. Before obtaining your present position as Professor in Central Europe.
A. Yes.

Q. Does your work as a Genetic Counsellor involve you actually seeing patients?
A. Yes.

Q. And I take it from the rarity of the phenomenon that your patients are not confined to people with heart conditions.
A. No. Yeah, various.

Q. And the slides that have been admitted into evidence this morning refer to an article of yours from 2011; is that right?
A. Which article was that?

Q. Referred to a published journal article--
A. Yeah, yeah.

Q. --from 2011.
A. Yeah.

Q. Was that an article describing the identification of a particular aspect of a rare neurological condition.
A. That's right.

Q. Thank you. Now, in your role as a Clinical Counsellor in Genetics, if you encountered a person who was diagnosed with a calmodulinopathy, what would you say to the parents?
A. Can you be a bit more--

Q. Very well. Would that be a situation in which you would be inclined to give conservative cautious advice?
A. Well, I mean, you know for a condition that's super new I mean I would, you know, establish what has been done here in the research capacity, you know, network and communication with, you know, the experts in the field, the..(not transcribable)..if you like, people who have published on..(not transcribable)..who just understand, you know, or confirm but I mean, it would depend on whether, you know, the variant was *de novo*, whether it was inherited. So I don't understand in what way conservative.

JUDICIAL OFFICER: I was about to say nor did I before.

WITNESS: Yes. So it - I mean, the standard counselling around this rare conditions is quite difficult particularly when it's inherited and when the penetrance is not, you know, complete. So I mean, we would segregate in the family. We would test family members clinically, you know, for - so it would be quite different to the scenario that we're faced I suppose here where we don't have that luxury.

WOODS

Q. And when you take a family history, that's a standard practice, is it?
A. Yes.

CALLAN: Sorry to interrupt, could you speak up a bit, Professor Arsov, thank you.

WITNESS: Sorry, yes. Sorry, yes, sorry.

WOODS

Q. Yes. And the history that you took from Kathleen Folbigg when you interviewed her--
A. Yes.

Q. --that was the standard approach you take.
A. Yes.

Q. Did you have any prior association with Kathleen Folbigg or her family?
A. I mean, as I said before, never before dealt with her or others in the family, and I don't think ever after, and truth be told - I mean, I didn't even know anything about this specific case before we were approached to--

Q. You understand, of course, the basic requirements of proper scientific practice?
A. Yes.

Q. That is to say, objectivity.
A. Yes.

Q. Correctly measuring things.
A. Yes.

Q. Correctly recording things.
A. Yes.

Q. Did you apply those principles--
A. I mean, to the best of my ability, yes.

Q. Yes. And did you seek to exaggerate or favour any particular position?
A. Not really.

Q. Now, in addition to interviewing Ms Folbigg at the gaol, did you also obtain material from her such as a saliva sample.
A. That's right.

Q. A buccal swab.
A. Yes.

Q. For DNA purposes.
A. Yes.

Q. And how many times have you performed the process of sequencing DNA material?
A. Many times.

Q. Did you apply the standard procedures in relation to Ms Folbigg?
A. Well, I mean it's - called next generation sequencing is handled differently centrally, so I guess my role from a technical perspective would've been to obtain the samples and deliver them to the lab, and then it's a lab process that I wouldn't have been involved hands on.

Q. You were asked some questions about the age of the children Sarah and Laura. Do you see the age as being an obstacle to the opinions that you've expressed about--
A. No, and when I say no I base that opinion on - I mean what I started the conversation today with, experience from other conditions and work that we've done in the past and some particularly pertaining to age, but also deferring to what we know from the Calmodulin Registry and for example Professor Schwartz's views, that whatever can happen at 30 or 40 months can happen at ten months and, yeah.

Q. In the slides to which you've been taken, I wonder if we can get slide 18 up, is that possible? Do you recall being asked some questions about a swimming event?
A. Yes.

Q. I won't go over that again, but does that slide 18 assist you in respect of that subject? Could you explain what slide 18 relates to?
A. Yeah, I mean it just shows that, you know, syncope is the recurring feature of previously published patients, so when you look at, you know, what they present with or what they tell the physician when they see them is that they faint, syncopian dizziness while running, syncope - syncope while swimming.

Q. As I understand it, the effect of your evidence is that from what you said or what you've heard from Ms Folbigg during the interview you have with her, you can't really remember beyond exactly what you've just told Counsel Assisting?
A. Right. Well, look, it's difficult to go back and I mean rehash the whole conversation and every word that has been said, I mean, yes, I guess you're asking me now, so, yeah, I can't - I can't be sure you know where this word came from, you know, dragged out, helped out, I mean we see in the transcript from the conversation that Professor Vinuesa had, I think it's pulled out or something - fetched out, fetched out I think maybe is the words that she is using in that conversation. Can we double-check? So, I mean to me it doesn't really make any difference in terms of assessing her potential phenotype or phenotype because there are other clues in the information she gives us and, you know, some of her ECG findings for example.

Q. Right, now could the witness be taken to slide 22 in that series? It starts

off, "Syncope: atypical presentations". Have you got that?
A. Yes, yes.

Q. Does that assist you in being able to explain why it was that you would've regarded the swimming incident as something that you would take a note of?
A. I will understand slide, can you show me which slide are you referring to?

Q. It's number 22, it should be - we can see it on the screen here.
A. Right.

CALLAN: I'm sorry, your Honour, to interrupt. My friend has just put it to the witness that you said that the swimming event was something you would've taken notice of. I'm not sure that he has given that evidence, Dr Woods.

JUDICIAL OFFICER: His earlier evidence was a little more nuanced than that.

CALLAN: Yes.

WOODS: Yes.

Q. In the conversation you had with Ms Folbigg, did she mention as a part of her story that something occurred in a swimming pool?
A. Yes. In a swimming race.

Q. In a swimming race?
A. In a swimming race she fainted, woke up at the side of the pool is what I remember being told.

Q. On the subject of syncope, how can we be assisted by slide 22, what does that mean?
A. Well, I mean, here it's a case of a 32-year old woman, so published by Nieves Gomez-Hurtado in Circular: Arrhythmia and Electrophysiology 2016, a ten year old at presentation, at – 32 at the time she was reported, she lost consciousness during exertion. So, whether, say for example, swimming or proximal to the swimming, it's still exertion and if we go to the transcript for example that - through the transcript that was from the conversation with Professor Vinuesa, she also volunteers these other syncopes related to exertion when she was young, you know, related to athletics, she mentioned in similar activities. Also, when she would have infections like measles or mumps, and so I think this during exertion sounds compatible. She's had 10 to 14 episodes of syncope, Ms Folbigg describes other episodes of syncope, you know, when she was pregnant, when she would get emotional, like maybe confined to a small space. You know, when she was transferred from one facility to another.

JUDICIAL OFFICER

Q. So it wasn't only the swimming event--
A. No, no, no, I mean there are many.

Q. --that you took into account?
A. There are many, I mean there is a whole list I think summarised in Professor Vinuesa's submission, and then there is - you know, interestingly ECG unremarkable. Apart from a prominent UV-wave, and you know, this wave has been seen in six out of eight, say for example with the CPVT, there are patients in the Calmodulin Registry and again it's in that summary I think that has been provided from Vinuesa that - I mean in one of the ECGs from 2000 - I can't remember the year, but there is a U-wave feature, then the stress test talks about single premature ventricular contraction. I guess, again, when the ECG's been described by the experts we also see some premature bigeminal - outlet kind of premature beats, and you know, interestingly I mean it just speaks to this idea that these are not fixed phenotypes in space or time, or within the family, so it is something that which was considered by the authors to be typical Long QTS evolved over time with something that's more consistent with CPVT. So, yeah, I mean it looks quite similar in this regard.

WOODS

Q. Leaving that for a moment and finally, you were asked a question about your involvement in the writing of the Brohus paper in 2021. You were asked in particular about the use of the language in terms of it being an odyssey to find something?
A. Yes.

Q. Now, in the course of your work as a genetic scientist, is it often long and complicated?
A. Look, I mean it's not a word that I invented, I mean this is a standard word that's used in genetic, the diagnostic odyssey is if you like an entity and it's recognised in international literature, in Australian literature as well that they did. It's often that people wait 20 years to get the genetic diagnosis, so it doesn't happen overnight.

Q. So it wasn't a literary flourish on your part, you were reflecting a usage--
A. Scientific literature, yes, and--

Q. --a usage in the genetic literature?
A. --exactly. I mean this is a known and established entity, diagnostic odyssey.

WOODS: Thank you. Thank you, nothing further, your Honour.

JUDICIAL OFFICER: How long will you be Mr Jordan?

JORDAN: Your Honour, I would hope to be - it's a little hard to predict but let's say I would be aiming for five to ten minutes. Maybe - hopefully five.
JUDICIAL OFFICER: Perhaps we should adjourn.

JORDAN: Yes, your Honour.

LUNCHEON ADJOURNMENT

JUDICIAL OFFICER: Yes, Mr Jordan.

JORDAN: Yes, thank you, your Honour.

<EXAMINATION BY MR JORDAN

Q. Professor Arsov, for your information I appear for the Director of Public Prosecutions. Can I try and save you some time by offering you some general propositions. To the extent that your reports offer opinions in relation to forensic pathology, do you generally defer to those other witnesses with specialised expertise in that field?
A. True.

Q. To the extent that your reports offer opinions in relation to paediatrics, do you generally defer to those other witnesses with specialised expertise in that field. You need to answer for the record, please.
A. Yes.

Q. And finally, to the extent that your reports offer opinions in relation to cardiology, do you generally defer to those other witnesses with specialised expertise in that field.
A. True.

Q. Thank you. Can I take you, please, to your first report, your first joint report which is item 5-06, tab 5-06, and I'm just going to ask you, please Professor, to go to red number 148.
A. Sorry, I don't think I have that.

Q. Well, it's page 33 of the report.
A. Just let me find it.

Q. I'm sorry, I should have given you notice but could that be brought up, please. Do you see that, Professor?
A. Yes.

Q. Now, in the bottom paragraph under the heading, "pseudoephedrine", I'll quote it for the record, "The reference to pseudoephedrine is an error in a Brohus article based on the formulation of adult Demazin not child Demazin". Do you see that?
A. Yep.

Q. Now, here you are quite properly identifying an inadvertent error that occurred in the Brohus report; correct?
A. That's right.

Q. Do you now have any recollection as to how that error came to occur?
A. I think it's Demazin we weren't aware has two formulations, so I mean it's not something that I particularly was involved in assessing or reviewing.

Q. Right. So this was not part of your work--

A. Exactly.

Q. --on the Brohus article.
A. Right.

Q. Okay. Do you know who was responsible for this part of the Brohus article?
A. I'm not sure, I can't answer that.

Q. Just before lunch when Dr Woods was asking you some questions.
A. Yes.

Q. He asked you a question which I think was along these lines. He asked you, "In preparing your reports, did you seek to exaggerate or favour any position?" That was the question Dr Woods asked you.
A. Right.

Q. And your answer was, "not really". What did you mean by that?
A. I meant not - not favouring a position. I was - whenever I wrote something, I was basing it on the science that I had in front of me.

Q. So when you said, "not really", did you mean to say no?
A. Yes.

Q. Why didn't you just say, "no".
A. Well, I'm saying it now, no.

Q. Okay, all right. Can I take you, please, to I think it's page 131 of the same report. That's using the red numbers.

JUDICIAL OFFICER: Page 24 of the report.

JORDAN: Yes, thank you, your Honour. It's page 16 I think, your Honour.

JUDICIAL OFFICER: I'm sorry.

JORDAN

Q. Do you have that before you, Dr Arsov?
A. Yes.

Q. So Ms Callan took you to this paragraph at the bottom of the page under the heading "opinion"; do you see that?
A. Yes.

Q. Just a few questions in relation to this paragraph, if I may. The paragraph begins with this. It says, "Given these discrete phenotypes in the Folbigg boys", what discrete phenotypes in the Folbigg boys are you referring to there?
A. Patrick's encephalopathy, epileptic encephalopathy.

Q. Yes.
A. And Caleb's respiratory problems, floppy larynx, laryngomalacia.

Q. You're characterising those as phenotypes.
A. Yes.

Q. Okay. Can I then take you to the concluding sentence of the paragraph and I'll read it on to the record. You and your colleagues say this:

> "It is also unreasonable to assume in the absence of us or the Sydney team having identified a genetic cause of death in the Folbigg boys that they did not carry a genetic variant or variants that substantially contributed to their deaths."

A. Yes.

Q. Do you see that?
A. Yes. I don't see the second part, but I'm assuming it's as you read it. I mean if I can go to - yes. Yes.

Q. Do you maintain that position?
A. Yes.

Q. Can I put it back to you in positive terms and ask you to reconsider?
A. Yes.

Q. The sentence as you've drafted it is put in terms of negatives. Let me attempt to put it back to you in a way which uses positive language but which is the same meaning. Consider this. It is reasonable to assume, in the absence of an identified genetic cause of death, that the boys did carry a genetic variant that substantially contributed to their deaths?

WOODS: I object to that, your Honour. That's not capable of being reversed in that fashion. Without losing a significant element of meaning.

JUDICIAL OFFICER: Mr Jordan, you can put it to him directly without reference to the sentence.

JORDAN

Q. Well, let me ask you this, do you believe that it is reasonable to assume that the boys carried a genetic variant that there was - sorry, do you regard it as reasonable to assume in the absence of having identified a genetic cause of death in the Folbigg boys that they did carry a genetic variant that substantially contributed to their deaths?
A. Right. So, I guess when we test in genetics we can test in two ways, we can test diagnostically, or we can test for something that's already known in the family. So if we don't find anything in a diagnostic test or when we - then we can't say really a negative result, we say uninformative result because we always leave room and space that there could be something that we don't

know of today. So in terms of the boys there are two things. So we don't know what all 20,000 genes do in the genome and, you know, what may eventuate in the future, whether we may not find new genes that, you know, are potentially capable of explaining their phenotypes. I suppose that's just the nature of where genetics is at the moment in genetic testing. The second thing is that, you know, without - I mean even if, you know, we had certain probability to find a variant without the paternal DNA becomes lower because we cannot really be sure about *de novo* variants. So, yes.

JUDICIAL OFFICER

Q. Is what you're in effect saying you don't know at the present time whether there was a genetic cause but one day in the future you might find out?
A. That's right. So we can't assume that - yes, that there isn't.

JUDICIAL OFFICER: Right.

JORDAN

Q. And that inherently involves a significant amount of speculation, correct?
A. I mean it's the state of the fact I think.

Q. You're talking about something that is unknown, correct?
A. Yes.

NO EXAMINATION BY MR FRASER, MS LOVE, MR HASTINGS, DR WATERHOUSE AND MS HORVATH

<EXAMINATION BY MS CALLAN

Q. Professor Arsov, you referred in answer to some questions from Dr Woods to a summary that had been done by Professor Vinuesa. Can I check so that we're clear that we understand what you're referring to? Professor Vinuesa prepared a report of 10 October 2022. For the record it's Exhibit 5-04. Do you have that report prepared by Professor Vinuesa of 10 October 2022?
A. I probably do but at the moment it's probably going to be quite hard to locate.

Q. No problem. We'll have the front page put on the screen.
A. Yes.

Q. If we could move through to the table of contents which is red page 65, it's page 3 of the report. Do you see that describes by reference to the headings what this report addresses? Including item 2, relevant phenotype information?
A. Yes. Yes.

Q. Turning over the page to page 6 of the report, page 68 in red, for instance, the report sets out per paragraph 2.1, "The clinical histories of Kathleen Folbigg, Craig Folbigg and their four children, which I considered relevant for the further genomic analysis". Do you see that?

A. Yes.

Q. Is this report from Professor Vinuesa a document you've seen before?
A. Yes.

Q. Is that the summary you said that, for instance, in answer to Dr Woods, Ms Folbigg had sustained many syncope as summarised in Professor Vinuesa's report or Professor Vinuesa's summary?
A. Yes.

Q. Is this the document you're referring to?
A. Could we go further down and - there's a specific reference for this U-wave.

Q. Yes. So, there's--
A. Further down.

Q. --the syncope history and then--
A. Yes, so that is the document.

Q. --over at 2.5 is the U-wave--
A. Yes, that's it, yes, yes.

Q. So that's the document you were referring to?
A. That is the document, yes.

CALLAN: All right. Your Honour, the only other thing is we proposed to tender the slides that Professor Arsov has referred to in his evidence. They come from a slide deck which includes slides that were not referred to. For the record I propose to tender slides 1 to 16 and then slide 18 and 22. Your Honour, a version will be prepared which only includes those slides and can I ask that when they're received they be marked Exhibit 5-10?

JUDICIAL OFFICER: Yes.

EXHIBIT #5-10 SLIDES 1 TO 16, 18 AND 22 SHOWN BY PROFESSOR TODOR ARSOV ON 14/02/23, ADMITTED WITHOUT OBJECTION

CALLAN: Thank you, Professor.

JUDICIAL OFFICER: Professor, thank you very much for coming and giving your assistance. We're very grateful for it. You can stay and listen if you like or you're free to go, whichever you prefer.

<THE WITNESS WITHDREW

<MARIA CAROLA GARCIA DE VINUESA DE LA CONCHA,
AFFIRMED(2.15PM)

<EXAMINATION BY MS CALLAN

Q. Could you confirm for the record your full name?
A. Yes, Maria Carola Garcia de Vinuesa de la Concha.

Q. Professor Vinuesa, the Inquiry has received a number of iterations of your curriculum vitae in circumstances where your first contribution to the question of Ms Folbigg and genetic variants occurred in 2019, and your professional career has advanced since that time. It appears to me the most recent version of your CV is located, for the record, your Honour, at Exhibit 5, tab 09. Can I ask that that be shown to Professor Vinuesa, either in hard copy or on the screen. Sorry? 5-09, page 218. Professor, the Inquiry received this copy of your curriculum vitae, I think in about February of this year. If you need to see all the way through, the document is seven pages long, do you recognise that as an up to date version of your CV?
A. Yes.

Q. And in relation to your professional qualifications and experience, is it - I just would be grateful to identify the key aspects of your background and qualifications which you bring to bear in your contribution to the work of this Inquiry, and to the extent it can be done by reference to your CV, I don't want to unnecessarily duplicate, but I understand that you obtained your medical degree in Madrid in 1993?
A. Yes.

Q. And it's the case, isn't it, that you undertook specialised clinical training in the United Kingdom?
A. Yes, I did three years of clinical training.

Q. And in that - during those three years, did that include rotations in cardiology and paediatrics?
A. Yes.

Q. Now, you were then, as I read your CV, awarded a fellowship to undertake a PhD in immunology, which you completed at the University of Birmingham in 2000?
A. Yes.

Q. And after finishing your PhD, you were awarded a research fellowship and you undertook postdoctoral training in immunogenetics at the Australian National University?
A. Yes.

Q. And was it in the context of the period of time that you worked at the Australian National University that you were first approached in relation to this case?
A. Yes, by then I was - I had moved on from that first doctoral work, yes.

Q. And in that respect, you had established a - sorry, I'll let you speak to it. Could you assist the Inquiry to understand the qualifications and the areas of study and experience you've had that you draw upon in order to provide your evidence to this Inquiry?
A. Yes, during my postdoctoral training, I acquired expertise in the discovery of genes and variants that would cause disease, initially in mice using forward genetics. So, ANU meet a geneticist to try and find novel causes of disease, and after my postdoctoral training, we were pioneers in Australia in using next generation sequencing to the discovery of genetic causes of human disease. So, we are - we got awarded the first NHMRC Centre of Research Excellence grant to use next generation sequencing to diagnose patients with immunological disorders or to - for a research purpose, discover novel genetic causes of disease and their mechanisms through functional validation.

Q. In terms of your background and experience, do you draw upon your clinical experience?
A. I think it is useful to put variants in context of clinical disease. I consider I have a general understanding, but of course I'm not specialist in any one area of medicine.

Q. And you've already spoken to the research work that you've undertaken over a number of years, in particular in relation to the topic of novel genetic variants?
A. Yes, over 20 years.

Q. Prior to your work in this matter, had you had experience in relation to cardiovascular genetic conditions.
A. No.

Q. Had you undertaken research or other work in relation to calmodulin.
A. No.

Q. After the 2019 Iinquiry, is it the case that you were troubled that you considered that not a single expert in genetics or heart arrhythmias nor an expert in CALM genes had been called to give evidence in that Inquiry.
A. The experts in calmodulinopathy.

Q. And you - and I'll come to it in a moment - but you sought out the views of Professor Schwartz towards the latter stages of the 2019 Inquiry.
A. Yes. It wasn't just Professor Schwartz. I contacted the top experts in the calmodulin field to ask for their opinion on this variant and on the question of whether any functional validation could be performed.

Q. And that in due course gave rise to the functional assays that were performed by Professor Toft Overgaard and others in relation to the variant which are reported in the Brohus article.
A. Yes.

Q. This Inquiry has now the contribution of the views of Professor Schwartz and Professor Toft Overgaard and a number of others, Professor Nyegaard,

Professor Guicheney, Professor Wilde, Professor Abrams, Professor McCrae and Professor Watkins. Would you put all of them in the category of being experts in the genetics of heart arrhythmias.
A. Yes, although calmodulinopathy is a very rare disease. We estimate only 1 in 35 million people suffer from it, so experts in calmodulinopathy would mainly be those that assemble the Registry and have access to data from more patients.

Q. And is that of the list of experts Professor Schwartz.
A. Yes.

Q. Anyone else?
A. I mean, I'm sure that others have contributed perhaps one or two patients but the Registry that contains 134 patients, that data will be available in its entirety to Professor Schwartz.

Q. And I'll come to it in relation to some specific topics and meaning no disrespect to your qualifications or expertise, but when it comes to some of the more challenging questions of cadiogenetics in this case, do you defer to those with the expertise in that field?
A. I would defer in everything to do with electrophysiology. I think in terms of genetics, given that these mutations are very rare, I don't think - I think I am qualified to speak about some aspects of the genetics.

Q. As I understand your evidence from a few moments ago, is that partly because of the particular focus of your work in relation to novel and rare genetics.
A. Yes.

Q. You mentioned a moment ago that you contacted Professor Schwartz; you sought him out, and other top experts in calmodulinopathy.
A. Yeah.

Q. Are any of the other experts that have given evidence to this Inquiry, people that you sought out at that time.
A. No. I sought out Schwartz, Ackerman and A. L. George.

Q. And was it the case that neither of the other two responded in a substantive way to your enquiry.
A. Yeah, I don't think I got a response from Ackerman and A. L. George responded saying that Professor Toft Overgaard would be the best person to conduct functional assays because he was the world expert in calmodulin function.

Q. And in due course you contacted Professor Toft Overgaard and we have a sense of what followed from that.
A. Mmm.

Q. Professor Vinuesa, I wanted to ask you about your direct dealings or conversations with Ms Folbigg. Have you personally spoken with Ms Folbigg

on the telephone.
A. Yes. I--

Q. How many times?
A. Three that I can remember before and after genetic testing, and around the mosaicism testing. Again, memory is not perfect. There could have been another one but I can't remember terribly well.

Q. And in terms of speaking to Ms Folbigg you said before and after genetic testing, that testing occurred in late 2018, do you recall?
A. Yes, well, I think we obtained her sample September/October. It was analysed throughout November and I think it was in the first weekend in December that Professor Arsov and I went through to do our own analysis of the raw data.

Q. And it was after doing your own analysis of the raw data did you speak to Ms Folbigg again about the results of the genetic testing.
A. Yes.

Q. And there is some evidence before this Inquiry that I'll have played in a moment of a conversation you had with Ms Folbigg in which she told you about a fainting incident at a swimming carnival.
A. Yes.

Q. And your recollection, have you discussed that topic with Ms Folbigg on any other occasion aside from this one telephone call that we've got a record of?
A. Not that I can remember.

CALLAN: Your Honour, can I ask to have that call played? Exhibit 14-11 is the transcript and the recording of the call.

JUDICIAL OFFICER: I assume we've got the capacity to do it, yes.

CALLAN: Yes, your Honour, and for the record, this is a telephone call which occurred on 3 January 2019.

Q. Professor Vinuesa, you've had a chance to listen to this tape and see the transcript?
A. Yes, and may I add that it was me that pointed you to this conversation, because I thought that when we were discussing about the incident I said I'm pretty sure it was recorded in the prison, so you could probably get a transcript, so. Because I know what you're going to ask me, so my memory was probably not as good as it should have been but I did point that out to you so that you could verify it, so I'm just putting that in here on the table because obviously my memory was not as good as it turned out to be, but it was me that told you to listen to this conversation.

Q. Professor Vinuesa, you've anticipated aspects of what I was going to raise with you.

A. Exactly. Exactly. Poor memory but that's life, and I am going to learn from this.

Q. Just to be clear, so there's no mystery on the transcript, you are referring to a recent conference in which you were asked to recall when you'd spoken to Ms Folbigg on the telephone and you referenced the fact that you'd spoken to her on occasion while she was in the gaol, and you pointed out your understanding that those telephone calls are recorded, because it's moderated through the gaol telephone system?
A. Yeah, I was talking specifically about what I remembered about the swimming incident. So I said I'm sure you could get that recording, because I remember so and so, and obviously my memory wasn't perfect, yeah.

Q. We might just, in a sense in fairness--
A. Yeah.

Q. --and recognising I think as you've anticipated, that the question of memory is a vexed one that Courts deal with all the time--
A. That I misremembered, yeah.

Q. --but we might play the call.
A. Yeah.

EXHIBIT 14-11 PLAYED TO COURT

CALLAN: We might stop there.

Q. Professor Vinuesa, the call continued, do you recall, and you might have more recently heard that in the recording, with a call shortly thereafter in which you continued to speak to Ms Folbigg about her going to get specialist cardiatric assistance or further investigation, and you explained to her a little bit more about the results, what you'd found, and the implications, and according to that call, you observed that she should be examined, at least to prove that you yourself have cardiac conditions, you say because of your own safety, and then of course that would provide some support to the possibility that this is part of what might have caused the children's death, do you recall saying that to Ms Folbigg?
A. Something like that, yes.

Q. Now, I think you pre-empted the implications of what we hear on that telephone call, in terms of what - the account Ms Folbigg gave to you of the swimming pool incident. That call occurred in January 2019. Now, we've heard there's six-minute calls, there's beeping going on, did you regard that as a slightly rushed way of communicating with someone about the results of sequencing, such as you'd done for Ms Folbigg?
A. Yeah, look, I've never had a conversation like that before. It's not the ideal scenario. You need to sit someone down, explain the implication, it's - it's - it's - it's terrible, really, to have to tell someone on the phone on a six-minute call that they - well, that there might be implications on a finding, but at the same time it might mean nothing. You know, it's a comparative, we're

trying to say well, it could be nothing, it could be but, you know, if it was something, you would need to be tested, and--

Q. Sure. Do you recall if you yourself took notes of what Ms Folbigg was telling you during the call?
A. No, I wish I had. In fact, so - I'm trying to think, I mean did I understand it properly, did I hear her properly, did I remember properly. So, no, I didn't take any notes.

Q. And again, getting to where I think you and I are both going, do you recall - so, that was in early January 2019?
A. Yes.

Q. You were asked in the evidence you gave in the 2019 inquiry on 16 April about - as to your recollection of a telephone call with Ms Folbigg regarding the swimming incident?
A. Yep, yep.

Q. And if we might have on the screen the transcript of that, which is - so, it's 16 April 2019, transcript page 507. So, just to situate you, and I hope the screen immediately in front of you has that on it as well.
A. Yep.

Q. I think, were you here in court earlier today when I asked Professor Arsov about the point that he was asked in the 2019 inquiry about what Ms Folbigg had told him about the swimming carnival?
A. Yeah, yeah.

Q. And you were in fact, back in 2019, both sitting together in the witness box, weren't you?
A. Yep, yep.

Q. So, you'd heard what he told the Court?
A. Yep.

Q. And then Counsel Assisting turned to you, and we can see that on page 507?
A. Yep.

Q. Line 11, Counsel Assisting asked, "Were you there Professor Vinuesa?", and you then refer to talking to Ms Folbigg on the phone to deliver the results?
A. Yep.

Q. And what you told the inquiry was that she said it was in the water as soon as she finished the race?
A. Yep.

Q. You were asked:

"Q. Did she fall to the bottom of the water?

A. She was - somebody looked after her, so I don't know whether she fell to the bottom of the water.

Q. Fainted and got out of the pool?
A. No, she just told me she fainted at the end of the race, and I don't know if she fell to the bottom of the pool.

Q. You don't know whether she fainted in the pool or out of the pool?
A. No, she did faint in the pool."

A. Yeah.

Q. So that was your recollection as at April 2019.
A. Yep.

Q. And you've had been reminded of the precise contents of the call.
A. Yeah.

Q. In which - when you checked with Ms Folbigg, whether it was in the pool or out of the pool, she said it was out of the pool.
A. I mean, if you actually read that it's quite vague what she's saying. I'm not - I mean, probably I mis-remember and I - or I misunderstood but actually when she says it, she finished the race, she's standing there, you can imagine also standing - her in the shallow end of the pool. Grammatically it's a little bit incorrect when she says, "I got out the end of the pool" or it could be read like "I got to the end of the pool". To be honest, what stuck with me probably is "I was fetched out" and fetched out in the context of a pool, you would imagine she's fetched out of the pool. Otherwise, where do you get fetched out of. So simply, that's probably what I remember. I probably mis-remembered, I don't know. I mean, if you read that, it is a bit vague. So I - as I say, I imagine that next time I'm going to take notes when I speak on the phone but it's - if it's a mistake, it is a very honest mistake.

Q. Certainly. And the consequence, though, of that honest mistake is that you have provided a number of subsequent reports including to this inquiry where you've been quite definite in asserting that Ms Folbigg suffered a syncope whilst swimming and that necessitated her being dragged out of the pool. You accept that?
A. I mean, it was - it was - the dragging out of the pool it was partly also the recollection of Todor and we read Raju's report which also said she was helped out of the pool. In the Brohus article, Dr Raju read and edited the part of Ms Folbigg's cardiac history.

Q. So are you saying you relied solely on Dr Raju for that description of "dragged out of the pool".
A. He edited the section of the cardiac history of Ms Folbigg.

Q. So do you say the responsibility lies at his feet for any error in the description of that event.

A. I think - I would say it's a joint thing but to be honest, I don't think it really has any consequence because we are talking about a history of recurring syncopes and we are saying that this is incompletely penetrant and BS2 doesn't apply anyway because of the penetrance. So I'm not sure why we are giving so much prominence to this.

Q. You've given some particular prominence to this--

JUDICIAL OFFICER: Can I just ask this.

Q. Professor, did you regard the information for fainting as important when she told you?
A. Excuse me?

Q. When Ms Folbigg told you of the fainting episode in the pool, if I can call it that, did you regard that as a matter of particular significance?
A. Look, over time - I mean, initially obvious - but probably we didn't because if you notice we didn't mention it in any of our reports. The first time that this came out was during the hearings of the inquiry and it was at the time of the hearings that there was a discussion about this. I'm not a cardiologist. To be honest, we expected there would have been a cardiologist's account.

Q. I just want to take you to the discussion which took place after it. If you go back to page 507 of the transcript. I think it's still up on the screen fortunately. Immediately after you told counsel assisting what was said, Dr Skinner immediately said that it "was a very important event and we need details of that faint" and gave the example she sank to the bottom of the pool, was pulled out by someone who's given resuscitation. That's one story. She just won the race, felt a bit dizzy and was pulled out and recovered. That's a completely different story. So the details are really important. After that, did you think back on what exact details you had been told by Ms Folbigg?
A. Well, I suppose after that the first thing that we thought is, you know, why does it rely on us to talk about the cardiology because we are not cardiologists.

Q. I understand you're not but Dr Skinner is, is he not? That's right, isn't it?
A. Exactly. Exactly so--

Q. And Doctor--
A. So we were trying to remember conversations--

Q. Please. Please, Professor.

CALLAN

Q. Could you please listen.
A. Yes.

JUDICIAL OFFICER

Q. Dr Skinner is a cardiologist and was saying it was terribly important the

circumstances in which this occurred.
A. Yes.

Q. And it was after that that you made your reports which are somewhat different to what Ms Folbigg told you or appeared to have told you in the telephone conversation.
A. Yes. Look, your Honour, I just said that's what I thought I remembered.

Q. I understand.
A. That's what I understood.

Q. I understand that but would you now agree that irrespective of what's in your report, the accurate account is the account which appears in that telephone conversation.
A. Well, that was one conversation. She had another conversation with Dr Arsov and another conversation with Dr Raju, and it's hard to remember which accounts do you end up remembering.

Q. I'm asking you about the account that she gave. She never told you anything to the contrary to that account, did she?
A. Sorry?

Q. She never said that that account she initially gave you was incorrect.
A. No. I'm just saying that that's what I understood or remembered and if I misunderstood or mis-remembered, then it's a mistake but you've heard the conversation. It was fast, rushed, vague, and I was there to try and explain to her genetic tests. I was imagining there would be a cardiologist taking a history at some point. I was not taking notes. If I misunderstood something, it's - I don't think, well, that's it, it's - you make these - these things happen and a telephone conversation from four year ago.

CALLAN

Q. Professor Vinuesa, do you accept that the best record that we have of what Ms Folbigg told you was the telephone call that was recorded that occurred on 3 January 2019?
A. While Dr Raju interviewed her and took notes, I wasn't taking notes, and this was a very rushed conversation; and very vague, I think she was saying things that didn't quite connect. Fetched out, where do you get fetched out from? I mean it's hard to imagine being fetched out or am I misunderstanding the meaning of fetched out? So, it's easy to understand something else on the basis of this call. The grammar is not correct as well when she talks about getting out the end of the pool. You would say, when I was getting to the end of the pool, so there is something that either you're hearing one way or interpreting another way, I would think - but as I say, you know, between the accents, the rush, the six minutes, I mean I try to be hyper accurate in what I do. I've written - you probably have seen nearly ten reports to this inquiry, I don't think you can find a fault in any of these reports because it's, you know, my reputation and the work that we do. If on this - particular circumstance I misheard or misremembered, it is definitely not out of, you know, I mean - so.

Q. Professor Vinuesa, you've explained several times the circumstance of the call and you have indicated that - I think as I understand your evidence - you obviously mis-recalled or--
A. Or misunderstood.

Q. --that call, or misunderstood that call when you gave evidence before the inquiry in 2019. Do you, is it your evidence the same that in your various reports when you have described the syncope as having occurred while swimming, and that Ms Folbigg was dragged out of the pool, that that on reflection does not accurately reflect what Ms Folbigg told you in January of 2019?
A. What is on the transcript, yes.

Q. In 2019, and his Honour has taken you to this portion of the transcript at 5-07, Professor Skinner suggested that that event in the swimming pool might've been an important event and she - he distinguished between sinking to the bottom of the pool versus finishing a race and feeling dizzy. You in your evidence a few minutes ago, as I think I heard it, suggested that the circumstances of that syncope were of no consequence. Do you defer to Professor Skinner in terms of the cardiac significance, one way or another?
A. Yes.

Q. Have you exaggerated the nature of that syncope at the swimming carnival to support a conclusion as to Ms Folbigg's pathogenicity?
A. No.

Q. Could I take you to the report you've provided to this inquiry of 25 October 2022 which is Exhibit 5-06, page 28, red page 143, the paragraph that commences, "The description of Ms Folbigg fainting while swimming"?
A. Yep.

Q. "As a pre-syncope rather than a syncope and the last inquiry was incorrect"--
A. Yeah.

Q. --"as Ms Folbigg suffered a complete loss of consciousness"?
A. Yeah.

Q. What was the information upon which you assert that she suffered a complete loss of consciousness?
A. Well, she said she fainted, fainting is suffering a loss of consciousness. She told Dr Arsov she woke up by the side of the pool and she told Dr Raju that there was - that again she had a fainting episode, which he described also as a syncope.

Q. You go on to describe it as, "Ms Folbigg was dragged out of the pool and found herself by the side of the pool when she regained consciousness"?
A. Yeah.

Q. I think you've already addressed that that was different to the way

Ms Folbigg described the event to you?
A. Well, again, I mean as I say, fetched out, dragged out, that's what I remembered, and - but yes, I - that's--

Q. Professor Vinuesa, maybe I should take you back to the transcript in fairness. Exhibit 14-11.
A. It's - no, it's all right I accept that it was a mishearing or a misunderstanding and--

Q. No, no - I - no. Professor Vinuesa, I'll take you back.

JUDICIAL OFFICER: Professor, let Ms Callan ask the question.

CALLAN

Q. I'll take you back to the transcript of the call at 14-11. It's red page 334. Do you see the fourth last line, transcript of the call. So, the sixth last box, commencing with the words from Ms Folbigg, "I remember a swimming carnival where I got out the end of the pool and just fainted, you know, sort of thing." You asked, "That was while swimming or while you were out of the pool?" Answer:

> "No, I finished swimming, I got the end of the race and was just standing there, you know, sort of waiting for whatever, and people just said they needed to fetch me off the ground sort of thing, you know."

And then she goes on to speak about pregnancy. Do you accept that the account Ms Folbigg gave you in that call does not indicate that she was dragged out of the pool?
A. Yes.

Q. Your report of 25 October goes on to say, "This was how the event was described to Professor Arsov when he collected a patient history from Ms Folbigg in 2018 and to Professor Vinuesa when she spoke to Ms Folbigg on the phone to explain the results of genetic testing in December 2018." Do you accept now, with the benefit of the call, that that reference to what she told you on the phone is incorrect?
A. Yes.

Q. And we can refer ourselves to what Professor Raju has reported in terms of when he collected the patient history?
A. Yes.

Q. Now, you go on to say in the report, you address the growing body of evidence that links syncope, including vasovagal syncope, with calmodulinopathy, and you address that in the balance of that page of your report?
A. Yep.

Q. And was that awareness of the link between syncope and calmodulinopathy, something that you first came to appreciate when Professor Skinner, in 2019 in the witness box, spoke about the potential importance of that event in the swimming pool?
A. To be honest, if I had clearly remembered the call, I would be mentioning the other syncope that she also mentioned that I think are highly relevant. You know, we've been talking about Brugada Syndrome in this inquiry. If I had remembered that she had had fainting with temperature, as she told me in that call, that is quite typical of Brugada Syndrome, and I would have brought it up, and I didn't because I didn't remember. She also said she fainted with nearly every childhood infection, and she gave me the example of measles. That's also typical of Brugada Syndrome. Had I remembered that conversation in full, I would have put all of that in every report because now that it turns out that calmodulin or this particular variant is a danger phase with a sodium channel and that its eventual phenotype could be Brugada Syndrome, this is now highly relevant.

Now obviously, I didn't remember that call properly. So, I don't think I'm either trying to exaggerate, one, or I'm just not remembering properly what was the conversation at the time, and if anything, that history is telling us that there's been recurring syncopes, many syncopes, I mean to me that is relevant, and I wish I had remembered this conversation in full because I would have made a very full account of that in our report. Now, memory plays tricks, and there comes a point that four years later I wish I remembered, and perhaps what I remember is a concoction of Hari Raju's report, the affidavit, Todor's account, and clearly it's a lesson, take notes and don't talk about telephone conversations that happened four years ago.

But that was my recollection. It's not accurate, I accept, but I think there are other things now in that transcript that are enormously useful for the current case, and I'm not making a big deal of them, and I wish I had remembered, but I didn't remember.

Q. I'll come back to it, but when you speak about this variant being associated with the danger phase in terms of the sodium channel, are you speaking of the more recent functional assay conducted by Professor Toft Overgaard?
A. I am.

Q. And do you accept that there is yet more work to be done to understand whether that has a moderating or an aggravating effect?
A. Absolutely, but we also--

Q. And so, to describe it as a danger phase may be overstating in circumstances where that's not yet known?
A. Yes, but can I say something. There has been a paper - there was a paper in 2018 of a Brugada Syndrome mutation, Tyrosine 1494, that showed that with that particular Brugada Syndrome mutation, the part of calmodulin that changed more in structure was exactly the few residues around G114. So, yet another piece of evidence that that particular region could be associated with Brugada Syndrome, and yesterday we had another paper just published that

the G114 variant also is important for interaction with the potassium channel. So, there is a lot to be learnt.

JUDICIAL OFFICER

Q. A lot of this was known to you, was it, at the time you had the conversation with Ms Folbigg?
A. No, but what I'm saying is if I had remembered the conversation correctly, I would have mentioned, for example in our latest report, where we already knew about the results from Dr Overgaard that there were all these incidents of fainting with fever and with measles, with infections, and I didn't remember correctly this conversation.

Q. To go back to the question that Ms Callan asked you, which I don't think you quite answered, was it when Dr Skinner raised it in the witness box when you first became aware of the potential significance of what happened in the swimming pool?
A. Probably yes.

CALLAN

Q. You say that as best you can recall you've had three telephone calls with Ms Folbigg, the first and second were either side of the genetic testing which was undertaken, and the third call was on the top of mosaicism.
A. Yes.

Q. And that's referred to in a report that I'll take you to shortly. Have you ever spoken to Ms Folbigg in person.
A. Yes, I went to visit her in prison in June 2021.

Q. And why did you do that.
A. Because it is a current ethical standard to inform patients of our research and let them know particularly when we end an investigation. We're expecting to - we are expected to let them know the aggregate results, particularly also before making them public. I had - I was leaving Australia. I was stopping my own investigation on the mutations in the children. We had concluded the mosaicism result, and as you've seen, this telephone conversations are less than opportune. In the ethical standard we are also supposed to communicate in a way that the patient understands and in a personalised manner. I do that routinely with all of my patients, particularly with all of the cases that we investigate for several years.

Q. After the particular investigation that you conducted on the topic of mosaicism, did you conduct any further investigations in relation to Ms Folbigg.
A. No.

Q. And you had spoken to her about the outcome of the mosaicism enquiry by phone.
A. No. I - I told her about those results in person.

Q. And that was when you visited her in the gaol in June of 2021.
A. Yes, that's what I remember. I mean, I'm sorry if there was - if I did talk to her about that some other time, I just don't remember.

Q. And why did you choose to do it in person rather than on the phone as you had done in relation to the previous instances of giving her information.
A. First, you've seen these kind of phone calls. You - I mean, they are very short, there is noise, you don't hear very well, and because normally these are delicate results and you have to explain them in a way that a patient understands and if you want to do it properly it takes a couple of hours. These are important things. It's, you know, children, mosaicism, not easy terms for anyone to understand that are not trained in medicine or genetics.

Q. And why hadn't you visited her in the gaol to give her the information about the outcome of the whole genome sequencing.
A. Well, that was a single one result, and it was very preliminary. We didn't know the significance. So there was - I mean, all I could say is that she probably needed to see a specialist but I couldn't tell her whether this was a variant that was pathogenic or likely pathogenic. In fact, I mentioned in the conversation at the point it was a variant of uncertain significance.

Q. By June of 2021 when you went to visit Ms Folbigg in the gaol, had you become obsessed over her case.
A. Well, I was obsessed about the science and about the science being accurately recorded and finished properly.

Q. Was that part of the reason why you visited her in person rather than have spoken to her over the phone.
A. No.

Q. By June of 2021 had you had an emotional reaction to the circumstances of her case.
A. I was very surprised with the result of the previous Inquiry because I thought the scientific data were sufficiently strong, particularly after we knew there was another family that had a mutation in the same residue that had had a death of a child and a cardiac arrest of a second child, to be dismissed so easily, so yes, that had - I had a surprised disappointed reaction to that.

Q. And does that form any part of the reason why you chose to visit her in gaol rather than speaking to her on the phone.
A. No. It is what I do with my patients. It's part of our professional - part of the research, you know. I've had recently, for example, a patient in Guatemala in which we discovered a mutation that we've just recently published in TLR7. I've spoken to her and her family several times, and for hours on occasions. I have a patient in Madrid I visited personally him and his parents to explain the condition. These are not easy things to explain on the phone or in writing.

Q. The report in which you describe your further investigations on mosaicism is your report of 10 October 2022. For the record, your Honour, that's

Exhibit 5-04. Do you have a copy of that report there with you?
A. Yes. Yep, I have it.

Q. Do you see at page 13, red page 75.
A. Page 13, yes.

Q. Paragraph 3.4 you refer to samples taken from Ms Folbigg in 2020.
A. Yes.

Q. And at paragraph 3.5 doing the Sanger sequencing.
A. Yes.

Q. And you say the results were ready on 24 September 2020.
A. Yes.

Q. And the sequencing results for the hair came through on 9 October 2020.
A. Yes.

Q. Did you wait until June of 2021 to give Ms Folbigg the results of the mosaicism.
A. Well, I had transferred them partially through the lawyers. I told the lawyers that I still thought that she was at risk of her cardiac arrhythmia because her results were still not definitive but probably negative, but I hadn't explained them to her in person.

Q. You explained the results of the outcome of the mosaicism by telephone, didn't you, to Ms Folbigg?
A. I'm not sure, I don't think I did. I might have done but I can't remember very well.

Q. When I asked you earlier as to the occasions when you recalled speaking to Ms Folbigg by phone you said, three that I recall, two which were either side of the genetic testing and one on the topic of mosaicism?
A. Yes, it was to ask to explain to her how to collect the samples.

Q. I see, so it was before the samples were taken?
A. Yes.

Q. After you got these results in September and early October of 2020, is it your evidence that the next time you spoke to Ms Folbigg was when you visited her in the gaol in June of 2021?
A. That's my recollection, if my memory is good that's my recollection. I hope I'm not getting that wrong.

Q. Why was it that there was such a delay between getting the results and telling her about them, Professor?
A. Well, I had initially told the lawyers about them, so I suppose the lawyers could transfer it. When my main reason to go to prison was because I was finishing my investigation and at the end of an investigation it is the right thing to do to involve the patient, let them know the aggregate results, so this was

the results on of everything we had done including our investigation on the variants in the boys.

Q. You've spoken already about the obligations that you felt to Ms Folbigg and the obligations you feel in relation to all your patients to explain results to them. Why was it in relation to the results as to mosaicism that you left it to her lawyers to explain to her?
A. Look, I mean, I am not the treating cardiologist, so for me it wouldn't be appropriate to be necessarily giving these results in isolation. I was going - for me the moment that I went to her was to say we have finished this investigation, normally you report both positive and negative findings, and it is the aggregate of all the experiments we had performed.

Q. Did you decide to finish the investigation because you were leaving the country and going off to undertake another professional path?
A. No, not exclusively. The areas where we were entering were beyond my area of expertise. In the case of the BSN I'm not a neuroscientist so I had talked to a neuroscientist that was interested in following up these potential effect of BSN, Dr Nathalie Dehorter, and the investigation was going to be continued by her because in any case I'm not a specialist in epilepsy.

Q. I'll come back to my question. Did you decide to finish your investigation in relation to Ms Folbigg at the point in time that you were moving overseas to pursue another professional opportunity, in June of--
A. I had finished what I could do. There was very little else. There - were just coming through for the BSN, we had done the preliminary testing of the temperature and there was nothing - I think it coincided in time, there was nothing else my team could do, and we were transferring that. So in timing it was more or less coinciding in time.

Q. Just to be clear, was explaining to her the results of the mosaicism something you did or did not do in June of 2021?
A. Look, again, I mean memory is a poor thing, I would imagine I would've taken through what we had done, but specifically how much we went through about everything in that conversation, for me it's difficult to tell, but I would have probably told her what I thought she could understand of everything that we had done.

Q. Did you want to meet her and say goodbye?
A. I thought it was a good thing to say as well. I mean thank you and goodbye, and that's what you normally do to patients when you finish an investigation.

Q. The investigations that were conducted in relation to the question of mosaicism, they're due to the conclusion expressed at paragraph 3.9 of this report, page 14, red page 76?
A. Yes.

Q. You say, "Given the lack of clear mosaicism in the tissue tested, we feel comfortable with the conclusions stated in Brohus that in this family the CALM2

variant was inherited from their extant mother who did not appear to be mosaic". Aside from the particular steps that were taken to deal with the question of mosaicism, it's the case that after the conclusion of the 2019 Inquiry you were very active in seeking out people who might perform functional assays in relation to the G114 variant?
A. That's not completely correct because when I sought Michael Toft Overgaard that was still before the conclusion of the 2019 Inquiry, and he took over that investigation. I didn't have to approach him again.

Q. I see, so it was before the conclusion of the 2019 Inquiry that you raised with Professor Toft Overgaard the prospect of functional assays being performed?
A. Yes.

Q. With that clarification as to timing, did you enlist him to undertake those functional assays?
A. I didn't enlist anyone. I asked for an opinion to three cardiologists. A. L. George referred me to Michael Toft Overgaard for his expertise. I wrote to him and he said he would be interested in conducting functional assays because that's exactly what he does, find novel variants and test them. I have never met Michael Toft Overgaard and I got his reference from one of the top cardiologists in the word that I had never met before either; and this is what we do in my field, we seek the experts in each domain to get their input.

Q. There have already been some questions asked, I think you've been in court already about the role that different people played as named authors of the Brohus article. Can I ask how do you describe your role in relation to the bringing together of the information in that article?
A. So, I contributed the information on the genetics, the sequencing, what we knew about the tissues that had been tested. I helped when there were a few people, more junior investigators that helped with different aspects of that. I sought a second opinion on the BSN variants from a reputable geneticist, and to see if there was anything else we had missed, Melanie Bahlo, so she's an author in the paper, and I think like together with the three senior authors, we wrote the paper together.

Q. And by three senior authors, it's yourself, Professor Schwartz, and Professor Toft Overgaard?
A. Yes.

Q. And who picked the title?
A. Professor Schwartz.

Q. And the others who were named authors, they had an opportunity to review the paper?
A. Yes.

Q. And the information in that - sorry, I'll start again. In your report of 25 October, and Professor Arsov has already been taken to this, there's a clarification on this topic of pseudoephedrine?

A. Yes.

Q. Where you, and I'll take you to it - sorry, page 33 of your report of 25 October 2022. Your Honour, it's Exhibit 5-06.
A. Yes, which page, sorry?

Q. It's page 33 of the report, red page 148.
A. Yep.

Q. The bottom of the page, you'll note the reference to pseudoephedrine is an error?
A. Yes.

Q. And you referenced Dr Cordner's report, Exhibit 2-Q, which had been tendered in the 2019 Inquiry, which describes the formulation of Demazin in a child, which does not contain pseudoephedrine?
A. Yeah.

Q. And when was the error brought to your attention?
A. I actually picked it up myself by reading Dr Cordner's report at the beginning of this Inquiry. It is ironic because Professor Cordner - well, not ironic, I think these are oversights. I had asked Professor Cordner to critically review our manuscript before we submitted it, and he actually had read it, so he also overlooked this formulation.

Q. Yes, and just to be clear, Professor, Dr Cordner's report in the 2019 Inquiry identifies the active ingredients of the child Demazin?
A. Yeah.

Q. Did you go yourself to the production - sorry, to the 1999 information that was available as to the contents?
A. No, I asked a junior co-author to find the formulation of Demazin and we got this formulation, which actually, if you go to the National Prescribing Service of Australia, in earlier years, for example, 2008, you will find this is the formulation that appears. So, having said that, it isn't of no consequence because the current formulation of the formulation that this infant had is actually equally toxic for Long QT Syndrome. I will add that when I noticed this error, I contacted the journal before anybody raised it to our attention, and it's in an email I can show you, you're saying, seeking a correction are the actual components, which are chlorpheniramine and phenylephrine, are equally contraindicated in Long QT Syndrome and Brugada Syndrome. Phenylephrine is an alpha-adrenergic, so it is one of those small errors that occur that was fixed as soon as we realised and does not change the conclusion.

Q. Can I move to the body of work that you've specifically contributed to this Inquiry. I've already taken you to the report of 10 October 2022, for the record, your Honour, is Exhibit 5-04. I just wanted to ensure that we identify things for the record that have come under your hand. There is then - could the witness be shown Exhibit 5-05, page 111, red page. You recognise, Professor Vinuesa, this is an email you sent to those assisting the Inquiry on 19 October

2022?
A. Yes.

Q. Responding to some requests for clarification?
A. Yes.

Q. Which had come having received your report of 10 October?
A. Yes.

Q. And then - and I've already taken you to it, I'm just working through the chronology - the Inquiry received a joint report that you prepared with Professors Arsov, Cook, and Vinuesa, dated 25 October 2022, and that's at Exhibit 5-06, and then was a report, Exhibit 5-07, of 23 January 2023, which again is a joint report of Professors Arsov, Cook and Vinuesa. You recognise or recall preparing and when that report was furnished.
A. Yes.

Q. And finally, from you we have what's described as the further report of Professor Cook and Vinuesa and it's at Exhibit 5-08. It's a report of 1 February which concerns the topic of modifier genes.
A. Yes.

Q. In terms of the content of these reports, each of them from 25 October onwards have been joint reports with others, Professor Cook on each occasion, and Professor Arsov on two occasions. Is there - could you give a sense of the extent to which you took the lead in terms of writing the content of these reports.
A. Obviously the first two about the mosaicism and the other things were mine. For example, the first big one, 25 October, we divided it according to areas that we each has felt more comfortable, first we wrote a part, but then we all reviewed each others, edited others and contributed to each others. And that's been the case with most reports. There has been different contributions. As you can imagine when you write joint reports, in some areas we all think exactly alike, in other areas there has to be a bit of compromise because it's very difficult to get identical views on everything for three people, but we were all generally happy that what was there was a reflection, read accurately of what each of us thought.

Q. If there's any parts of these reports that I take you to that you wish to emphasise with the product of that experience, that is it fell more within someone else's domain and you were relatively comfortable.
A. Yes.

Q. But it's not, as it were, your contribution, please indicate that.
A. Yep.

Q. After receiving these various reports, in February - if you've got the folders there, at tab 5-09.
A. Yeah.

Q. The Inquiry received a document headed "statement for the Inquiry".
A. Yes.

Q. Do you recall signing that document.
A. Yes.

Q. And was that in or about early February of this year?
A. Yes.

Q. And why did you do so?
A. Because I realised that's when I was reading other experts' reports that everybody was writing the statement and we were asked to do it by the Inquiry and I realised that in none of our reports we realised we had written that statement.

Q. And the statement says that you acknowledge for the purpose of a particular rule that you've read the expert witness code of conduct. Do you recall a copy of that code of conduct accompanied the letter of instruction you received from the Inquiry.
A. I think so.

Q. Did you read it?
A. I would have read it, yes. I think I would have read it. I definitely read it for the first Inquiry.

Q. In this document that you've signed, you say that you acknowledge - you say that you have read the code of conduct and agree to be bound by it; do you see that?
A. Yes.

Q. And you don't recall specifically reading it for the purposes of this Inquiry.
A. I read it for the first Inquiry and I would imagine it would have been the same.

Q. Just to be clear, when you signed this document and said you had read the expert witness code of conduct, that's a reference to having read it back in 2019.
A. Yes.

Q. And when you signed this document, did you have in your mind that the expert witness code of conduct required that an expert witness not be an advocate for a party.
A. Yes.

Q. And did you understand that the expectation was that an expert's paramount duty is to assist the Court impartially on matters relevant to the area of expertise.
A. Absolutely. Since the appointment to this Inquiry.

Q. And it's stated here in your acknowledgement the code goes on to

emphasise the importance that the opinions given by experts are wholly or substantially based on specific knowledge and expertise, and you say that the opinions in your reports are wholly and substantially based on your specific knowledge and expertise in genetics. Yes?
A. Yes, and there are other areas that I understand, yes.

Q. And do you say you've confined yourself in your reports to the area of genetics.
A. Whenever we have talked about other areas, we have said we can talk from what's on the literature.

Q. Okay. Now, the expert witness code expresses expectations in terms of experts not being an advocate and being impartial. I suggest a similar theme is central to the scientific method and that is objectivity.
A. Yes.

Q. And I want to ask you about whether you consider that you have maintained independence and objectivity in relation to your work on the Folbigg matter.
A. I have, and I can give you some examples if you wish.

Q. I'll make sure that you have that opportunity. Your colleague Professor Schwartz has said in one of his reports that's just been made available to you, and your Honour, for the record it's his report of 8 November 2022, Exhibit 8-04. I don't need it to be turned up. He said:

> "I have no idea about whether Kathleen Folbigg has killed her children or not and even though this is not a nice thing to say, to a certain extent I don't really care, this is not for me to say".

Professor Vinuesa, do you take the same attitude to this case?
A. Yes in certain respects. I am not the person that's going to say whether she killed them or not and we cannot draw - I wouldn't be able to draw a definitive conclusion. What I can do is have a personal opinion as the extension of my professional work.

Q. You do hold a personal opinion as an extension of your professional work, don't you?
A. Well I have - I can draw some conclusions from our work. That doesn't mean that the conclusions - I mean I don't think anybody in this room can say whether she killed them or not, but I think there is reasonable evidence that we have some natural causes of death; and that's more or less what I've implied in our reports.

Q. Do you accept, Professor Vinuesa that over the years since the 2019 Inquiry you have written articles or spoken to the media in which you've expressed your personal view about Ms Folbigg's innocence?
A. I have expressed a view that was the extension of my professional work, yes.

Q. Do you or did you do that as a form of advocacy for her, Ms Folbigg?
A. As advocacy for the science.

JUDICIAL OFFICER

Q. Did you participate at all in the preparation of the material which led to the petition going to the Attorney-General which formed the base of this Inquiry?
A. No, I didn't prepare that material.

CALLAN

Q. Did you participate in any way in the preparation of that material, Professor?
A. I had provided the Brohus article, I don't think I contributed in a different - in another way.

JUDICIAL OFFICER

Q. Let me ask you this. Regardless of the personal opinion you held of the merits of Ms Folbigg's case, did you endeavour putting - giving your evidence to this Inquiry to give it objectively, having regard to the scientific findings that you made?
A. I did try to do it objectively. I mean I - if I may say, you know, when I was first approached I had never heard of Ms Folbigg. I, to this date, you know, I haven't been paid a cent for the work we've done, it's taking us numerous reports, numerous hours of my work, both, you know, during working hours and out of hours. I do this because I believe in the science that we do and I like to, you know, draw some conclusions on the science in the way that we can do it. I have no personal interest - I mean I do take personal interest in the cases that I work, but it's not about the individuals, it is about the science.

CALLAN

Q. Do you recall being interviewed by a journalist Oscar Schwartz, for an article which was published in WIRED in December of 2021?
A. Yes, I remember having some long conversations with Oscar Schwartz and, you know when you talk to people you never know when what's on the record and off the record, so I did read that article, yes.

Q. To clarify, did you understand that there was any part of your conversation with the journalist Oscar Schwartz that was off the record?
A. Well, I was hoping there would be areas that would be off the record, yes.

Q. You didn't clarify that with him?
A. Look, I hadn't had so much experience with journalists. I think I've learned by now that certain things have to be clarified.

Q. When you read the article, did you consider it was accurate?
A. Well I wish there were certain things that hadn't been said in the article, but I guess it did reflect some views.

Q. So, I'll come again, was it accurate?
A. It's a - it's a - there was a lot of things in there I mean I could have - I would have to go through it all in detail.

Q. Okay, sure, I'll give you that opportunity. Can I ask that the article published in WIRED by the journalist Oscar Schwartz be provided to Professor Vinuesa? We have a copy of it on the screen your Honour.
A. Yes.

Q. In its printed form this is a 30-page article which describes the circumstance in which you came to be involved in relation to Ms Folbigg's case and the work that you've undertaken up to that point in time that the article was published.
A. Yep.

Q. Could I take you to the bottom, to page 4 of 30?
A. Yep.

Q. Where you described that you wrote an email to Folbigg's lawyers and said you were in?
A. Yes.

Q. It describes how you dug into the investigation and says, you had no idea over the course of the two all-consuming years you would end up confronting painful questions about her own life as a scientist and as a parent. Do you see that there?
A. Yes.

Q. Now, that's the way the journalist has described it, is that how you would describe it? The experience over those two years?
A. Well, I don't think it was the case I'd really brought up, I think I did tell the experience that as a mother, you know, when my child was sick, I often considered myself guilty of her colon pain and colic and screaming, and that very often I also wished that she would not be so difficult. But I don't think it was this confrontation with the Folbigg case, I was just explaining my experiences as a mother.

Q. Okay. It describes an email you wrote to the lawyer, I understand that's Ms Folbigg's lawyer, which said, "As a mother, I cannot think of any more worthy cause to invest time and effort in. I find it hard to believe there is someone sitting in gaol for this." Do you see that?
A. Yep.

Q. Did you write that email?
A. Yes.

Q. At that point in time, you'd done - you'd read the Folbigg family's medical records, is that right?
A. Yes.

Q. Had you undertaken any genomic analysis?
A. No.

Q. You related to the case as a mother, and you regarded it as a worthy cause to invest your time in?
A. Yes.

Q. You say that you find it hard to believe there is someone sitting in gaol for this. At that point in time, had you formed a view as to Ms Folbigg's guilt or innocence?
A. When I had read about the children, particularly two of them being very sick and one having myocarditis, which is a very frequent cause of death, and the fact that there had been these, you know, probability mentioned. So, I thought it definitely warranted a genetic investigation.

Q. Your reference to being a mother, and you've expanded on that already. Have you had an emotional reaction to Ms Folbigg's case because you were a mother yourself?
A. I'm not sure I would describe it emotionally, but I would have thought about having four sick children and, you know, feeling self-blame or guilt when you have very sick children.

Q. What do you say to the suggestion that that reaction that you've described has affected the objectivity with which you have undertaken your work in relation to this matter?
A. Look, I think I try always very carefully to separate my personal feelings with my professional work, because it is very important that we are completely objective, and that's why we bring co-authors and why we try and check and triple check our results and repeat and reproduce, and in our case, our contribution was finding a variant that is verifiable, you can go back to Ms Folbigg's tissues and sequence that over and over again. So, that was our contribution, and that is infallible. In the same way as the mosaicism gave us contradictory results, and I didn't settle on the first mosaicism result. As you know, we did find a mosaicism result in the urine before the paper was published. I would have very easily put that in the paper because it would have settled the case.

She's a mosaic, therefore this variant meets all the criteria for pathogenicity, and I did not do that because I know that it is ideal to repeat an experiment twice, so it would have been so easy to put that urine sample - if you look at it, it is a perfect mosaic forward and reverse sequencing. If I had let my emotions or any type of bias come through, I would have pushed that through. That result came in September. The paper was not published until November, and I said we cannot do this because it's too early, we need to repeat sample to be convinced. Now, many papers published an N equals 1, you know, and I had some of my co-authors say wow, this is a mosaic. So, even though I might have my personal opinion, my professionalism doesn't allow me to do anything that I consider it is not scientifically accurate, and I do know very well how to separate my personal opinion or the conclusions I might be drawing from my science from what we report or what we put in terms of scientific data.

Q. Could I take you to page 19.
A. Yeah.

Q. About the middle of the page, the journalist writes, "Vinuesa's goal was different, it was to cast doubt on the prosecution's original argument that four unexplained infant deaths implied murder. She was hunting for alternate possibilities." Is that how you conceived of your goal or your task?
A. No. Well, that's a way to put it. I was trying to find the bottom. I was trying to find the truth, and we had a genetic mutation that looked very suspicious that we knew that that same mutation - that same recidivism in another family had killed two children and we wanted to try and know whether it was functional. That was my goal. There was - there's a lot of colour in this report, and that is not my profession, but we were trying to get to the bottom and understand this variant.

JUDICIAL OFFICER: Professor, could I ask you this--

WOODS: Sorry, your Honour, the witness wants some water.

JUDICIAL OFFICER: I'm so sorry.

Q. Professor, can I ask you this.
A. Yes.

Q. You gave an interview to this journalist which resulted in this article.
A. Which what, sorry.

Q. Which resulted in this article?
A. Yeah.

Q. Did the journalist ever give you a chance to review a draft of it?
A. It didn't - it didn't contain all the parts that are here and I did complain about that.

Q. I understand.
A. I saw an early draft and I didn't see this final one. And most journalists don't even show you the first draft and you are probably are aware with that. So I was--

Q. I've had some experience of that, Ms Callan.
A. Sorry?

Q. I've had some experience of that myself.
A. Yeah.

Q. With my former occupation.

CALLAN

Q. There's reference in that article to a point in time when the Folbigg case

had distracted you, so it's said. This is at the bottom of page 22 and it says, "Every night after work she was responding to some email from Folbigg's legal team or reading papers on the calmodulin genes." Do you recall a point in time when you were engaging in direct email communication with Ms Folbigg's legal team?
A. Yes. At some point she was going to be transferred prisons and they asked me to assess the risk she would be of a lethal cardiac arrhythmia due to stress because we had already established that during the 2017 transfer she had a syncope and it was put down to stress. She herself had acknowledged it had been due to stress and we thought that could be CPVT. During COVID as well, they contacted me to ask me what was my thinking as to whether she was at a particularly high risk in prison because of COVID and the possibility of myocarditis and cardiac arrhythmias due to COVID. There were - those are two occasions for example that I remember where - where I had correspondence back and forth. I was asked for papers so around the topic.

Q. The article describes that you were emailing with Ms Folbigg's legal team every night. Is that what you told the journalist?
A. No. And I think it might mean every night with this and that and the other. I mean, I had to write my report. We were doing the mosaicism. I definitely was not corresponding every night so again, I think there is some colour here that I don't recognise.

Q. Have you been in regular email communication with Ms Folbigg's legal team since you became involved in this matter in 2019.
A. Absolutely not.

Q. Why do you say, "absolutely not".
A. Because I can't even remember that there's been - there's been barely any communication. There's been--

Q. No conferences?
A. Perhaps once before each of these - so perhaps once before when we went to have a hearing in November that was cancelled, and once before this particular hearing of one hour each.

Q. And other than those conferences, no communications?
A. Very little. There has been the odd email but I will count them with the fingers of one hand.

Q. Can I move on, you might be relieved to hear, to the question of pathogenicity of G114R.
A. Yes.

Q. Now, you've heard me ask this of Professor Arsov. The task of assessing pathogenicity is a probabilistic exercise. Do you agree with that?
A. Yes.

Q. Your current view is that the variant satisfies the ACMG criteria for pathogenic.

A. Yes. I mean, I would be flexible. I would be happy between likely pathogenic and pathogenic. We think it can be pathogenic but given that there is a bit of a grey area with PS3, that PS3 could be moderate instead of strong and then we could be in the likely pathogenic band so I'm happy with both. I still think that because of the stacking of functional evidence, which is contemplated by ACMG, and there's five different lines of functional evidence, plus the one that is this, you know, massively deep mutational scanning that's recognised as the future way of classifying these variants, my feeling is that it does reach the strong PS3 criterion but I would be happy to leave it as likely pathogenic if - if people feel that that's a more appropriate boundary because it's true that - because calmodulin is so special and there are not benign variants, it is always - it is always going to be impossible to have sufficient controls in those assays, but instead of having one assay with 11 controls we can have five functional assays that don't duplicate the readout and ACMG's flexible in that and allows that to substitute for one perfect clinical grade. So in my view, it could be pathogenic but I would be happy to leave it as likely pathogenic.

Q. You invoke or refer to the ACMG criteria. In particular you've referenced PS3 which is a criteria which concerns whether there are well-established functional studies. Again, I raised this with Professor Arsov. I think you were in the room at the time. You, in joint reports with him, have suggested that the ACMG criteria is not particularly apt for this current situation. That is, it's not a clinical setting.

A. Yes. It's mainly designed for a clinical setting because normally you need quite a bit of information. This is like being able to score against criterion. You have to tally up all of the criteria. As we mentioned in our original report here, we do simply lack information. We didn't have paternal DNA. We couldn't establish *de novo*. We didn't have enough information - I mean, ECGs for example. So we are limited in to the information but having said that, despite those limitations we are confident that now we can apply it even in its very strict terms and still reach the pathogenicity or likely pathogenic classification.

Q. Does the fact that you consider you can now apply it in its strict terms strengthen the confidence you have in the conclusions that you've reached about the pathogenicity?

A. Well it's that and the - I mean accumulating evidence, I mean as the time goes by and particularly since the 2019 Inquiry we've had significant more information coming from the Brohus article, from the new data from Professors Toft Overgaard and Nyegaard, the article that was published yesterday, pre-print, about yet another potassium channel affected by - the G114 interacting yet with another potassium channel, so I think my confidence is increasing not just because of the ACMG criteria but because of everything that we are learning about this particular variant thanks to all of this functional work.

Q. The functional studies and the way you referred to them, can I take you to the most recent report on that topic which is your report of 23 January 2023, it's at Exhibit 5-07. Your Honour, it's red page 197, page 15 of your report. Do you see there you refer to the particular criteria and the way that you've

approached the ACMG criteria--
A. Yes.

Q. --based on the information available? Under the blue heading "PS3", that's the code for well-established functional studies showing a deleterious effect?
A. Yes.

Q. You mentioned a few minutes ago in your evidence about the fact that because of the nature of calmodulin undertaking functional assays with controls, that is a benign variant is a real challenge - it's not possible you say?
A. Yes.

Q. But you refer instead to the stacking of the functional assays that have been?
A. Yes.

Q. Is it that inability to undertake functional assays which are controlled which cause you to acknowledge that the application of PS3 might for by at least some people be downgraded?
A. Yes, but I have to say even though these papers suggest that, most as is the clinic for ACMG classification do not include 11 controls, so this is - might be like a gold standard, but this not what routine clinics do. Having said that, we respect these and, you know, this is why we then go forward in this article where it starts saying, well, this might not be the only way to do it, you could stack evidence for cases that are a bit more problematic, and different assays that look at different readouts so long as there no duplication can also be taken into account. Particularly if you can reach some type of here they talk about lots of pathogenicity, we've referred to perhaps the low likelihood ratio according to a Floyd et al variant effect mark. So there is flexibility in this description of what a PS3 could look like.

Q. In Professor Schwartz's report from December 2022 - for the record that's at Exhibit 8-04 - he observed that the clinical reality may be much more complex than what is apparent on the results of functional assays. Do you disagree with that view?
A. No, completely, I mean - and we've been talking here that at the moment everything has been done in a very minimalistic way, one channel at a time. At the moment we've only had really a bit of evidence on binding to calcium, binding to the Cav1.2, binding to the Nav1.5, I mean in reality there are many more molecules that calmodulin interacts with. I had a presentation I was hoping to take you through, but doesn't matter. We've just heard yesterday about yet another potassium channel and it is again just looking at one at a time the realities that they are all interacting together, this would be much more complex than we anticipate for sure.

Q. That complexity and the potential for unexpected clinical consequences, means that the functional assays, whilst of value, have their limits?
A. Yes, but I think if I'm honest, every single assay has pointed to pathogenicity. There hasn't been a single assay that has pointed to it being benign. If anything, every new assay points to it having a damaging effect,

and the Weile et al paper is really intriguing in that respect and we've discussed that in one of our teleconferences. I mean glycine 114 is one of the only two amino acids in calmodulin that cannot be substituted by any other residue. So, if we were having contradicting findings but every new functional assay yet again points to pathogenicity, yes, we could speculate in - the some of the results might do nothing but I think the evidence is stacking for something very unusual and potentially very damaging.

Q. You say we can speculate, some might do nothing, do you accept that we are at a point in time when it is speculative as to what these--
A. Look, I don't want to speculate. I will just say that the five assays to date say it is pathogenic or it is damaging for a protein function.

Q. As to how that translates into the clinical picture, would you not--
A. It's beyond my expertise.

JUDICIAL OFFICER

Q. Firstly, you just draw a distinction between pathogenic and damaging to the protein function. Is there any real distinction between the two?
A. Depending on whether we have ACMG criteria in mind. When we talk about ACMG, pathogenic has a meaning, but even in - when I publish and I don't talk about ACMG, I refer to pathogenic as a residue that has a pathogenic, a damaging effect on function. So, I'm sorry if at some point I might use these two terms--

Q. But they're, that's why I wanted to make clear that they were interchangeable, that's all?
A. Yes, at the moment I was referring to ACMG, which again, many cardiologists and non-cardiologists find it's a very clunky system. It's mainly designed for pathologists sitting in laboratories that do not have experience with these particular diseases. So, you have to give them a framework against which to classify variants. I mean normally, and I have to say because I, myself, participate in a ClinGen panel, in a gene curation expert panel. Experts are scientists and clinicians that have spent many years in a focus area, and they help interpret and provide feedback to those that apply ACMG criteria. So, in a way, this is designed to educate and create a framework for pathologists to find it easier to score.

But eventually, in the end you have to ask the experts, like Professor Toft Overgaard, Nyegaard, and other calmodulin experts as to how do they - how pathogenic they feel this mutation is, and if I may say something again, I want to reiterate what my colleague said, BS2 cannot be applied because BS2 does not refer to the individual variant, it refers to when we talk about it can only be applied to conditions that are fully penetrant at a young age, and here the condition is calmodulinopathy, we are not talking about any one variant in calmodulin. So, calmodulinopathy is not penetrant at a young age. We have plenty of examples in the Registry. Therefore, simply because of that, BS2 cannot be applied. It's not about whether she's healthy or not, it's about - it's not adequate in a condition that's not fully penetrant at a young age.

CALLAN

Q. Just to be clear for the transcript, you're saying BS2, B for benign?
A. Yes, BS2.

CALLAN: Is that a convenient time, your Honour.

JUDICIAL OFFICER: Yes. We'll resume at 10 o'clock tomorrow morning.

CALLAN: Thank you.

<THE WITNESS WITHDREW

AUDIO VISUAL LINK CONCLUDED AT 4.01PM

ADJOURNED PART HEARD TO WEDNESDAY 15 FEBRUARY 2023